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Piecewise-linear Lyapunov functions for structural stability of biochemical networks☆

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ABSTRACT

We consider the problem of assessing structural stability of biochemical reaction networks with monotone reaction rates, namely of establishing if all the networks with a certain structure are stable regardless of specific parameter values. We investigate stability by absorbing the network equations in a linear differential inclusion and seeking for a polyhedral Lyapunov function proper to the considered network structure. A numerical recursive procedure is devised to test stability. For a wide class of mono- and bimolecular reaction networks, which we name *unitary*, the procedure is shown to be very efficient since, due to the particular structure of the problem, it requires iterations in the space of integer-valued matrices. We also consider a similar, less conservative procedure that allows us to test, even when the Lyapunov function cannot be found, whether the system evolution is structurally bounded. In this case, we absorb the equations in a positive linear differential inclusion. To show the effectiveness of the proposed procedure, we report the outcomes of both a stability and a boundedness test, for many non-trivial biochemical reaction networks, and we analyze well established models in the literature.

1. Introduction

A vast literature agrees on the fact that chemical and biochemical networks suffer from a major trouble: their parameters are widely uncertain, time varying and depending on unpredictable factors due to specific working conditions. On the other hand, it is also recognized that particular behaviors depend on particular structures, regardless of specific parameter values. Structural investigation aims at explaining how and why certain systems perform the proper tasks in completely different conditions (Alon, 2006).

If all the systems of a class characterized by a structure have a certain property regardless of parameter values, such a property is called structural (see for instance Blanchini & Franco, 2011, Franco & Blanchini, 2012, Nikolov, Yankulova, Wolkenhauer, & Petrov, 2007). This concept is deeply related with robustness (Chesi & Hung, 2008; El-Samad, Prajna, Papachristodoulou, Doyle, & Khammash, 2006), with the difference that the latter concept is usually attributed to systems which can work under large parameter variations.

Structural analysis of chemical reaction networks, begun in the early seventies (Horn, 1973a,b; Horn & Jackson, 1972), has provided fundamental results. Among the most celebrated are the zero-deficiency theorem and the one-deficiency theorem (Feinberg, 1987, 1995a,b). The zero-deficiency theorem provides a structural general sufficient condition (0-deficiency) assuring that a chemical network described by mass action kinetics admits a single positive stable equilibrium; 0-deficiency is immediately verifiable from an easy test on the network structure (*i.e.* the reactions) and the proof nicely adopts the system entropy as a Lyapunov function. These results are still attracting a lot of attention (Anderson, 2008; Chaves, 2006; Craciun & Feinberg, 2005, 2006; Hangos, 2010). One 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 in Sontag, 2001). This is a widely accepted assumption; still there are cases in which it is not necessarily satisfied, for instance non-perfectly mixed systems.

In this paper we investigate stability without the mass action kinetics assumption: we only require monotonicity of reaction rates. We make use of polyhedral Lyapunov functions, which have been successfully employed in the robustness analysis of uncertain systems (see Blanchini & Miani, 2008 for a literature

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survey) and have been used to prove the stability of compartmental systems (Maeda, Kodama, & Ohta, 1978). Compartmental systems are special cases of monotone systems (Smith, 2008) and can be thought as monomolecular chemical reactions in which each species can be transformed into another (*e.g.* $A \xrightarrow{g(a)} B$). Under the assumption of increasing reaction rate, stability can be proved by adopting as a Lyapunov function the 1-norm, which is a particular polyhedral (or piecewise-linear) norm.

Recent attempts in using polyhedral norms as candidate Lyapunov functions for biochemical networks have been proposed in Blanchini and Franco (2011), Franco and Blanchini (2012), although applied to quite specific problems.

The main idea of this paper is to investigate structural stability of a wide category of chemical reaction networks by adopting as candidate Lyapunov functions polyhedral norms, including the 1-norm as a special case. The main result is a procedure to generate piecewise-linear Lyapunov functions which may certify the stability of all chemical reaction networks with a certain structure. To have an intuition of how a *structure* looks like, we suggest the reader to give a preliminary look at Fig. 4, where several possible cases are depicted. If a piecewise-linear Lyapunov function is derived, network stability is structural, in the sense that, under some general monotonicity assumptions, it is assured for all reaction rate functions. Consider, for example, the network corresponding to the graph named Brahms5 in Fig. 4. The degradation reaction $A + E \rightharpoonup \emptyset$ introduces a negative feedback from the final product E to A, which could be potentially destabilizing. Yet, by finding a suitable polyhedral Lyapunov function, we can demonstrate that the system is structurally stable, for any choice of the reaction rate functions.

The contributions of the paper can be summarized as follows.

- We consider general chemical networks, both isolated and with external inputs, under general monotonicity assumptions on the involved reaction rate functions, thus without restricting to mass action kinetics reactions.
- Based on the network structure only, we seek a polyhedral Lyapunov function (actually a norm) for the system, by absorbing the nonlinear system in a linear differential inclusion.
- We show that the existence of a polyhedral Lyapunov function is equivalent to the stability of a proper discrete difference inclusion.
- A recursive procedure, based on the discrete difference inclusion, is employed to generate the unit ball of the polyhedral norm. In the case of *unitary* reaction networks, in which the stoichiometric matrix has coefficients in $\{-1, 0, 1\}$, the procedure enormously benefits from the fact that iterations occur in the set of integer-valued matrices.
- The results in Maeda et al. (1978) follow as a special case, since the procedure generates the 1-norm for compartmental systems.
- We show that a similar procedure can be adopted, when structural stability is not satisfied, to prove at least boundedness of the state variables.
- We show that, once a polyhedral Lyapunov function is found, we can investigate local stability of the equilibrium in isolated systems within the stoichiometric compatibility class.
- We investigate structural stability of an extensive set of networks by our method. Surprisingly enough, non-trivial systems can be managed without difficulties, providing either a positive certificate (by finding a piecewise linear function with quite a small number of vertices) or a negative certificate (nonexistence of such a function).

2. Structural stability analysis

2.1. Model description and assumptions

We denote chemical species with uppercase letters and their concentrations with the corresponding lowercase letter. We consider the class of models

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

where the state $x \in \mathbb{R}^n_+$ represents the concentration of biochemical species, $g(x) \in \mathbb{R}^m$ 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.

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.

Decreasing trends can be considered as well: in some cases, this just requires changing sign to g. An important case is that of a species which is present in a total amount $\bar{x}_i > 0$ and can be either active, x_i, or inactive, x_i^*, with $x_i + x_i^* = \bar{x}_i$. Since $0 \leq x_i \leq \bar{x}_i$, the activation term must be the only positive term in the right side of the equation. For instance, the equation

$$\dot{a} = -g_{\text{in}}(a, b) + g_{\text{act}}(\bar{a} - a, c) \tag{2}$$

includes the inhibition term g_{in} and the activation term g_{act}.

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.

Assumption 2, ensuring that for $x_i = 0$ we have $\dot{x}_i \geq 0$, is required to guarantee that (1) is a positive system. For instance, $g_{\text{in}}(a, b)$ in (2) can be of the form $\kappa \frac{ba}{1+a}$, but not $\kappa \frac{b}{1+a}$.

Example 2.1. The chemical reactions (Blanchini & Franco, 2012; Kim & Winfree, 2011)

$$A + B \xrightarrow{g_{ab}(a,b)} A^*, \qquad B^* \xrightarrow{g_b(b^*)} B,$$
$$C + A^* \xrightarrow{g_{ac}(a^*,c)} A + B^*, \qquad \emptyset \xrightarrow{c_0} C$$

involve the genelet species A (and its inactive form A^*), the inhibitor strand B (and its inactive form B^*) and the RNA output C. Along with the mass conservation constraints $\bar{a} = a + a^*$ and $\bar{b} = b + b^* + a^*$, these reactions correspond to the following ODEs for $x = \begin{bmatrix} a & b & c \end{bmatrix}^\top$:

$$\dot{a} = g_{ac}(\bar{a} - a, c) - g_{ab}(a, b)$$
$$\dot{b} = g_b(\bar{b} - \bar{a} + a - b) - g_{ab}(a, b)$$
$$\dot{c} = c_0 - g_{ac}(\bar{a} - a, c).$$

In this case we have

$$S = \begin{bmatrix} 1 & -1 & 0 \\ 0 & -1 & 1 \\ -1 & 0 & 0 \end{bmatrix}, \qquad g(x) = \begin{bmatrix} g_{ac}(\bar{a} - a, c) \\ g_{ab}(a, b) \\ g_b(\bar{b} - \bar{a} + a - b) \end{bmatrix},$$
$$g_0 = \begin{bmatrix} 0 & 0 & c_0 \end{bmatrix}^\top.$$

A (non-exhaustive) list of possible reactions, together with the corresponding reaction terms appearing in the proper equations, is reported next.