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Robust sensitivity analysis for uncertain biochemical networks: some vertex results

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Abstract We consider the problem of computing the sensitivity of uncertain biochemical networks in the presence of input perturbations around a stable steady state. The uncertain system parameters are assumed to take values in a hyperrectangle. Recent literature has shown that, for systems admitting the BDC-decomposition, this analysis can be efficiently carried out by means of vertex algorithms, namely by considering exclusively the vertices of the hyperrectangle in the parameter space. Here we consider a broader class of systems: totally multilinear systems, where any minor of the Jacobian matrix is a multilinear function of the uncertain parameters. For this broader class, we prove that analogous vertex results hold for assessing robust nonsingularity and for providing robust sensitivity bounds. We also discuss vertex-type approaches to robustly assess the assumed stability of the steady state.

Keywords: Biochemical networks, Chemical reaction networks, BDC decomposition, Sensitivity analysis, Influence matrix, Mapping Theorem.

1. INTRODUCTION

In this paper we consider the steady-state sensitivity analysis for a vast class of uncertain nonlinear dynamical systems, including the interesting special case of biochemical reaction networks. It is known that this type of analysis can be approached by considering the linearised system and computing the input-output steady-state characteristic.

For systems with parametric uncertainty the problem can be faced by solid methods coming from robustness analysis; see for instance the book by Barmish (1994). In particular, the problem can be solved through the solution of nonlinear systems with parametric rank-one uncertainties as in the work by Polyak and Nazin (2004); Mohsenizadeh et al. (2014).

This fact has been recently exploited by Giordano et al. (2016) and Blanchini and Giordano (2019) to deal with structural influence analysis; however, this work only considers uncertain Jacobian matrices having a linear structure of the form

$$A = \sum_k \delta_k A_k,$$

where A_k are rank-1 matrices: the Jacobian matrix can be decomposed as $A = BDC$, where D is a diagonal matrix carrying the δ_k on the diagonal, while B and C are constant matrices such that $A_k = B_k C_k^\top$, where B_k denotes the kth column of B and $C_k^\top$ the kth row of C.

Motivated by a significant class of biochemical systems, we show that these results can be extended to the class of matrices that depend polynomially on the uncertain coefficients δ_k and are totally multilinear, namely, the determinant of every submatrix is a multilinear function of the parameters.

We finally point out several properties of the class of multilinear systems. They are amenable for robust stability tests based on the mapping theorem, cf. the book by Barmish (1994). Based on an earlier idea by Garofalo et al. (1993), we propose a vertex type of test (well known for systems with affine uncertainties) to check whether a given positive definite function, either smooth or convex, is a Lyapunov function.

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2. PRELIMINARIES

Consider the class of systems

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

where g is a vector function whose components g_j are monotonic in all variables. The model in Equation (1) is quite general and includes (bio)chemical reaction networks and gene networks, as well as compartmental systems and generic flow systems in engineering. In the case of chemical reaction networks, S is a stoichiometric matrix representing a structure, while g is the reaction rate function.

Definition 1. Function f is called BDC-decomposable if its Jacobian, computed at any point x, has the form

$$\frac{\partial f}{\partial x} = BD(x)C, \tag{2}$$

where B and C are constant matrices and $D(x) = \mathrm{diag}(\delta)$ is a diagonal matrix of strictly positive functions $\delta = [\delta_1 \dots \delta_q]^\top$.

All systems of the form (1) are BDC-decomposable (Blanchini and Giordano 2014, Giordano et al. 2016, Blanchini and Giordano 2019). Matrices B, $D(x)$ and C can be built as follows. B is a selection of (possibly repeated) columns of S, $D(x)$ includes the absolute values of all the nonzero partial derivatives, $\delta_k = |\partial g_h/\partial x_j|$; correspondingly in the kth row of C only one element, say the jth, is nonzero and equal to 1 if δ_k is a derivative with respect to x_j.

We henceforth assume rectangular bounds of the form

$$\delta \in \mathscr{D} = \{d : \delta^- \leq d \leq \delta^+\}, \tag{3}$$

where the inequalities hold componentwise. We also consider the set of vertices of $\mathscr{D}$, which is

$$\hat{\mathscr{D}} = \left\{d : d_k \in \{\delta_k^-, \delta_k^+\}\right\}. \tag{4}$$

Example 1. The chemical reaction network

$$\emptyset \xrightarrow{g_1} X_1, \qquad \emptyset \xrightarrow{g_2} X_2,$$
$$X_1 + X_2 \xrightarrow{g_{12}} X_3, \qquad X_1 + X_3 \xrightarrow{g_{13}} \emptyset, \qquad X_3 \xrightarrow{g_3} \emptyset,$$

where all the reaction rate functions g_k are increasing in all their variables, correspond to the system of equations

$$\begin{aligned} \dot{x}_1 &= g_1 - g_{12}(x_1,x_2) - g_{13}(x_1,x_3) \\ \dot{x}_2 &= g_2 - g_{12}(x_1,x_2) \\ \dot{x}_3 &= g_{12}(x_1,x_2) - g_{13}(x_1,x_3) \end{aligned}$$

Then the Jacobian matrix can be decomposed as

$$J = \begin{bmatrix} -1 & -1 & -1 & -1 & 0 \\ -1 & -1 & 0 & 0 & 0 \\ 1 & 1 & -1 & -1 & -1 \end{bmatrix} \begin{bmatrix} \alpha & 0 & 0 & 0 & 0 \\ 0 & \beta & 0 & 0 & 0 \\ 0 & 0 & \gamma & 0 & 0 \\ 0 & 0 & 0 & \rho & 0 \\ 0 & 0 & 0 & 0 & \varepsilon \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 1 \end{bmatrix},$$

where we have set

$$\alpha := \frac{\partial g_{12}}{\partial x_1},\ \beta := \frac{\partial g_{12}}{\partial x_2},\ \gamma := \frac{\partial g_{13}}{\partial x_1},\ \rho := \frac{\partial g_{13}}{\partial x_3},\ \varepsilon := \frac{\partial g_3}{\partial x_3}.$$

3. STEADY-STATE SENSITIVITY ANALYSIS

Consider the system

$$\dot{x}(t) = f(x(t),u(t)), \ \ y(t) = Hx(t),$$

with state vector $x \in \mathbb{R}^n$, input $u \in \mathbb{R}$ and output $y \in \mathbb{R}$. We assume that the system is at a *stable* steady state, say $\bar{x} \in \mathbb{R}^n$, corresponding to the constant scalar input $\bar{u}$ (i.e., $f(\bar{x},\bar{u}) = 0$).

More in general, the variable u can be an input signal or a parameter. We wish to assess how the steady-state output value $\bar{y} \to \bar{y}+w$ changes due to variations of the input value $\bar{u} \to \bar{u}+v$.

For small perturbations, we can consider the linearisation of the system around the stable equilibrium. Assuming $\frac{\partial f}{\partial u} = E$ this boils down to considering the system

$$\dot{z}(t) = BDCz(t) + Ev(t), \quad w(t) = Hz(t), \tag{5}$$

where $z = x - \bar{x}$. Then the input-output sensitivity is

$$\Sigma(\delta) = \frac{\partial w}{\partial v} = -H(BDC)^{-1}E = \frac{\det \begin{bmatrix} -BDC & -E \\ H & 0 \end{bmatrix}}{\det[-BDC]} \tag{6}$$

Since singularity of BDC would invalidate the expression of Σ, first of all we need to check robust nonsingularity of BDC.

Theorem 1. (Giordano et al. 2016, Blanchini and Giordano 2019.) Matrix BDC is nonsingular for all $\delta \in \mathscr{D}$ if and only if the determinant $\det[-BDC]$ has the same sign (either positive or negative) for all $\delta \in \hat{\mathscr{D}}$, namely on all the vertices of $\mathscr{D}$.

Since the equilibrium needs to be stable, $\det[-\frac{\partial f}{\partial x}] > 0$ must hold. Therefore we work under the following assumption.

Assumption 1. For all $\delta \in \mathscr{D}$, $\det[-BDC] > 0$.

The next result by Blanchini and Giordano (2019) shows that exact bounds can be computed for Σ.

Theorem 2. Under Assumption 1, denote by

$$\Sigma^- = \min_{\delta \in \hat{\mathscr{D}}} \Sigma(\delta), \quad \Sigma^+ = \max_{\delta \in \hat{\mathscr{D}}} \Sigma(\delta)$$

Then the sensitivity can be lower- and upper-bounded as

$$\Sigma^- \leq \Sigma(\delta) \leq \Sigma^+, \quad \forall \delta \in \mathscr{D},$$

and the bounds are tight.

Theorem 2 provides a vertex result along the lines of those by Barmish (1994). In fact, we can compute the maximum and the minimum of $\Sigma(\delta)$ in the whole parameter space $\mathscr{D}$ by considering its minimum and maximum on the vertices of $\mathscr{D}$. These bounds have been shown to hold also for large variations, as long as the bounds (3) are valid for all the derivatives.

Remark 1. Assuming robust nonsingularity of the system Jacobian matrix is necessary. For instance, in the scalar case with $B = [1\ 1]$, and $C = [1\ -1]^\top$ (i.e., $BDC = \delta_1 - \delta_2$), with $E = H = 1$ and with bounds $0.1 \leq \delta_1, \delta_2 \leq 1$, we have $\Sigma(\delta) = (\delta_2 - \delta_1)^{-1}$, which is unbounded and not even defined for $\delta_1 = \delta_2$.

4. MAIN RESULTS

We assume that the linearised system has the form

$$\dot{z}(t) = A(\delta)z(t) + Ev(t), \quad w(t) = Hz(t), \tag{7}$$

where now the Jacobian $A(\delta)$ is a polynomial matrix in δ, whose entries $A_{ij}(\delta)$ are multilinear functions of $\delta_1, \ldots, \delta_q$. We remind that a function is multilinear if it is linear in each variable (note that, in the case of *BDC*-decomposable systems, the Jacobian entries are linear functions of $\delta_1, \ldots, \delta_q$).

Definition 2. Matrix $A(\delta)$ is totally multilinear if its determinant and any minor (i.e., the determinant of any submatrix of $A(\delta)$) are multilinear functions of $\delta_1, \ldots, \delta_q$.

Chemical reaction networks with mass-action kinetics fall within the category of totally multilinear systems.

Example 2. Consider the chemical reaction network in Example 1, where now the reaction rate functions are assumed to follow mass-action kinetics. Hence, we denote as

$$p := g_{12} = k_{12}x_1x_2, \quad q := g_{13} = k_{13}x_1x_3, \quad r := g_3 = k_3x_3,$$

and

$$s := \frac{1}{x_1}, \quad t := \frac{1}{x_2}, \quad w := \frac{1}{x_3},$$

Then, the Jacobian matrix

$$J = \begin{bmatrix} -(p+q)s & -pt & -qw \\ -ps & -pt & 0 \\ (p-q)s & pt & -(q+r)w \end{bmatrix}$$

is totally multilinear.

The results in Theorem 1 and Theorem 2 remain valid also for the class of systems of the form (7), which is larger than the class of BDC-decomposable systems. In fact, we can prove the next theorems, which are entailed by multilinearity.

Theorem 3. (**Robust nonsingularity check.**) Assume that $A(\delta)$ is totally multilinear. Then it is nonsingular for all $\delta \in \mathscr{D}$ if and only if $\det[-A(\delta)]$ has the same sign (either positive or negative) for all $\delta \in \hat{\mathscr{D}}$, namely on all the vertices of $\mathscr{D}$.

Proof: If $A(\delta)$ is totally multilinear, then $\det[-A(\delta)]$ is multilinear. Recall that a multilinear function defined on a hyperrectangle takes its maximum and minimum values on the vertices of the hyperrectangle (see Barmish (1994)). Then, necessity is immediate because, if the function is positive (respectively negative) at all the vertices, it cannot be zero inside the whole hyperrectangle. Sufficiency can be proved by contradiction. Assume that the function takes values of opposite sign on two different vertices: $\det[-A(\delta^{(1)})] > 0$ and $\det[-A(\delta^{(2)})] < 0$, with $\delta^{(1)}, \delta^{(2)} \in \hat{\mathscr{D}}$; then, since the determinant is a continuous function of the matrix entries, there must exist some $\delta^{(3)} \in \mathscr{D}$ such that $\det[-A(\delta^{(3)})] = 0$. ∎

Theorem 4. **(Robust sensitivity bounds.)** Assume that $A(\delta)$ is totally multilinear and that $\det[-A(\delta)] > 0$ for all $\delta \in \mathscr{D}$. The sensitivity

$$\Sigma(\delta) = \frac{\partial w}{\partial v} = -H[A(\delta)]^{-1}E = \frac{\det \begin{bmatrix} -A(\delta) & -E \\ H & 0 \end{bmatrix}}{\det[-A(\delta)]}$$

is lower- and upper-bounded as

$$\Sigma^- \leq \Sigma(\delta) \leq \Sigma^+, \quad \forall \delta \in \mathscr{D},$$

where

$$\Sigma^- = \min_{\delta \in \hat{\mathscr{D}}} \Sigma(\delta), \quad \Sigma^+ = \max_{\delta \in \hat{\mathscr{D}}} \Sigma(\delta),$$

and the bounds are tight.

Proof: We begin by noticing that both the numerator $n(\delta) := \det \begin{bmatrix} -A(\delta) & -E \\ H & 0 \end{bmatrix}$ and the denominator $d(\delta) := \det[-A(\delta)]$ of the sensitivity are multilinear functions of $\delta_1, \dots, \delta_q$, because $A(\delta)$ is totally multilinear. We prove the result for the lower bound (the proof for the upper bound is identical). We have that $n(\delta)/d(\delta) \geq k$ for all $\delta \in \mathscr{D}$ if and only if $\rho(\delta, k) := n(\delta) - kd(\delta) \geq 0$ for all $\delta \in \mathscr{D}$. In view of multilinearity of n and d, $\rho(\delta, k)$ is also multilinear in the variables $\delta_1, \dots, \delta_q$. Therefore, the condition is equivalent to $\rho(\delta, k) \geq 0$ for all $\delta \in \hat{\mathscr{D}}$, which is in turn equivalent to the vertex condition $n(\delta)/d(\delta) \geq k$ for all $\delta \in \hat{\mathscr{D}}$. Then, k must be equal to the smallest value that the function $n(\delta)/d(\delta)$ actually takes on the vertices $\delta \in \hat{\mathscr{D}}$, hence $k = \Sigma^-$, and the bound is tight. ∎

5. SOME REMARKS ABOUT STABILITY ANALYSIS

In our sensitivity analysis, we have assumed stability of the steady state. We now discuss vertex-type approaches to robustly check whether this assumption is actually satisfied.

For systems of the form (7), the well-known mapping theorem holds; see, e.g., the book by Barmish (1994). Then, we can write the characteristic polynomial

$$p(s, \delta) = \det[sI - A(\delta)]$$

and check its stability for a given value δ^*. The zero exclusion theorem ensures that robust stability holds if the value-set

$$\mathscr{V}(j\omega) = \{s = p(j\omega, \delta), \ \ \delta \in \mathscr{D}\}$$

does not include the origin. Drawing this set in the complex plane is hard.

However, the mapping theorem ensures that $\mathscr{V}(j\omega)$ is in the convex hull of the vertex points $p(j\omega, \hat{\delta})$, namely,

$$\mathscr{V}(j\omega) \subset \mathscr{C}(j\omega) = \mathrm{conv}\left\{s = p(j\omega, \hat{\delta}), \ \ \hat{\delta} \in \hat{\mathscr{D}}\right\}. \tag{8}$$

A sufficient criterion for robust stability can therefore be based on the following procedure:

1. check stability for an arbitrary value $\delta^* \in \mathscr{D}$
2. check the exclusion for the convex hull: $0 \notin \mathscr{C}(j\omega)$.

The stability analysis at step 1 can be based on Lyapunov functions and to this aim we propose the following theorem.

Theorem 5. Let $V(z)$ be a positive definite radially unbounded function, which is either smooth or convex. Then it is a Lyapunov function for system (7), in the sense that

$$D^+V(z, \delta) \leq -\beta V(z), \quad \text{for all} \ \ \delta \in \mathscr{D},$$

if and only if

$$D^+V(z, \hat{\delta}) \leq -\beta V(z), \quad \text{for all} \ \ \hat{\delta} \in \hat{\mathscr{D}}.$$

Proof: If $V(z)$ is smooth, the proof is simple, because for any z

$$\psi(z, \delta) := \nabla V(z) A(\delta) z$$

is a multilinear function of $\delta_1, \dots, \delta_q$, hence it takes its maximum value on the vertices of $\hat{\mathscr{D}}$. Therefore, denoting by $\psi^+(z) = \max_{\delta \in \hat{\mathscr{D}}} \psi(z, \delta)$, we have that, if $D^+V(z, \delta) \leq -\beta V(z)$ for all $\delta \in \hat{\mathscr{D}}$, then

$$\begin{aligned} D^+V(z, \delta) &= \nabla V(z) A(\delta) z + \nabla V(z) E v \\ &\leq \psi^+(z) + \nabla V(z) E v \leq -\beta V(z) \ \text{ for all } \ \delta \in \mathscr{D}. \end{aligned}$$

For quadratic functions the result was shown by Garofalo et al. (1993).

For non-smooth but convex functions, including the polyhedral Lyapunov functions considered by Al-Radhawi and Angeli (2016) and Blanchini and Giordano (2014), the proof can be carried out along the same lines, but it is more involved since we need to resort to the subgradient. ∎

REFERENCES

Al-Radhawi, M. A. and Angeli, D. (2016). New approach to the stability of chemical reaction networks: Piecewise linear in rates Lyapunov functions. *IEEE Trans. Autom. Control*, 61(1), 76-89.

Barmish, B. R. (1994). New Tools for Robustness of Linear Systems. Macmillan.

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

Blanchini, F. and Giordano, G. (2019). BDC-decomposition for global influence analysis. *IEEE Control Systems Letters*, 3(2), 260-265.

Garofalo, F., Celentano, G., and Glielmo, L. (1993). Stability Robustness of Interval Matrices Via Lyapunov Quadratic Forms. *IEEE Trans. Autom. Control*, 38(2), 281-284.

Giordano, G., Cuba Samaniego, C., Franco, E., and Blanchini, F. (2016). Computing the structural influence matrix for biological systems. *J. Math. Biol.*, 72(7), 1927-1958.

Mohsenizadeh, D. N., Keel, L. H., and Bhattacharyya, S. P. (2014). An extremal result for unknown interval linear systems. *Proceedings of the 19th IFAC World Congress*, Cape Town, South Africa.

Polyak, B. T., and Nazin, S. A. (2004). Interval solutions for interval algebraic equations. *Mathematics and Computers in Simulation*.