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Structural Stability of Biochemical Networks: Quadratic vs. Polyhedral Lyapunov Functions

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Abstract: Due to the intrinsic uncertainty and variability affecting biochemical reaction networks, it is fundamental to assess their structural stability, *i.e.*, to establish if all the networks having a given structure are stable independent of specific parameter values. For basic motifs in biochemical networks, we show that stability cannot be structurally proved by quadratic Lyapunov functions. However, structural stability of these motifs can be shown resorting to piecewise–linear Lyapunov functions, based on the results by Blanchini and Giordano (2014), who provide a theoretical framework and efficient numerical methods to evaluate structural stability of biochemical reaction networks with monotone reaction rates.

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1. INTRODUCTION

In biochemical networks, parameters are often uncertain, time varying and unpredictably dependent on the environment. Nevertheless, characteristic behaviours have been shown to depend on particular structures, often called *motifs* (Alon (2007)), independent of parameter values. Only a *structural* investigation can explain how and why some biochemical systems keep on performing their specific task in completely different conditions (Alon (2006)). A *structural* property is satisfied by all the systems belonging to a class characterised by a structure, *regardless of parameter values* (Nikolov et al. (2007); Blanchini and Franco (2011)). This concept is deeply related with robustness (Chesi and Hung (2008); El-Samad et al. (2006)), a less demanding requirement: usually a property is *robust* if preserved under *large parameter variations*.

Structural analysis of chemical reaction networks (Horn and Jackson (1972); Horn (1973a,b)) has provided fundamental results: the zero–deficiency theorem and the one–deficiency theorem by Feinberg (1987, 1995a,b), for instance, have inspired a lot of subsequent work (Craciun and Feinberg (2005, 2006); Chaves (2006); Anderson (2008); Hangos (2010)). The zero–deficiency theorem assures that a chemical network admits a single positive stable equilibrium if a structural sufficient condition holds (which can be easily tested based on the network structure); in the proof, the system entropy is adopted as a (logarithmic) Lyapunov function. A fundamental assumption in the zero–deficiency theorem requires the reaction kinetics to be of the mass action type (hence polynomial, although a possible generalization is proposed by Sontag (2001)). Yet there are cases in which this assumption is not satisfied, and still we would like to successfully carry out a structural investigation.

Blanchini and Giordano (2014) investigate structural stability of a wide category of (bio)chemical reaction networks for which only monotonicity of reaction rates is required. The analysis is carried out by absorbing the nonlinear system equations in a linear differential inclusion and then looking for a polyhedral Lyapunov function (actually a norm, including the 1–norm as a special case, see Blanchini and Miani (2008)), based on the network structure only. The existence of a polyhedral Lyapunov function is shown to be equivalent to the stability of a proper discrete difference inclusion, based on which a numerical recursive procedure is devised to test stability and generate the unit ball of the polyhedral norm. The results by Maeda et al. (1978) – who proved the stability of compartmental systems, special monotone systems (Smith (2008)) which can be seen as chemical networks exclusively formed by monomolecular reactions, by adopting the 1–norm as a Lyapunov function – follow as a special case. If a polyhedral (or piecewise–linear) Lyapunov function is derived, network stability is structurally certified: under some general monotonicity assumptions, stability is assured for all reaction rate functions.

Piecewise–linear Lyapunov functions have been adopted for analysing specific chemical reaction networks by Blanchini and Franco (2011). Piecewise linear in rate Lyapunov functions for the analysis of chemical reaction networks have been recently considered by Al-Radhawi and Angeli (2013, 2014, 2015).

In this paper, we consider biochemical networks under general monotonicity assumptions on reaction rate functions – and we wonder if the same structural (parameter–free) stability results can be achieved resorting to different candidate Lyapunov functions, the quadratic ones, which have a successful history for the robustness analysis of uncertain systems (Zhou et al. (1996); Sanchez Pena and Sznaier (1998); Boyd et al. (2004)).

It is well known that, for proving *robust* stability of linear differential inclusions, quadratic Lyapunov functions are conservative, while polyhedral Lyapunov functions are not (Brayton and Tong (1980); Molchanov and Pyatnitskiy (1986, 1989)). Consistently with previous work, we show that *structural* stability of some fundamental motifs, formed by simple chemical reaction networks, cannot be proved by means of quadratic Lyapunov functions. Conversely, polyhedral Lyapunov functions allow us to prove that these motifs are structurally stable. The proposed results substantiate the effectiveness of a polyhedral–Lyapunov–function approach to the *structural* stability analysis of biochemical networks.

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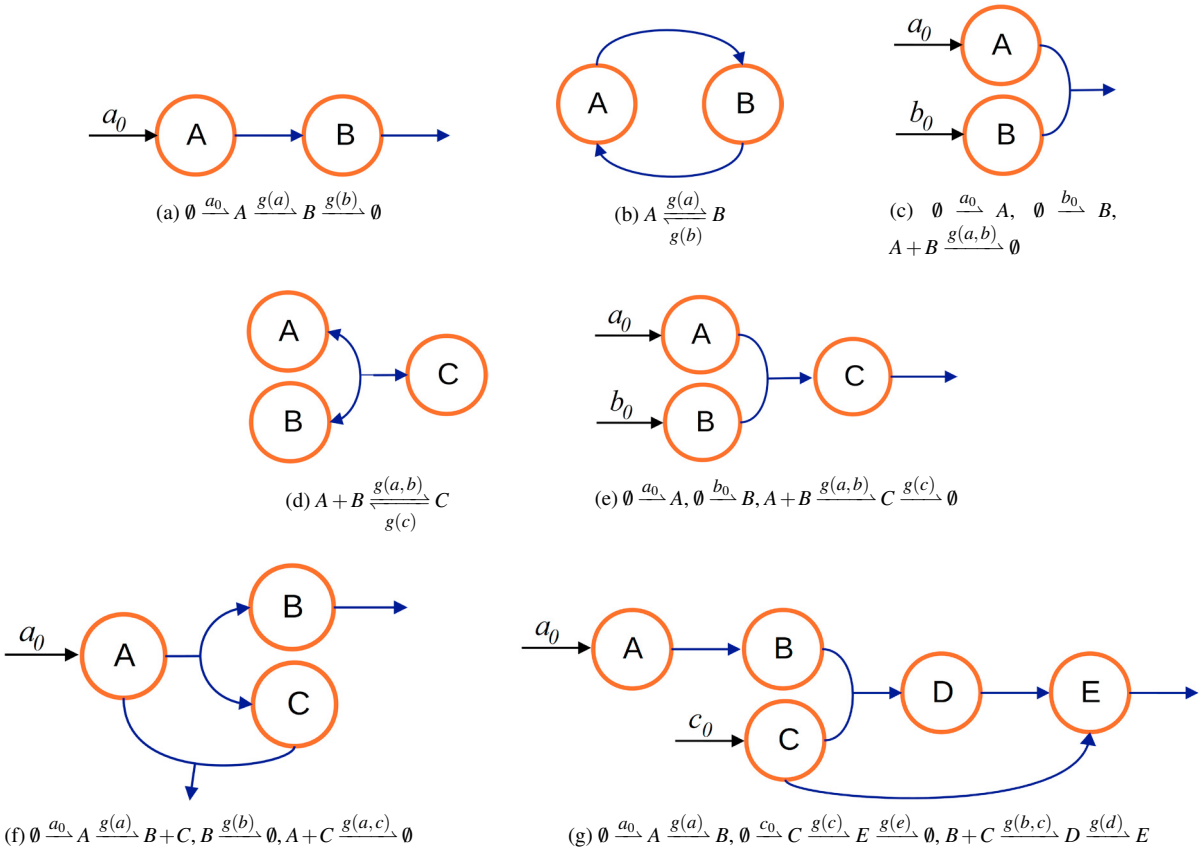


Fig. 1. Graph representation of biochemical reaction motifs and networks.

2. BIOCHEMICAL MODELS AND FRAMEWORK

In this section we summarise some of the results proposed by Blanchini and Giordano (2014).

Consider models in the class

$$\dot{x} = Sg(x) + g_0, \tag{1}$$

where the state $x \in \mathbb{R}^n_+$ represents the concentration of biochemical species (chemical species are denoted by uppercase letter), $g(x) \in \mathbb{R}^m$ is a vector of functions representing the reaction rates and $g_0 \geq 0$ is a vector of constant influxes; $S \in \mathbb{Z}^{n\times m}$ is the stoichiometric matrix of the system, whose entries s_{ij} represent the net amount of the ith species produced or consumed by the jth reaction, excluding the contribution of constant influxes.

For isolated systems ($g_0 = 0$), the solution is forced to stay in the *stoichiometric compatibility class* $\mathscr{C}(x(0))$:

$$x(t) \in \mathscr{C}(x(0)) = \{x(0) + \mathrm{Ra}[S]\} \cap \mathbb{R}^n_+.$$

Assumption 1. All the component functions of vector $g(x)$ are nonnegative and continuously differentiable. All their partial derivatives are positive in the positive orthant.

Assumption 2. Each component function of vector $g(x)$ is zero if and only if at least one of its arguments is zero. Moreover, if $s_{ij} < 0$, then g_j must depend on x_i.

The latter assumption assures that for $x_i = 0$ we have $\dot{x}_i \geq 0$ and is required in order for (1) to be a positive system.

Biochemical networks can be visually represented by graphs, as shown in Fig. 1: nodes are associated with biochemical species, while arcs represent interactions among them.

Assumption 3. Functions $g_j(\cdot)$ in which each argument depends on a single variable x_i are admitted if $s_{ij}\partial g_j/\partial x_i < 0$ for each argument. Functions having as an argument the sum or difference of more variables, such as $g_j(\pm x_i \pm x_k)$, are admitted if they appear in a single equation, $\dot{x}_k = \ldots$, and $s_{kj}\partial g_j/\partial x_k < 0$.

Hence the diagonal entries of the Jacobian of $Sg(x)$ are negative and no autocatalytic reactions are considered.

Example 4. The chemical reaction network shown in Fig. 1 (e) is associated with the ODE system

$$\begin{aligned} \dot{a} &= a_0 - g_{ab}(a,b) \\ \dot{b} &= b_0 - g_{ab}(a,b) \\ \dot{c} &= g_{ab}(a,b) - g_c(c) \end{aligned} \tag{2}$$

corresponding to the general model (1) with $x = [a\ b\ c]^\top$,

$$S = \begin{bmatrix} -1 & 0 \\ -1 & 0 \\ 1 & -1 \end{bmatrix}, \quad g(x) = \begin{bmatrix} g_{ab}(a,b) \\ g_c(c) \end{bmatrix}, \quad g_0 = \begin{bmatrix} a_0 \\ b_0 \\ 0 \end{bmatrix}.$$

For a structural analysis, consider the ε–modified system

$$\dot{x}(t) = -\varepsilon x(t) + Sg(x(t)) + g_0, \tag{3}$$

with $\varepsilon > 0$ arbitrarily small (infinitesimal degradation) and the following definitions.

Definition 5. System (1) is

- *structurally stable* if any equilibrium point $\bar{x}$ of the system with $g_0 = 0$ is Lyapunov stable: there exists a continuous, strictly increasing and unbounded function $\omega : \mathbb{R}_+ \to \mathbb{R}_+$, with $\omega(0) = 0$, such that $\|x(t) - \bar{x}\| \leq \omega(\|x(0) - \bar{x}\|)$;
- *structurally convergent* if it is structurally stable and, for any $\varepsilon > 0$ and $g_0 \geq 0$, the perturbed system (3) has

globally bounded solutions and admits an equilibrium which is globally asymptotically stable in $\mathbb{R}^n_+$.

Since the considered parameters values are sign definite but unknown (hence can be arbitrarily close to zero), a natural degradation of each species, represented by $\varepsilon > 0$ in (3), is in general needed to assess asymptotic stability. The degradation term is necessary for the system to tolerate persistent positive inputs and its introduction does not lead to a "false" stability certificate for systems which are unstable.

To absorb the system in a differential inclusion, assume that an equilibrium $\bar{x} = \bar{x}(\varepsilon)$ exists $\forall \varepsilon > 0$.[1] Denote $z \doteq x - \bar{x}$. Since $0 = S\, g(\bar{x}) - \varepsilon \bar{x} + g_0$, we have

$$\dot{z}(t) = S\,[g(z(t)+\bar{x}) - g(\bar{x})] - \varepsilon z(t). \tag{4}$$

Proposition 6. System (4) can be equivalently written as

$$\dot{z}(t) = BD(z(t))C\, z(t) - \varepsilon z(t), \tag{5}$$

where matrix $B \in \mathbb{Z}^{n\times q}$ is formed by a selection of columns of S, $C \in \mathbb{Z}^{q\times n}$ and $D(z)$ is a diagonal matrix with nonnegative diagonal entries. q is the number of possible partial derivatives with respect to all arguments ($q \geq n$, $q \geq m$).

Example 7. For the reaction network (2) in Example 4, let $\alpha = \partial g_{ab}(a,b)/\partial a$, $\beta = \partial g_{ab}(a,b)/\partial b$ and $\gamma = \partial g_c(c)/\partial c$ be positive parameters. Then $D = \mathrm{diag}(\alpha, \beta, \gamma)$,

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

Denoting by b_i the ith column of B and by $c_i^\top$ the ith row of C, the following results hold.

Theorem 8. Consider the linear differential inclusion

$$\dot{x}(t) = \left[-\varepsilon I + \sum_{i=1}^{q} b_i d_i(t) c_i^\top \right] x(t), \quad x(0) = x_0 \tag{6}$$

where $d_i(t)$ are arbitrary nonnegative scalar piecewise continuous functions. Then:

- stability of (6) for $\varepsilon = 0$ implies structural stability of any equilibrium of (1);
- asymptotic stability of (6) for $\varepsilon > 0$ implies structural convergence of (3).

Corollary 9. If the differential inclusion (6) is asymptotically stable, then (3) admits an equilibrium.

Proposition 10. Stability of (6) for $\varepsilon = 0$ is equivalent to its asymptotic stability for $\varepsilon > 0$.

To analyse stability of the differential inclusion, a proper discrete–time difference inclusion can be considered such that:

- if all the possible discrete transitions starting from the vertices of the diamond (the unit ball of $\|x\|_1$) remain bounded, then the continuous–time solution remains trapped inside the convex hull of the reached points (stable case);
- if the difference inclusion diverges, so does the differential inclusion, since there exist continuous–time solutions arbitrarily close to the discrete–time solutions.

For any state value $x \in \mathbb{R}^n$, the set of all derivatives is included in a cone of directions $\pm b_i$:

$$\dot{x} \in \{v:\ v = \sum_{i=1}^{q} v_i d_i,\ \ d_i \geq 0\},\ \ \text{where}\ \ v_i = b_i c_i^\top x.$$

Hence, if a common convex Lyapunov function exists for all systems

$$\dot{x} = b_i c_i^\top x, \qquad i = 1, \ldots, q, \tag{7}$$

then the same function is a Lyapunov function for the differential inclusion (and the nonlinear system). Reasoning along these lines, the following results can be achieved.

Theorem 11. Robust stability of the differential inclusion

$$\dot{x}(t) = BD(t)Cx(t),\ \ d_i(t) \geq 0 \tag{8}$$

is equivalent to robust stability of the difference inclusion

$$y_{k+1} = \Phi(k) y_k,\ \ \Phi(k) \in \mathscr{F}, \tag{9}$$

where $\mathscr{F}$ is the family of matrices

$$\mathscr{F} = \left\{ \Phi_i \doteq \left[I - \frac{b_i c_i^\top}{c_i^\top b_i} \right],\ \ i = 1, \ldots q \right\}. \tag{10}$$

Corollary 12. (9) is marginally stable and has a weak polyhedral Lyapunov function if and only if (8) is marginally stable and has the same weak Lyapunov function.

Theorem 13. If (9) admits a weak Lyapunov function, then

- (6) is stable for $\varepsilon = 0$;
- (6) is asymptotically stable for $\varepsilon > 0$;
- (1) is structurally convergent.

Corollary 12 and Theorem 13 refer to generic *weak Lyapunov functions*, which may be *polyhedral*, as well as *quadratic*.

2.1 Polyhedral Lyapunov functions

Given a full row rank matrix $X \in \mathbb{R}^{n\times s}$, the function

$$V_X(x) = \inf\{\|w\|_1:\ Xw = x,\ w \in \mathbb{R}^s\}.$$

is a polyhedral norm. The vertices of its unit ball are the columns of matrix X and their opposites. Given a full column rank matrix $F \in \mathbb{R}^{s\times n}$, we have the dual function

$$V^F(x) = \|Fx\|_\infty.$$

In this case, denoting by F_k the kth row of F, the facets of the unit ball are on the planes $F_k x = 1$ or $F_k x = -1$.

$V_X(x)$ ($V^F(x)$) is positive definite; it is a weak Lyapunov function if it is non–increasing along all possible system trajectories.

The efficient algorithm proposed by Blanchini and Giordano (2014) can be used (and will be used in the following sections) to compute the unit ball of the polyhedral Lyapunov function for a biochemical system under our assumptions, thus proving its structural stability (or at least its structural convergence) according to Theorem 13.

2.2 Quadratic Lyapunov functions

The positive definite function

$$V_P(x) = x^\top P x, \qquad P \succ 0,$$

is a weak quadratic Lyapunov function for the system with state matrix A if $A^\top P + PA = -Q$ for a proper $Q \succeq 0$, or equivalently if $A^\top P + PA \preceq 0$.

3. STRUCTURAL STABILITY OF BASIC MOTIFS

We consider the fundamental chemical reaction motifs whose graphs are in Fig. 1 (a)–(e) and we structurally inquire their

[1] If the system passes the computational test proposed by Blanchini and Giordano (2014), such an equilibrium indeed exists.

stability by means of both quadratic and polyhedral Lyapunov functions. We achieve the following main result.

Proposition 14. The chemical reaction networks in Fig. 1(a)–(e) are structurally stable, but they are not structurally *quadratically* stable. Their structural stability can be proved resorting to polyhedral Lyapunov functions.

Proof. Monomolecular reactions chain: Fig. 1 (a). The network is associated with the ODE system

$$\dot{a} = a_0 - g_a(a)$$
$$\dot{b} = g_a(a) - g_b(b)$$

having Jacobian matrix

$$A_m = \begin{bmatrix} -\alpha & 0 \\ \alpha & -\beta \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & 0 \\ 1 & -1 \end{bmatrix}}_{=B} \underbrace{\begin{bmatrix} \alpha & 0 \\ 0 & \beta \end{bmatrix}}_{=D} \underbrace{\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}}_{=C},$$

where $\alpha = \partial g_a(a)/\partial a > 0$ and $\beta = \partial g_b(b)/\partial b > 0$.

The system would be structurally quadratically stable if there existed a symmetric positive definite matrix

$$P = \begin{bmatrix} a & b \\ b & c \end{bmatrix} \succ 0$$

such that

$$A_m^\top P + P A_m = \begin{bmatrix} -2\alpha(a-b) & -\alpha(b-c) - \beta b \\ -\alpha(b-c) - \beta b & -2\beta c \end{bmatrix} \preceq 0$$

for any choice of α and β. Equivalently, we should have that $-2\alpha(a-b) \leq 0$ (which is true for any α, provided that $a \geq b$) and that the determinant is non–negative:

$$\alpha\beta(4ac - 2bc - 2b^2) - \alpha^2(b-c)^2 - \beta^2 b^2 \geq 0.$$

Yet this latter condition is not satisfied if we take either α or β (not both) small enough.
Structural stability of the motif, however, is proved by the existence of polyhedral Lyapunov functions with

$$X = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}, \qquad F = \begin{bmatrix} 1 & 0 & 1 \\ 0 & 1 & 1 \end{bmatrix}^\top.$$

Reversible monomolecular reaction: Fig. 1 (b). The network corresponds to the system

$$\dot{a} = g_b(b) - g_a(a)$$
$$\dot{b} = g_a(a) - g_b(b)$$

and the Jacobian matrix

$$A_{rm} = \begin{bmatrix} -\alpha & \beta \\ \alpha & -\beta \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}}_{=B} \underbrace{\begin{bmatrix} \alpha & 0 \\ 0 & \beta \end{bmatrix}}_{=D} \underbrace{\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}}_{=C},$$

where $\alpha = \partial g_a(a)/\partial a > 0$ and $\beta = \partial g_b(b)/\partial b > 0$.

To prove structural quadratic stability, we should look for

$$P = \begin{bmatrix} a & b \\ b & a \end{bmatrix} \succ 0$$

(note that $P_{11} = P_{22}$ because, since α and β can be swapped, if $P = \begin{bmatrix} k & b \\ b & h \end{bmatrix}$ is a suitable choice then $P = \begin{bmatrix} h & b \\ b & k \end{bmatrix}$ is suitable as well, therefore also $P = \begin{bmatrix} (h+k)/2 & b \\ b & (h+k)/2 \end{bmatrix}$ is suitable, and $a \doteq \frac{h+k}{2}$), such that $A_{rm}^\top P + P A_{rm} =$

$$\begin{bmatrix} -2\alpha(a-b) & \alpha(a-b) + \beta(a-b) \\ \alpha(a-b) + \beta(a-b) & -2\beta(a-b) \end{bmatrix} \preceq 0$$

for any choice of α and β. Although $-2\alpha(a-b) \leq 0$ for $a \geq b$, the condition $-(\alpha-\beta)^2(a-b)^2 \geq 0$ is not structurally satisfied. However, structural stability is proved since the network admits the same polyhedral Lyapunov functions as in case (a).

Bimolecular reaction: Fig. 1 (c). The system

$$\dot{a} = a_0 - g_{ab}(a,b)$$
$$\dot{b} = b_0 - g_{ab}(a,b)$$

has Jacobian matrix

$$A_{bim} = \begin{bmatrix} -\alpha & -\beta \\ -\alpha & -\beta \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & -1 \\ -1 & -1 \end{bmatrix}}_{=B} \underbrace{\begin{bmatrix} \alpha & 0 \\ 0 & \beta \end{bmatrix}}_{=D} \underbrace{\begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}}_{=C},$$

where $\alpha = \partial g_{ab}(a,b)/\partial a > 0$ and $\beta = \partial g_{ab}(a,b)/\partial b > 0$.

Since this system corresponds to that in Fig. 1 (b) after a change of variables (for instance, $\hat{a} = -a$), it cannot admit a structural quadratic Lyapunov function as well.
It instead admits polyhedral Lyapunov functions with the same X as in case (b) and

$$F = \begin{bmatrix} 1 & 0 & -1 \\ 0 & 1 & 1 \end{bmatrix}^\top.$$

Bimolecular reversible reaction: Fig. 1 (d). The system

$$\dot{a} = g_c(c) - g_{ab}(a,b)$$
$$\dot{b} = g_c(c) - g_{ab}(a,b)$$
$$\dot{c} = g_{ab}(a,b) - g_c(c)$$

has Jacobian matrix

$$A_{br} = \begin{bmatrix} -\alpha & -\beta & \gamma \\ -\alpha & -\beta & \gamma \\ \alpha & \beta & -\gamma \end{bmatrix}$$
$$= \underbrace{\begin{bmatrix} -1 & -1 & 1 \\ -1 & -1 & 1 \\ 1 & 1 & -1 \end{bmatrix}}_{=B} \underbrace{\begin{bmatrix} \alpha & 0 & 0 \\ 0 & \beta & 0 \\ 0 & 0 & \gamma \end{bmatrix}}_{=D} \underbrace{\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}}_{=C},$$

where $\alpha = \partial g_{ab}(a,b)/\partial a > 0$, $\beta = \partial g_{ab}(a,b)/\partial b > 0$ and $\gamma = \partial g_c(c)/\partial c > 0$.

After a state space transformation, we rewrite the Jacobian as

$$\hat{A}_{br} = \begin{bmatrix} -\alpha & -(\beta+\gamma) & \gamma \\ -\alpha & -(\beta+\gamma) & \gamma \\ 0 & 0 & 0 \end{bmatrix} = \begin{bmatrix} \hat{A}_{11} & \hat{A}_{12} \\ \mathbf{0} & \mathbf{0} \end{bmatrix}.$$

Then we seek

$$P = \begin{bmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{bmatrix} \succ 0 \tag{11}$$

such that

$$\hat{A}_{br}^\top P + P \hat{A}_{br} = \begin{bmatrix} \hat{A}_{11}^\top P_{11} + P_{11}\hat{A}_{11} & \hat{A}_{11}^\top P_{12} + P_{11}\hat{A}_{12} \\ \hat{A}_{12}^\top P_{21} + P_{21}\hat{A}_{11} & \hat{A}_{12}^\top P_{12} + P_{21}\hat{A}_{12} \end{bmatrix} \preceq 0$$

for any choice of the parameters. Yet this can be true only if $\hat{A}_{11}^\top P_{11} + P_{11}\hat{A}_{11} \preceq 0$ for $P_{11} \succ 0$ and arbitrary α, β, γ, which is clearly impossible in view of the considerations for the case (c). However, the system is structurally stable because it admits the polyhedral Lyapunov function with

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

and the dual with

$$F = \begin{bmatrix} 1 & 0 & 0 & -1 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 0 & 1 & 1 \end{bmatrix}^\top.$$

The unit ball of $V_X(x)$ is shown in Fig. 2 (a).

Bimolecular–monomolecular reaction chain: Fig. 1 (e). The network corresponds to system (2), with Jacobian matrix

$$A_{bm} = \begin{bmatrix} -\alpha & -\beta & 0 \\ -\alpha & -\beta & 0 \\ \alpha & \beta & -\gamma \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & -1 & 0 \\ -1 & -1 & 0 \\ 1 & 1 & -1 \end{bmatrix}}_{=B} \underbrace{\begin{bmatrix} \alpha & 0 & 0 \\ 0 & \beta & 0 \\ 0 & 0 & \gamma \end{bmatrix}}_{=D} \underbrace{\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}}_{=C},$$

where $\alpha = \partial g_{ab}(a,b)/\partial a > 0$, $\beta = \partial g_{ab}(a,b)/\partial b > 0$ and $\gamma = \partial g_c(c)/\partial c > 0$.

After a state space transformation, we rewrite the Jacobian as

$$\hat{A}_{bm} = \begin{bmatrix} -\alpha & -\beta & 0 \\ -\alpha & -\beta & 0 \\ 0 & \gamma & -\gamma \end{bmatrix} = \begin{bmatrix} \hat{A}_{11} & \mathbf{0} \\ \hat{A}_{21} & \hat{A}_{22} \end{bmatrix}.$$

Then we look for a positive definite matrix P of the form (11) such that $\hat{A}_{bm}^\top P + P\hat{A}_{bm} =$

$$\begin{bmatrix} \hat{A}_{11}^\top P_{11} + P_{11}\hat{A}_{11} + \hat{A}_{21}^\top P_{21} + P_{12}\hat{A}_{21} & \hat{A}_{11}^\top P_{12} + \hat{A}_{21}^\top P_{22} + P_{12}\hat{A}_{22} \\ P_{21}\hat{A}_{11} + P_{22}\hat{A}_{21} + \hat{A}_{22}^\top P_{21} & \hat{A}_{22}^\top P_{22} + P_{22}\hat{A}_{22} \end{bmatrix} \preceq 0$$

for any choice of the parameters. This requires the $(1,1)$–block to be structurally negative semidefinite. But, if we choose γ small enough, the dominant term is $\hat{A}_{11}^\top P_{11} + P_{11}\hat{A}_{11}$, which cannot be structurally negative semidefinite due to the previous considerations for the case (c).

Yet the system is structurally stable: it admits the polyhedral Lyapunov function with the same F as before and the dual with

$$X = \begin{bmatrix} 1 & 0 & 0 & 0 & -1 \\ 0 & 1 & 0 & -1 & 0 \\ 0 & 0 & 1 & 1 & 1 \end{bmatrix},$$

whose unit ball is shown in Fig. 2 (b). ■

Remark 15. One could argue that the counterexamples are valid for the differential inclusion, not for the original system. Yet we remind that we are seeking *structural* (parameter–free) results. Consider the linearised original system in (4). Its Jacobian, at the equilibrium $\bar{z} = 0$, has the same form of the state matrix of system (5):

$$J = BDC - \varepsilon I.$$

Therefore, if there is no quadratic Lyapunov function for the differential inclusion, there cannot be a local quadratic Lyapunov function independent of parameter values.

4. EXAMPLES

We consider now more complex chemical reaction networks, which include some of the basic motifs in Fig. 1 (a)–(e). For these networks, according to Proposition 14, there is no hope to prove structural stability based on quadratic Lyapunov functions. However, the existence of a polyhedral Lyapunov function assures their structural stability, independent of parameters.

Example 16. The reaction network whose graph is represented in Fig. 1 (f) corresponds to the system

$$\begin{aligned} \dot{a} &= a_0 - g_a(a) - g_{ac}(a,c) \\ \dot{b} &= g_a(a) - g_b(b) \\ \dot{c} &= g_a(a) - g_{ac}(a,c) \end{aligned}$$

with Jacobian matrix

$$J_3 = \begin{bmatrix} -(\alpha+\delta) & 0 & -\gamma \\ \alpha & -\beta & 0 \\ \alpha-\delta & 0 & -\gamma \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & 0 & -1 & -1 \\ 1 & -1 & 0 & 0 \\ 1 & 0 & -1 & -1 \end{bmatrix}}_{=B} \underbrace{\begin{bmatrix} \alpha & 0 & 0 & 0 \\ 0 & \beta & 0 & 0 \\ 0 & 0 & \gamma & 0 \\ 0 & 0 & 0 & \delta \end{bmatrix}}_{=D} \underbrace{\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{bmatrix}}_{=C},$$

where $\alpha = \partial g_a/\partial a$, $\beta = \partial g_b/\partial b$, $\gamma = \partial g_{ac}/\partial c$ and $\delta = \partial g_{ac}/\partial a$ are positive parameters.

The network includes the motif in Fig. 1 (c), since $A + C \xrightarrow{g(a,c)} \emptyset$, and it is not structurally quadratically stable. Yet it is structurally stable: it admits the polyhedral Lyapunov function with

$$F = \begin{bmatrix} 0 & 1 & 1 & -1 & 1 & 0 \\ 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & -1 & -1 \end{bmatrix}^\top,$$

and the dual with

$$X = \begin{bmatrix} 1 & 0 & 0 & 0 & -1 \\ 0 & 1 & 0 & 1 & 1 \\ 0 & 0 & 1 & 1 & 0 \end{bmatrix},$$

having the unit ball shown in Fig. 2 (c).

Example 17. The reaction network in Fig. 1 (g) has equations

$$\begin{aligned} \dot{a} &= a_0 - g_a(a) \\ \dot{b} &= g_a(a) - g_{bc}(b,c) \\ \dot{c} &= c_0 - g_{bc}(b,c) - g_c(c) \\ \dot{d} &= g_{bc}(b,c) - g_d(d) \\ \dot{e} &= g_d(d) - g_e(e) + g_c(c) \end{aligned}$$

and Jacobian matrix

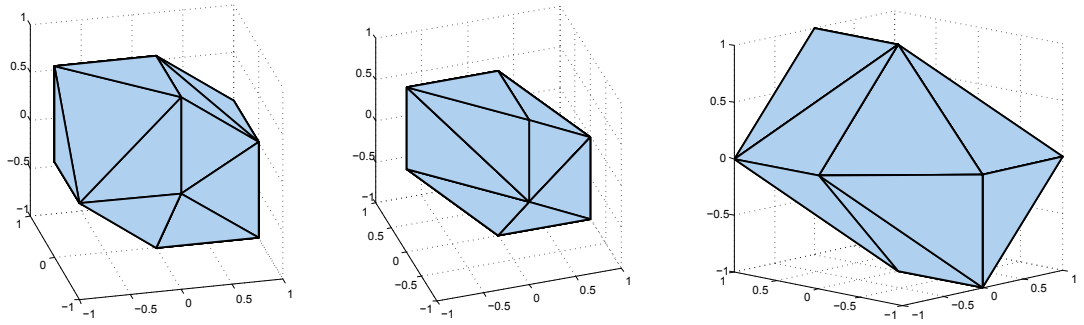
$$J_5 = \begin{bmatrix} -\alpha & 0 & 0 & 0 & 0 \\ \alpha & -\beta & -\gamma & 0 & 0 \\ 0 & -\beta & -(\gamma+\psi) & 0 & 0 \\ 0 & \beta & \gamma & -\delta & 0 \\ 0 & 0 & \psi & \delta & -\varphi \end{bmatrix} = \underbrace{\begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & -1 & 0 & 0 \\ 0 & -1 & -1 & -1 & 0 & 0 \\ 0 & 1 & 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & 0 & 1 & -1 \end{bmatrix}}_{=B} \underbrace{\begin{bmatrix} \alpha & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma & 0 & 0 & 0 \\ 0 & 0 & 0 & \delta & 0 & 0 \\ 0 & 0 & 0 & 0 & \psi & 0 \\ 0 & 0 & 0 & 0 & 0 & \varphi \end{bmatrix}}_{=D} \underbrace{\begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}}_{=C},$$

where $\alpha = \partial g_a/\partial a$, $\beta = \partial g_{bc}/\partial a$, $\gamma = \partial g_{bc}/\partial c$, $\delta = \partial g_d/\partial d$, $\psi = \partial g_c/\partial c$, $\varphi = \partial g_e/\partial e$ are positive parameters.

Since the network includes the motifs in Fig. 1 (a), (c), (e), its structural stability cannot be proved by quadratic Lyapunov functions; however, it admits polyhedral Lyapunov functions (whose unit balls have 22 vertices in the primal case, 68 facets in the dual case) and is thus structurally stable.

5. CONCLUDING DISCUSSION

To compare the effectiveness of polyhedral and quadratic Lyapunov functions for proving structural stability of chemical reaction networks, under the assumption of monotonicity of reaction rates, we have considered a basic set of *motifs*. We have



(a) Motif in Fig. 1 (d). (b) Motif in Fig. 1 (e). (c) Network in Fig. 1 (f).

Fig. 2. Unit ball of the polyhedral Lyapunov functions associated with some of the analysed biochemical networks.

shown that none of them is structurally quadratically stable, although each of them *is* structurally stable, as can be proved resorting to polyhedral Lyapunov functions and applying the algorithm proposed by Blanchini and Giordano (2014).

The networks we have analysed are simple but fundamental, being actual building blocks for huge and complex chemical reaction networks. The outcome of our analysis reveals that, for any network which contains one of these building blocks (practically, any reaction network), stability cannot be *structurally* investigated by means of quadratic Lyapunov functions. We also conjecture that, when considering more general reaction rates than mass action kinetics, the same negative result holds for logarithmic Lyapunov functions, since a logarithmic candidate Lyapunov function can be approximated as a quadratic function in a neighborhood of the equilibrium. Polyhedral Lyapunov functions are still the best theoretic and computational tool for the structural stability analysis of biochemical networks.

REFERENCES

Al-Radhawi, M.A. and Angeli, D. (2013). Piecewise linear in rates Lyapunov functions for complex reaction networks. In *52rd IEEE Conference on Decision and Control, December 10-13, 2013, Florence, Italy*, 4595–4600.

Al-Radhawi, M.A. and Angeli, D. (2014). Robust Lyapunov functions for complex reaction networks: An uncertain system framework. In *53rd IEEE Conference on Decision and Control, December 15-17, 2014. Los Angeles, California, USA*, 3101–3106.

Al-Radhawi, M.A. and Angeli, D. (2015). New approach to the stability of chemical reaction networks: Piecewise linear in rates Lyapunov functions. *IEEE Trans. on Autom. Control, to appear*.

Alon, U. (2007). Network motifs: theory and experimental approaches. *Nature Reviews Genetics*, 8(6), 450–461.

Alon, U. (2006). *An Introduction to Systems Biology: Design Principles of Biological Circuits*. Chapman & Hall/CRC.

Anderson, D. (2008). Global asymptotic stability for a class of nonlinear chemical equations. *SIAM Journal on Applied Mathematics*, 68(5), 1464–1476.

Blanchini, F. and Miani, S. (2008). *Set-theoretic methods in control*, volume 22 of *Systems & Control: Foundations & Applications*. Birkhäuser, Boston.

Blanchini, F. and Franco, E. (2011). Structurally robust biological networks. *BMC Systems Biology*, 5(1), 74.

Blanchini, F. and Giordano, G. (2014). Piecewise–linear Lyapunov functions for structural stability of biochemical networks. *Automatica*, 50(10), 2482–2493.

Boyd, S., El Ghaoui, L., Feron, E., and Balakrishnan, V. (2004). *Linear Matrix Inequalities in System and Control Theory*. SIAM.

Brayton, R. K. and Tong, C. H. (1980). Constructive stability and asymptotic stability of dynamical systems. *IEEE Trans. Circuits and Systems*, 27(11), 1121–1130.

Chaves, M. (2006). Stability of rate-controlled zero-deficiency networks. In *45th IEEE Conference on Decision and Control*, 5766–5771.

Chesi, G. and Hung, Y. (2008). Stability analysis of uncertain genetic sum regulatory networks. *Automatica*, 44(9), 2298–2305.

Craciun, G. and Feinberg, M. (2005). Multiple equilibria in complex chemical reaction networks: I. the injectivity property. *SIAM Journal on Applied Mathematics*, 1526–1546.

Craciun, G. and Feinberg, M. (2006). Multiple equilibria in complex chemical reaction networks: II. the species-reaction graph. *SIAM Journal on Applied Mathematics*, 66(4), 1321–1338.

El-Samad, H., Prajna, S., Papachristodoulou, A., Doyle, J., and Khammash, M. (2006). Advanced methods and algorithms for biological networks analysis. *Proceedings of the IEEE*, 94(4), 832–853.

Feinberg, M. (1987). Chemical reaction network structure and the stability of complex isothermal reactors I. the deficiency zero and deficiency one theorems. *Chemical Engineering Science*, 42, 2229–2268.

Feinberg, M. (1995a). The existence and uniqueness of steady states for a class of chemical reaction networks. *Archive for Rational Mechanics and Analysis*, 132(4), 311–370.

Feinberg, M. (1995b). Multiple steady states for chemical reaction networks of deficiency one. *Archive for Rational Mechanics and Analysis*, 132(4), 371–406.

Hangos, K.M. (2010). Engineering model reduction and entropy-based Lyapunov functions in chemical reaction kinetics. *Entropy*, 12(4), 772–797.

Horn, F. (1973a). On a connexion between stability and graphs in chemical kinetics. I. stability and the reaction diagram. *Royal Society of London Proceedings Series A*, 334, 299–312.

Horn, F. (1973b). On a connexion between stability and graphs in chemical kinetics. II. stability and the complex graph. *Royal Society of London Proceedings Series A*, 334, 313–330.

Horn, F. and Jackson, R. (1972). General mass action kinetics. *Archive for Rational Mechanics and Analysis*, 47(2), 81–116.

Maeda, H., Kodama, S., and Ohta, Y. (1978). Asymptotic behavior of nonlinear compartmental systems: Nonoscillation and stability. *IEEE Transactions on Circuits and Systems*, 25(6), 372–378.

Molchanov, A. P. and Pyatnitskii, E. S. (1986). Lyapunov functions that define necessary and sufficient conditions for absolute stability of nonlinear nonstationary control systems. *Autom. Remote Control*, I: 47(3), 344–354; II: 47(4), 443–451; III: 47(5), 620–630.

Molchanov, A. and Pyatnitskiy, Y. (1989). Criteria of asymptotic stability of differential and difference inclusions encountered in control theory. *Systems & Control Letters*, 13(1), 59 – 64.

Nikolov, S., Yankulova, E., Wolkenhauer, O., and Petrov, V. (2007). Principal difference between stability and structural stability (robustness) as used in systems biology. *Nonlinear Dynamics, Psychology, and Life Sciences*, 11(4), 413–33.

Sanchez Pena, R. and Sznaier, M. (1998). *Robust systems, Theory and Applications*. Wiley, New York.

Smith, H.L. (2008). *Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems*. American Mathematical Society.

Sontag, E.D. (2001). Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-Cell receptor signal transduction. *IEEE Trans. Autom. Control*, 46, 1028–1047.

Zhou, K., Doyle, J., and Glover, K. (1996). *Robust and Optimal Control*. Prentice-Hall, Englewood Cliff, NJ.