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Checking structural stability of BDC-decomposable systems via convex optimisation

Franco Blanchini^a, Graziano Chesi^b, Patrizio Colaneri^c and Giulia Giordano^d

Abstract—In this paper we show how the problem of assessing structural local stability of BDC-decomposable systems, left open in recent literature, can be solved via convex optimisation. First we give a simple test, based on a sufficient condition, that requires checking the strict co-positivity of a multivariate polynomial. Then we provide a stronger test, based on a necessary and sufficient condition, which can be numerically implemented via LMI-based convex optimisation. The proposed approach certifies the structural stability of non-trivial systems, including a biological network discussed in the literature.

Index Terms—BDC-decomposition, Biomolecular systems, Convex optimisation, Structural stability, Systems biology.

I. INTRODUCTION

CHECKING whether all the systems in a qualitative class share a relevant property is fundamental to reveal the robustness of peculiar behaviours in spite of uncertain or time-varying parameters. A property is *structural* [7], [12], [21] if it is enjoyed by all the systems with the same *structure*, which we define as the topology of the system interaction graph, independent of parameter values. Looking for structural properties is particularly important to explain the incredibly robust behaviour of biological systems [1], [23], which can preserve their function despite the huge variability of environmental conditions [7], [19], [23], [26], and also to design robust biomolecular controllers in synthetic biology [13].

In particular, the structural stability of biochemical systems [19] can be investigated by means of piecewise-linear [7], [8], [9], [10], [11], piecewise-linear-in-rates [2], [3], [4], [5] and piecewise-quadratic [25] Lyapunov functions. The existence of a Lyapunov function ensures structural *global* stability of a biochemical network, but it can be a very conservative condition if we are interested in a local analysis based on linearisation (and a suitable function is typically hard to find).

Here we perform a structural *local* stability analysis, as done for chemical reaction networks in the pioneering work by Clarke [17]. The *parametric uncertainty* approach to *robust* stability analysis [6] relies on assuming that the uncertain parameters lie within known bounds; if this is the case, then the mapping theorem and value-set analysis are very powerful.

However, we assume that the parameters are positive numbers with no available finite bounds, which makes value-set analysis impossible. When no quantitative bounds for the uncertain parameters are known, interesting results are available in the literature, under the name of *qualitative stability* [18, Chapter 6.5], for systems whose state matrix has the interval structure, meaning that all its coefficients vary independently. We consider here BDC-decomposable systems [21], [22], which admit interval-structure systems as a special case; indeed, the BDC-decomposition can capture generic system structures, taking into account possible cross-constraints among coefficients.

The most effective techniques to solve robust stability analysis of linear time-invariant systems affected by structured time-invariant parameters are based on parametric quadratic Lyapunov functions; in particular, pioneering methods proposed sufficient conditions by exploiting quadratic Lyapunov functions depending linearly on the parameters, see for instance [17], [20]. In order to reduce the conservatism, methods based on quadratic Lyapunov functions depending polynomially on the parameters were proposed, see for instance [15] and references therein. However, to the best knowledge of the authors, these methods generally consider that the set of admissible parameters is compact and, hence, do not allow one to address the problem considered in this paper, where the set of admissible parameters is open.

Here, we first formulate the problem of structural local stability analysis. We show that it boils down to checking that a nonnegative multivariate polynomial of the unknown parameters, which is a sum of squares of polynomials (in short, SOS), is strictly co-positive (i.e., it is positive for all positive values of its variables). This is a sufficient condition that can be tested via computer-algebra.

Then we suggest a strategy based on convex optimisation and quadratic Lyapunov functions depending polynomially on the parameters, which leads to a *necessary and sufficient* condition expressed in terms of the solution of semidefinite programs (SDPs). We show that our approach can assess structural stability in non-trivial cases, unsolved in previous literature, including a biological system describing a signal transduction network.

II. STRUCTURAL STABILITY OF BDC-DECOMPOSABLE SYSTEMS: PROBLEM FORMULATION

Consider a nonlinear system of the form

$$\dot{x}(t) = Sf(x(t)) + f_0, \quad (1)$$

where $x \in \mathcal{D} \subseteq \mathbb{R}^n$ is the state, $S \in \mathbb{Z}^{n \times r}$ is the system “stoichiometric” matrix, $f : \mathcal{D} \subseteq \mathbb{R}^n \rightarrow \mathbb{R}^r$ is a vector

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of *unknown* continuously differentiable functions with *sign-definite partial derivatives*, \mathcal{D} is an open, convex domain, and $f_0 \in \mathbb{R}^n$ is a constant vector. At the equilibrium point \bar{x} , $Sf(\bar{x}) + f_0 = 0$.

This class of models includes chemical reaction networks and all phenomenological biomolecular models (gene regulatory models, signalling networks, etc.) that can be written as an equivalent chemical reaction network, as well as ecological models and population dynamics. In these cases, $\mathcal{D} = \mathbb{R}_{\geq 0}^n$. Any system of the form (1) admits a BDC-decomposition, where D is a diagonal matrix including the *unknown* positive parameters $|\partial f_j / \partial x_i|$, while the known matrices B and C representing the system *structure* can be built systematically, based on matrix S and on qualitative information about $f(\cdot)$.

Proposition 1 ([21], [22]): Any system of the form (1) admits a BDC-decomposition: its Jacobian at any point $x \in \mathcal{D}$ can be written as the positive linear combination of rank-one matrices

$$J(x) = BD(x)C = \sum_{i=1}^q d_i(x) B_{\bullet i} C_{i \bullet} \in \mathbb{R}^{n \times n}, \quad (2)$$

where $B = [B_{\bullet 1} \dots B_{\bullet q}]$ and $C = [C_{1 \bullet} \dots C_{q \bullet}]^\top$, while $D(x) = \text{diag}\{d_i(x)\}$ is a positive definite diagonal matrix.

Matrices B and C can be computed as follows: in B , the k th column S_k of S is repeated a number of times equal to the number of arguments (hence of partial derivatives) of the corresponding entry f_k of the vector function f ; the same number of rows is placed in C , where each row has a 1 corresponding to the argument index and is zero elsewhere.

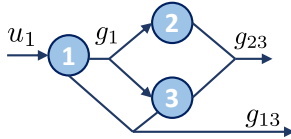


Figure 1: The structure of the system in Example 1. Nodes represent chemical species (associated with the system variables x_i), arcs represent reactions (associated with the system rates g_k). The chemical reactions are $\emptyset \xrightarrow{u_1} X_1$, $X_1 \xrightarrow{g_1} X_2 + X_3$, $X_2 + X_3 \xrightarrow{g_{23}} \emptyset$, $X_1 + X_3 \xrightarrow{g_{13}} \emptyset$.

Example 1: The system structure represented in Fig. 1 (named Frescobaldi3 in [8]) is associated with equations

$$\dot{x}_1 = -g_1(x_1) - g_{13}(x_1, x_3) + u_1 \quad (3)$$

$$\dot{x}_2 = g_1(x_1) - g_{23}(x_2, x_3) \quad (4)$$

$$\dot{x}_3 = g_1(x_1) - g_{13}(x_1, x_3) - g_{23}(x_2, x_3) \quad (5)$$

where all functions in $f = [g_1 \ g_{23} \ g_{13}]^\top$ are increasing in all arguments. For this system

$$S = \begin{pmatrix} -1 & 0 & -1 \\ 1 & -1 & 0 \\ 1 & -1 & -1 \end{pmatrix}, \quad f_0 = \begin{pmatrix} u_1 \\ 0 \\ 0 \end{pmatrix}.$$

Then, the system Jacobian can be written as $J(x) = BD(x)C$, with

$$D(x) = \text{diag} \left\{ \frac{\partial g_1}{\partial x_1}, \frac{\partial g_{23}}{\partial x_2}, \frac{\partial g_{23}}{\partial x_3}, \frac{\partial g_{13}}{\partial x_1}, \frac{\partial g_{13}}{\partial x_3} \right\},$$

$$B = \begin{pmatrix} -1 & 0 & 0 & -1 & -1 \\ 1 & -1 & -1 & 0 & 0 \\ 1 & -1 & -1 & -1 & -1 \end{pmatrix}, \quad C = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$

Note that nothing beyond the structure in Fig. 1 and monotonicity of the functions in $f(x)$ is specified. Since the procedure to generate a polyhedral Lyapunov function [8] does not converge for this system, not even in rate coordinates [5], [10], its structural stability is an open question.

The BDC-decomposition captures the system *structure*, equivalently described by the matrix pair (B, C) identifying a whole class of systems, while matrix D includes all the unknown parameters: any fixed choice of $D \succ 0$ identifies a single element of the class. A *structural property* holds for all systems belonging to the class identified by the given matrices (B, C) , for all possible values of the diagonal matrix $D \succ 0$.

We are now ready to formulate the considered problem.

Problem 1: Structural local stability. Assume that BDC is Hurwitz (i.e., all its eigenvalues have negative real part) for some diagonal $D = \text{diag}\{d_i\} \succ 0$ (nominal stability). Check whether

$$BDC \text{ is Hurwitz for all diagonal } D \succ 0. \quad (6)$$

If BDC is Hurwitz for a choice of $D \succ 0$, a necessary and sufficient condition for structural local stability is that, for any $D \succ 0$, BDC has no eigenvalues on the imaginary axis (see [6, Section 5.7.8]). We introduce the following working assumption on the known matrices B and C .

Assumption 1: Matrix BC is Hurwitz.

As a first step, we rule out eigenvalues at zero. Structural non-singularity can be easily assessed with a vertex test.

Proposition 2 ([8], [22]): Given the known matrices B and C , the function $\det(BDC)$ is non-zero for all possible diagonal matrices $D = \text{diag}\{d_i\} \succ 0$ if and only if (i) $\det(BC) \neq 0$, and (ii) $\det(BDC)$ has the same sign as $\det(BC)$, or is zero, for all possible choices of $d_i \in \{0, 1\}$, corresponding to the vertices of the unit hypercube $0 \leq d_i \leq 1$.

The procedure suggests a test that requires the computation of 2^q determinants (e.g., if $q = 2$, those corresponding to $(0, 0)$, $(1, 0)$, $(0, 1)$, $(1, 1)$); note that we can restrict the test to the unit hypercube without loss of generality.

Assumption 1 implies that $\det(-BC) > 0$ (in fact, $\det(-BC)$ is the constant term of the characteristic polynomial associated with matrix BC). Then, under Assumption 1, assuming that the non-singularity test has been successfully performed is equivalent to the following assumption.

Assumption 2: For all diagonal matrices $D \succ 0$, we have $\det(-BDC) > 0$.

Therefore, our structural local stability problem amounts to ruling out imaginary eigenvalues.

Problem 2: Under Assumptions 1 and 2, check whether

$$\det(j\omega I - BDC) \neq 0 \quad (7)$$

for all real scalars $\omega > 0$ and all diagonal matrices $D \succ 0$.

Remark 1: In [17], the stability analysis problem was reduced to a D -stability problem. A stable matrix M is D -stable if MD is Hurwitz stable for all positive diagonal D .

Here, we could consider matrix CBD , which has the same eigenvalues as BDC plus the 0 eigenvalue. As discussed in [17], a sufficient D -stability condition is the existence of a diagonal Lyapunov matrix Σ such that $\Sigma CB + (CB)^\top \Sigma \leq 0$. However, this sufficient condition is conservative and, as we have verified adopting the CVX LMI software, it is not satisfied by any of the examples considered in this paper – apart from the illustrative Example 6, which is a particular case since any 2×2 matrix with non-positive diagonal entries is D -stable if it is Hurwitz stable. The approach we propose in the following sections allows us to prove structural Hurwitz stability of many examples to which the results in [17] cannot be applied.

III. A SIMPLE TEST BASED ON STRICT CO-POSITIVITY

Problem 2 is equivalent to checking the strict co-positivity of the polynomial

$$\psi(D) \doteq \det(I + jBDC) \det(I - jBDC) = \varphi(D)\varphi^*(D). \quad (8)$$

Indeed, dividing by $\omega > 0$, (7) becomes $\det(jI - B(D/\omega)C) = \det(jI - BD'C) \neq 0$, because the diagonal entries of D are arbitrary positive numbers. Moreover, for any complex number z , $z \neq 0$ is equivalent to $zz^* > 0$.

A polynomial is *multi-affine* if, when freezing all variables but one, we get a first degree polynomial; an example is $xyz + xz - 2zy + z + y + 3$. A polynomial is *multi-quadratic* if, when freezing all variables but one, we get a second degree polynomial; an example is $x^2yz + xy^2z - 2zy + z^2 + y^2 + 3$ (in any monomial, each variable has power at most two).

Proposition 3: The polynomial (8): (I) is SOS, hence non-negative; (II) is multi-quadratic; (III) is even: $\psi(-D) = \psi(D)$.

Proof: If we split real and imaginary part of $\varphi(D)$, $\det(I + jBDC) = \varphi_R(D) + j\varphi_I(D)$, we have that $\psi(D) = \varphi_R(D)^2 + \varphi_I(D)^2$, hence $\psi(D)$ is SOS. Since $\varphi_R(D)$ and $\varphi_I(D)$ are multi-affine polynomials, $\psi(D)$ is multi-quadratic. Since $\psi(-D) = \det(I + jB(-D)C) \det(I - jB(-D)C) = \det(I - jB(D)C) \det(I + jB(D)C) = \psi(D)$, we have that $\psi(D)$ is even. ■

Example 2: Consider the system structure (named Albin3 in [8]) associated with matrices

$$B = \begin{pmatrix} -1 & -1 & -1 & 1 & 0 \\ 0 & -1 & -1 & 0 & 1 \\ 1 & 0 & 0 & -1 & 0 \end{pmatrix}, C = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & -1 & 0 \end{pmatrix}.$$

Replacing d_k by letters ($d_1 = a, d_2 = b, \dots$), we get

$$\begin{aligned} \psi &= a^2c^2 + 2a^2ce + a^2e^2 + a^2 + 2abcd + 2abce + 2abe^2 \\ &+ 2ab + 2ac^2d + 2ac^2e + 2acde + 2ace^2 + 2ade^2 \\ &+ 2ad + b^2d^2e^2 + b^2d^2 + b^2e^2 + b^2 + 2bcd^2e^2 + 2bcd^2 \\ &+ 2bce^2 + 2bc + c^2d^2e^2 + c^2d^2 + c^2e^2 + c^2 + d^2e^2 \\ &+ d^2 + e^2 + 1 = (a + b + c + d + e - bde - cde)^2 \\ &+ (1 - ac - ae - bd - be - cd - ce - de)^2. \end{aligned}$$

Since in the expanded expression of ψ there are no negative terms, BDC cannot have purely imaginary eigenvalues.

Example 3: The fact that ψ is a SOS does not imply stability. As an example, consider the nominally stable system

with

$$B = \begin{pmatrix} 1 & -1 \\ 3 & -2 \end{pmatrix}, C = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}.$$

Setting $d_1 = a$ and $d_2 = b$, we get the SOS polynomial

$$\psi(D) = a^2b^2 + a^2 - 6ab + 4b^2 + 1 = (ab - 1)^2 + (a - 2b)^2,$$

which is not strictly co-positive: it is 0 for $a = 1/b = \sqrt{2}$.

The peculiar properties of the polynomial $\psi(D)$ allow us to prove the following result.

Proposition 4: For any index k , the polynomial (8) can be written by collecting d_k as

$$\psi(D) = d_k^2 \psi_2^{(k)}(D) + d_k \psi_1^{(k)}(D) + \psi_0^{(k)}(D), \quad (9)$$

where $\psi_2^{(k)}$, $\psi_1^{(k)}$ and $\psi_0^{(k)}$ do not depend on d_k and are multi-quadratic polynomials. Moreover $\psi_2^{(k)}$ and $\psi_0^{(k)}$ are nonnegative and even, while $\psi_1^{(k)}$ is odd.

Proof: The first claim is a consequence of $\psi(D)$ being multi-quadratic. To prove nonnegativity of $\psi_2^{(k)}$, assume by contradiction $\psi_2^{(k)} < 0$ for fixed $\bar{d}_1, \bar{d}_2, \dots, \bar{d}_{k-1}, \bar{d}_{k+1}, \dots, \bar{d}_q$. For $d_k \rightarrow \infty$, $\psi \rightarrow -\infty$; then, by continuity, ψ would be negative for some D , which is impossible since ψ is a sum of squares. Nonnegativity of $\psi_0^{(k)}$ can be proved similarly by considering $d_k \rightarrow 0$. Since ψ is even (see Proposition 3), it must be a sum of even terms; $\psi_2^{(k)}$ and $\psi_0^{(k)}$ are multiplied by an even power of d_k , hence they must be even, while $\psi_1^{(k)}$ is multiplied by d_k , an odd power, hence it must be odd. ■

This result yields a sufficient condition to solve Problem 2.

Proposition 5: If, for some variable d_k , the polynomial $\psi_1^{(k)}$ in (9) is co-positive, namely

$$\psi_1^{(k)} > 0 \quad \text{for all } d_i > 0, \quad i \neq k,$$

then $\det(j\omega I - BDC) \neq 0$ for all $\omega > 0$ and all diagonal matrices $D \succ 0$.

Example 4: Consider the structure (named Gounod in [8]) corresponding to the matrices

$$B = \begin{pmatrix} -1 & -1 & 0 & 0 & 0 & 0 \\ -1 & -1 & 0 & -1 & -1 & 0 \\ 1 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & -1 \end{pmatrix}, C = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

Replacing d_k by letters ($d_1 = a, d_2 = b, \dots$), we can write $\psi = a^2\psi_2^{(a)} + a\psi_1^{(a)} + \psi_0^{(a)}$, where

$$\begin{aligned} \psi_1^{(a)} &= (4bc^2d^2 + 6bc^2df + 4bec^2d + 2bc^2f^2 + 2becdf \\ &+ [2\mathbf{bc}^2 - 2\mathbf{bcd} + 2\mathbf{bd}^2] + 4bdf + 2bed + 2bf^2 + 2b) > 0, \end{aligned}$$

because the only negative term $-2bcd$ in $\psi_1^{(a)}$ is compensated by $2bc^2$ and $2bd^2$. Hence, the system passes the test.

By means of computer algebra, we can compute the coefficients of the polynomial and get rid of possible negative terms by means of square completion, as in the next example.

Example 5: For the structure Frescobaldi3 in Example 1,

$$\begin{aligned} \psi_{(a,b,c,d,e)} &= a^2b^2d^2 + a^2b^2 + 2a^2bc + 2a^2bd + a^2c^2 + 4a^2cd + \\ &+ [4\mathbf{a}^2\mathbf{d}^2] + a^2 + 2ab^2e + 4abce + 2abd^2 + 2abde + 2ac^2e + 4acde \\ &+ [-2\mathbf{ad}] + 2ae + b^2d^2 + 2b^2de + b^2e^2 + b^2 + 2bcde + 2bce^2 + 2bc \\ &+ c^2e^2 + c^2 + 2cd + d^2 + 2de + e^2 + [1] \end{aligned}$$

The only negative term in ψ is $-2ad$, which is compensated

by the terms $4a^2d^2$ and 1, hence the polynomial is strictly co-positive and the system passes the test.

IV. SDP-BASED STABILITY TEST

Here we derive a numerical test based on convex optimisation to solve Problem 1. Let $d \in \mathbb{R}^q$, and let $V(d) = V(d)' \in \mathbb{R}^{n \times n}$ be a matrix polynomial to be determined of degree not greater than δ , where δ is a nonnegative integer. Let $\zeta, \xi \in \mathbb{R}$ be scalars to be determined, and let us define the matrix polynomials

$$\begin{cases} X_1(d) &= V(d) \\ X_2(d) &= -V(d)\hat{J}(d) - \hat{J}(d)'V(d) - \zeta I \\ &\quad + \xi I(1 + \sum_{i=1}^q d_i)^{\delta+1} \end{cases} \quad (10)$$

where

$$\hat{J}(d) = B(\text{diag}(d) + I)C. \quad (11)$$

Let us introduce the following definition, see for instance [14] and references therein.

Definition 1: A matrix polynomial $P(d) = P(d)' \in \mathbb{R}^{n \times n}$, $d \in \mathbb{R}^q$, is a *sum of squares of matrix polynomials (in short, SOS)* if there exist matrix polynomials $P_i(d) \in \mathbb{R}^{n \times n}$, $i = 1, \dots, k$, such that $P(d) = \sum_{i=1}^k P_i(d)'P_i(d)$.

Let us define the function

$$\text{sq}(d) = (d_1^2, \dots, d_q^2)' \quad (12)$$

and the SOS programs

$$\begin{aligned} \xi^* &= \inf_{\xi, V(d)} \xi \\ \text{s.t.} \quad &\begin{cases} X_i(\text{sq}(d)) \text{ is SOS for all } i = 1, 2 \\ \deg(V(d)) \leq \delta \\ \xi \geq 0, \zeta = 1 \end{cases} \end{aligned} \quad (13)$$

and

$$\begin{aligned} \zeta^* &= \sup_{\zeta, V(d)} \zeta \\ \text{s.t.} \quad &\begin{cases} X_i(\text{sq}(d)) \text{ is SOS for all } i = 1, 2 \\ \deg(V(d)) \leq \delta \\ \xi = 0. \end{cases} \end{aligned} \quad (14)$$

Let us observe that the SOS programs (13)–(14) are SDPs. Indeed, the matrix polynomials $X_i(\text{sq}(d))$ depend affine linearly on the decision variables, and the conditions that such matrix polynomials are SOS can be equivalently expressed through linear matrix inequalities (LMIs) by exploiting the Gram matrix method (also known as square matrix representation), see for instance [14] and references therein.

The following result provides a necessary and sufficient condition for establishing whether (6) holds based on the indexes ξ^* and ζ^* .

Theorem 1: The condition (6) holds if and only if there exists a nonnegative integer δ such that $\xi^* = 0$ (or, equivalently, $\zeta^* = +\infty$).

Proof: First of all, let us observe that $\xi^* = 0$ is equivalent to $\zeta^* = +\infty$. Indeed, suppose $\xi^* = 0$. Let $V^*(d)$ be $V(d)$ evaluated for the found optimal values of the decision variables in the SDP (13). This means that $V^*(d)$ and $-V^*(d)\hat{J}(d) - \hat{J}(d)'V^*(d) - I$ are SOS. Hence, $\zeta V^*(d)$ and $-\zeta V^*(d)\hat{J}(d) - \zeta \hat{J}(d)'V^*(d) - \zeta I$ are SOS for all $\zeta > 0$, and, therefore,

$\zeta^* = +\infty$. Also, suppose $\zeta^* = +\infty$. Let $V^*(d)$ be $V(d)$ evaluated for the found optimal values of the decision variables in the SDP (14). This means that $V^*(d)$ and $-V^*(d)\hat{J}(d) - \hat{J}(d)'V^*(d) - \zeta I$ are SOS for all $\zeta > 0$, in particular for $\zeta = 1$, and, therefore, $\xi^* = 0$.

Sufficiency. Suppose that $\xi^* = 0$ for some δ . Let $V^*(d)$ be $V(d)$ evaluated for the found optimal values of the decision variables in the SDP (13). It follows that $X_i(\text{sq}(d)) \succeq 0$ for all d for all $i = 1, 2$. Hence, $V^*(d) \succeq 0$ and $-V^*(d)\hat{J}(d) - \hat{J}(d)'V^*(d) - I \succeq 0$ for all $d \in \mathbb{R}_+^q$, where \mathbb{R}_+^q is the subset of vectors in \mathbb{R}^q with nonnegative entries. The latter inequality implies that $V^*(d)$ is nonsingular for all $d \in \mathbb{R}_+^q$. Therefore, $x'V^*(d)x$ is a Lyapunov function for the system $\dot{x} = \hat{J}(d)x$ for all $d \in \mathbb{R}_+^q$, and, consequently, $\hat{J}(d)$ is Hurwitz for all $d \in \mathbb{R}_+^q$. This means that BDC is Hurwitz for all diagonal D such that $\lambda_{\min}(D) \geq 1$. From the linearity of BDC on D , it follows that (6) holds.

Necessity. Suppose that (6) holds. From the linearity of BDC on D , this implies that BDC is Hurwitz for all diagonal D such that $\lambda_{\min}(D) \geq 1$, and, hence, that $\hat{J}(d)$ is Hurwitz for all diagonal $d \in \mathbb{R}_+^q$. From this, one has that the Lyapunov equation $\hat{V}(d)\hat{J}(d) + \hat{J}(d)'\hat{V}(d) + I = 0$ has a unique positive definite solution $\hat{V}(d) = \hat{V}(d)' \in \mathbb{R}^{n \times n}$ for all $d \in \mathbb{R}_+^q$. This solution $\hat{V}(d)$ is a matrix rational function that can be obtained by rewriting the Lyapunov equation as $A(d)v(d) + b = 0$ where the vectors $v(d)$ and b contain the independent entries (associated with the upper triangle) of $\hat{V}(d)$ and I , respectively, and $A(d)$ is a square matrix that depends linearly on $\hat{J}(d)$. Let us observe that $A(d)$ is nonsingular for all $d \in \mathbb{R}_+^q$ since the solution of the Lyapunov equation is unique in such cases. Let us define $\tilde{V}(d) = \beta \text{sgn}(\det(A(d_0))) \det(A(d)) \hat{V}(d)$, where β is a positive scalar, d_0 is any chosen vector in \mathbb{R}_+^q and $\text{sgn}(\cdot)$ is the sign function. It follows that $\tilde{V}(d)$ is a positive definite matrix polynomial for all $d \in \mathbb{R}_+^q$. Moreover, β can be chosen to satisfy $-\tilde{V}(d)\hat{J}(d) - \hat{J}(d)'\tilde{V}(d) - I \succ 0$ for all $d \in \mathbb{R}_+^q$. Next, since $\tilde{V}(\text{sq}(d)) \succ 0$ for all d , there exists a nonzero polynomial $s_1(d)$ such that $1 + s_1(\text{sq}(d))$ and $(1 + s_1(\text{sq}(d)))\tilde{V}(\text{sq}(d))$ are SOS, see for instance Section III-B in [14] and references therein. Let $s_2(d)$ be a polynomial to be determined such that $1 + s_2(\text{sq}(d))$ is SOS. Let us define the matrix polynomial $V(d) = (1 + s_1(d))(1 + s_2(d))\tilde{V}(d)$. It follows that $X_1(\text{sq}(d))$ is SOS. Moreover, let δ be the degree of $V(d)$. One has:

$$\begin{aligned} &X_2(\text{sq}(d)) \\ &= -V(\text{sq}(d))\hat{J}(\text{sq}(d)) - \hat{J}(\text{sq}(d))'V(\text{sq}(d)) - I \\ &\quad + \xi I(1 + d'd)^{\delta+1} \\ &= (1 + s_1(\text{sq}(d)))(1 + s_2(\text{sq}(d)))(-\tilde{V}(\text{sq}(d))\hat{J}(\text{sq}(d)) \\ &\quad - \hat{J}(\text{sq}(d))'\tilde{V}(\text{sq}(d))) - I + \xi I(1 + d'd)^{\delta+1} \\ &= (1 + s_2(\text{sq}(d)))X_3(\text{sq}(d)) + (s_1(\text{sq}(d)) + s_2(\text{sq}(d)) \\ &\quad + s_1(\text{sq}(d))s_2(\text{sq}(d)))I + \xi I(1 + d'd)^{\delta+1} \end{aligned}$$

where $X_3(d) = (1 + s_1(d))(-\tilde{V}(d)\hat{J}(d) - \hat{J}(d)'\tilde{V}(d) - I)$. Since $X_3(\text{sq}(d)) \succ 0$ for all d , the polynomial $s_2(d)$ can be chosen such that $1 + s_2(\text{sq}(d))$ and $(1 + s_2(\text{sq}(d)))X_3(\text{sq}(d))$ are SOS, see again Section III-B in [14] and references therein. This implies that $X_2(\text{sq}(d))$ is SOS for all $\xi \geq 0$. ■

Theorem 1 provides a strategy for testing whether (6) holds through convex optimisation, in particular, the SDPs (13)–(14). Let us observe that, although either one of these SDPs can be used to prove (6), the theorem considers both of them for two main reasons. The first reason is to provide a more reliable answer since SDPs are solved with finite precision. Indeed, checking both indexes rather than one only may help in some situations. Also, the SDP (14) is unbounded when it recognises that (6) holds, and several SDP solvers like the one used for the examples in this paper [27] are capable of detecting that the solution is unbounded. The second reason is that the SDP (13) may be useful to establish also whether (6) does not hold. Indeed, by analyzing the null space of the found Gram matrices in this SDP, one may get candidates for instability, as showcased by the examples in the sequel.

The numerical complexity of the SDPs (13)–(14) mainly depends on the number of LMI scalar variables. In this regard, the reader is referred to [16], where formulas for determining the number of LMI scalar variables required to establish if a matrix polynomial is SOS are reported for the general case and for the case of matrix polynomials that are symmetric with respect to all axes, i.e., that depend on the variable $\text{sq}(d)$.

In the following examples, the degree δ used is the smallest nonnegative integer that allows us to conclude whether (6) holds or not.

Example 6: Let us consider a simple system for which stability is trivially guaranteed for all positive D :

$$B = \begin{pmatrix} 0 & 1 \\ -2 & -1 \end{pmatrix}, \quad C = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}.$$

With $\delta = 1$, we find $\xi^* = 4.6 \cdot 10^{-9}$ and $\zeta^* = +\infty$. Hence, from Theorem 1, we conclude that (6) holds. The number of LMI scalar variables in each SDP is 22.

Example 7: Let us take B and C as in Example 3. With $\delta = 0$, we find $\xi^* = 0.606$ and $\zeta^* = -1.743 \cdot 10^{-12}$, which do not allow us to conclude whether (6) holds or not through Theorem 1. Hence, we consider $X_2(\text{sq}(d))$ evaluated for the found optimal values of the decision variables in the SDP (13), and we denote this matrix polynomial as $X_2^*(\text{sq}(d))$. We find that $X_2^*(\text{sq}(d))$ is asymptotically singular along the direction $\bar{d} = (1, 0)'$. Hence, we test the spectrum of BDC for $D = \text{diag}(\bar{d}) + \varepsilon I$, where $\varepsilon = 10^{-3}$ is introduced to avoid considering a singular D . We find that the spectrum is $\{0.001, 0.998\}$, which means that (6) does not hold. The number of LMI scalar variables in each SDP is 4.

Example 8: Let us consider the structure named Chopin4 in [8], associated with the matrices

$$B = \begin{pmatrix} -1 & 0 & 0 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 & -1 & -1 \\ 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & -1 & -1 \end{pmatrix}, \quad C = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

As shown in [8], the system admits a structural polyhedral Lyapunov function; hence it is considered here to “check” the procedure, whose outcome is expected, being the system (globally) structurally stable. With $\delta = 2$, we find that $\xi^* = 3.002 \cdot 10^{-10}$ and $\zeta^* = +\infty$. Hence, from Theorem 1, we conclude that (6) holds. The number of LMI scalar variables

in each SDP is 2969.

Example 9: For the structure named Gershwin4 in [21],

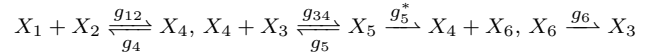
$$B = \begin{pmatrix} -1 & -1 & 1 & 0 & 0 & 0 & 1 & 0 \\ 1 & 0 & -1 & -1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & -1 & -1 & 0 & -1 \\ 0 & 1 & 0 & 0 & 0 & -1 & -1 & -1 \end{pmatrix},$$

$$C = \begin{pmatrix} 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 \end{pmatrix}^\top,$$

With $\delta = 2$, we find $\xi^* = 1.358 \cdot 10^{-5}$ and $\zeta^* = 7.043 \cdot 10^{-10}$, which do not allow us to conclude whether (6) holds or not through Theorem 1. Hence, we consider $X_2(\text{sq}(d))$ evaluated for the found optimal values of the decision variables in the SDP (13), and we denote this matrix polynomial as $X_2^*(\text{sq}(d))$. We find that $X_2^*(\text{sq}(d))$ is asymptotically singular along the direction $\bar{d} = (0.755, 0, 0.657, 0, 0, 0, 0, 0)'$. Hence, we test the spectrum of BDC for $D = \text{diag}(\bar{d}) + \varepsilon I$, where $\varepsilon = 10^{-3}$ is introduced to avoid considering a singular D . We find that the spectrum is $\{-1.414, -0.009, 0.002 \pm j0.006\}$, which means that (6) does not hold. The number of LMI scalar variables in each SDP is 6211.

V. CASE STUDY: A SIGNAL TRANSDUCTION NETWORK

We consider here a biological example of a signal transduction network, for which [2, Section 8.3.8] reports that assessing stability remains an open problem. The biochemical reactions



describe a *two-component signalling pathway* where X_1 is the receptor, X_2 is the ligand, X_4 is the active receptor-ligand complex, X_3 is the active response regulator protein and X_6 is its inactive (dephosphorylated) version, while X_5 is a receptor-ligand-regulator intermediate complex. This type of pathway, identified in several bacterial species, enables a transmembrane receptor protein (X_1) to transmit information across the cell membrane and into the cell, beyond the intracellular membrane surface where it is lodged, by activating via phosphorylation a cytosolic messenger protein (X_3) able to diffuse through the cytosol and convey the information, typically resulting in a change in gene expression [24].

Denoting species concentrations with the corresponding lowercase letter, we can write the corresponding system

$$\begin{aligned} \dot{x}_1 &= -g_{12}(x_1, x_2) + g_4(x_4) = \dot{x}_2 \\ \dot{x}_3 &= -g_{34}(x_3, x_4) + g_5(x_5) + g_6(x_6) \\ \dot{x}_4 &= g_{12}(x_1, x_2) - g_4(x_4) - g_{34}(x_3, x_4) + g_5(x_5) + g_5^*(x_5) \\ \dot{x}_5 &= g_{34}(x_3, x_4) - g_5(x_5) - g_5^*(x_5) \\ \dot{x}_6 &= g_5^*(x_5) - g_6(x_6) \end{aligned}$$

Enforcing the conservation laws $x_1 = k_1 + x_2$, $x_2 = k_2 - x_4 - x_5$ and $x_3 = k_3 - x_5 - x_6$, where k_i ($i = 1, 2, 3$) are positive constants, leads to the reduced order model

$$\begin{aligned} \dot{x}_4 &= g_{12}(k_1 + k_2 - x_4 - x_5, k_2 - x_4 - x_5) - g_4(x_4) \\ &\quad - g_{34}(k_3 - x_5 - x_6, x_4) + g_5(x_5) + g_5^*(x_5) \\ \dot{x}_5 &= g_{34}(k_3 - x_5 - x_6, x_4) - g_5(x_5) - g_5^*(x_5) \\ \dot{x}_6 &= g_5^*(x_5) - g_6(x_6) \end{aligned}$$

whose structure is described by the matrices

$$B = \begin{pmatrix} 1 & 1 & -1 & -1 & -1 & 1 & 1 & 0 \\ 0 & 0 & 0 & 1 & 1 & -1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix},$$

$$C = \begin{pmatrix} -1 & -1 & 1 & 0 & 1 & 0 & 0 & 0 \\ -1 & -1 & 0 & -1 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 1 \end{pmatrix}^\top.$$

For this system, the procedure in [8], as well as its dual [10], does not converge, hence no polyhedral Lyapunov function can be computed. Also, no piecewise-linear-in-rate Lyapunov function can be constructed, even though the system is reported to exhibit a stable behaviour in many simulations [2, Section 8.3.8].

Structural local stability can be proven with the approach in Section III, exploiting the sufficient condition in Proposition 5. Replacing d_k by letters (a, b, \dots), the polynomial $\psi(D)$ in (8) can be written as $\psi = a^2\psi_2^{(a)} + a\psi_1^{(a)} + \psi_0^{(a)}$, where $\psi_1^{(a)}$ has only positive terms, hence it is positive for all $d_i > 0$.

We can also adopt the approach in Section IV. With $\delta = 2$, we find $\xi^* = 1.063 \cdot 10^{-9}$ and $\zeta^* = +\infty$. Hence, from Theorem 1, we conclude that (6) holds. The number of LMI scalar variables in each SDP is 3511.

VI. CONCLUSIONS AND FUTURE WORK

We have tackled the problem of structurally assessing local stability of systems admitting a BDC-decomposition, for all possible values of the positive parameters d_i . On the one hand, we have shown that – under structural non-singularity assumptions, which can be easily checked by means of a vertex algorithm – the problem boils down to checking the strict co-positivity of a SOS polynomial, which is multi-quadratic and even, and we have provided a simple sufficient condition that can be checked by means of computer algebra. On the other hand, we have addressed the problem directly by means of an LMI-based convex optimisation approach aimed at finding quadratic Lyapunov functions depending polynomially on the parameters, which provides a necessary and sufficient condition. The proposed approach has enabled us to certify the structural local stability of non-trivial systems, including the case study of a relevant biological network that represents a bacterial two-component signalling pathway, whose stability analysis was left in previous literature as an open problem.

The proposed convex optimisation algorithms can analyse stability of BDC for any matrix pair (B, C) . An interesting direction for future work is to tailor the approach more specifically to chemical reaction networks, and exploit the fact that the corresponding B and C always have integer entries, which often take values in the set $\{-1, 0, 1\}$.

Another interesting direction is to investigate the possible reduction of the computational burden of the SDPs, which quickly grows with the size of the matrices and with the number of parameters, as shown in the examples by the number of LMI scalar variables. Although the examples presented in this paper can be solved in a reasonable time (from less than one second in Example 6 to less than twenty minutes in Example 9 on a standard personal computer), researchers often need to test examples with much bigger dimensions. Such possible

reduction could be realised by further exploiting the properties of the matrices B and C .

REFERENCES

- [1] U. Alon, *An Introduction to Systems Biology: Design Principles of Biological Circuits*. Chapman & Hall/CRC, 2006.
- [2] M. A. Al-Radhawi, *New Approach to the Stability and Control of Reaction Networks*, Ph.D. thesis, Imperial College London, UK, December 2015.
- [3] M. A. Al-Radhawi and D. Angeli, “Piecewise linear in rates Lyapunov functions for complex reaction networks”, *52nd IEEE Conference on Decision and Control*, pp. 4595–4600, 2013.
- [4] M. A. Al-Radhawi and D. Angeli, “Robust Lyapunov functions for complex reaction networks: An uncertain system framework”, *53rd IEEE Conference on Decision and Control*, pp. 3101–3106, 2014.
- [5] M. A. Al-Radhawi and D. Angeli, “New approach to the stability of chemical reaction networks: Piecewise linear in rates Lyapunov functions”, *IEEE Transactions on Automatic Control*, 61(1):76–89, 2016.
- [6] B. R. Barmish, *New Tools for Robustness of Linear Systems*. Macmillan, 1994.
- [7] F. Blanchini and E. Franco, “Structurally robust biological networks”, *BMC Systems Biology*, 5(1):74, 2011.
- [8] F. Blanchini and G. Giordano, “Piecewise-linear Lyapunov functions for structural stability of biochemical networks”, *Automatica*, 50(10):2482–2493, 2014.
- [9] F. Blanchini and G. Giordano, “Structural stability of biochemical networks: quadratic vs. polyhedral Lyapunov functions”, *8th IFAC Symposium on Robust Control Design (ROCOND’15)*, pp. 277–282, 2015.
- [10] F. Blanchini and G. Giordano, “Polyhedral Lyapunov functions for structural stability of biochemical systems in concentration and reaction coordinates”, *54th IEEE Conference on Decision and Control*, pp. 3110–3115, 2015.
- [11] F. Blanchini and G. Giordano, “Polyhedral Lyapunov functions structurally ensure global asymptotic stability of dynamical networks iff the Jacobian is non-singular”, *Automatica*, 86(12):183–191, 2017.
- [12] F. Blanchini, E. Franco and G. Giordano, “Determining the structural properties of a class of biological models”, *51st IEEE Conference on Decision and Control*, pp. 5505–5510, 2012.
- [13] C. Briat, A. Gupta and M. Khammash, “Antithetic integral feedback ensures robust perfect adaptation in noisy biomolecular networks”, *Cell Systems*, 2(1):15–26, 2016.
- [14] G. Chesi, “LMI techniques for optimization over polynomials in control: a survey”, *IEEE Transactions on Automatic Control*, 55(11):2500–2510, 2010.
- [15] G. Chesi, A. Garulli, A. Tesi and A. Vicino, *Homogeneous Polynomial Forms for Robustness Analysis of Uncertain Systems*. Springer, 2009.
- [16] G. Chesi, “On the complexity of SOS programming and applications in control systems”, *Asian Journal of Control*, 20(5):2005–2013, 2018.
- [17] B. L. Clarke, *Stability of Complex Reaction Networks*. In *Advances in Chemical Physics* (eds I. Prigogine and S. A. Rice), 1980.
- [18] L. Edelstein-Keshet, *Mathematical Models in Biology*. Volume 46 of *Classics in Applied Mathematics*. SIAM, Philadelphia, 2005.
- [19] M. Feinberg, “Chemical reaction network structure and the stability of complex isothermal reactors: I. the deficiency zero and deficiency one theorems”, *Chemical Engineering Science*, 42(10), 2229–2268, 1987.
- [20] J. C. Geromel, M. C. de Oliveira and L. Hsu, “LMI characterization of structural and robust stability”, *Linear Algebra and its Applications*, 285(1):69–80, 1998.
- [21] G. Giordano, *Structural Analysis and Control of Dynamical Networks*, Ph.D. thesis, University of Udine, Italy, March 2016.
- [22] G. Giordano, C. Cuba Samaniego, E. Franco and F. Blanchini, “Computing the structural influence matrix for biological systems”, *Journal of Mathematical Biology*, 72(7):1927–1958, 2016.
- [23] H. Kitano, “Biological robustness”, *Nature Reviews Genetics*, 5(11):826–837, 2004.
- [24] B. P. Ingalls, *Mathematical Modeling in Systems Biology: an Introduction*. MIT Press, 2013.
- [25] M. Pasquini and D. Angeli, “On piecewise quadratic Lyapunov functions for piecewise affine models of gene regulatory networks”, *57th IEEE Conference on Decision and Control*, pp. 1071–1076, 2018.
- [26] G. Shinar and M. Feinberg, “Structural sources of robustness in biochemical reaction networks”, *Science*, 327(5971):1389–1391, 2010.
- [27] J. F. Sturm, “Using SeDuMi 1.02, a MATLAB toolbox for optimization over symmetric cones”, *Optimization Methods and Software*, 11-12:625–653, 1999.