GLOBAL INJECTIVITY AND MULTIPLE EQUILIBRIA IN UNI- AND BI-MOLECULAR REACTION NETWORKS

CASIAN PANTEA, HEINZ KÖPPL, AND GHEORGHE CRACIUN

Abstract. Dynamical system models of complex biochemical reaction networks are high-dimensional, nonlinear, and contain many unknown parameters. The capacity for multiple equilibria in such systems plays a key role in important biochemical processes. Examples show that there is a very delicate relationship between the structure of a reaction network and its capacity to give rise to several positive equilibria. In this paper we focus on networks of reactions governed by mass-action kinetics. As is almost always the case in practice, we assume that no reaction involves the collision of three or more molecules at the same place and time, which implies that the associated mass-action differential equations contain only linear and quadratic terms. We describe a general injectivity criterion for quadratic functions of several variables, and relate this criterion to a network's capacity for multiple equilibria. In order to take advantage of this criterion we investigate in detail general conditions that imply non-vanishing of polynomial functions on the positive orthant. In an example we describe how these methods may be used for designing multistable chemical systems in synthetic biology.

1. Introduction

A chemical reaction network is usually given by a finite list of reactions that involve a finite set of chemical species. As an example, consider the reaction network with species $X_1, X_2, \ldots, X_6$ given in (1), which consists of 20 reactions.

$$X_1 + X_2 \rightleftharpoons X_4,\ X_2 + X_3 \rightleftharpoons X_5,\ X_3 \rightleftharpoons 2X_1,\ 2X_3 \rightleftharpoons X_6 \tag{1}$$

$$X_1 \rightleftharpoons 0,\ X_2 \rightleftharpoons 0,\ X_3 \rightleftharpoons 0,\ X_4 \rightleftharpoons 0,\ X_5 \rightleftharpoons 0,\ X_6 \rightleftharpoons 0.$$

To keep track of the temporal variation of the state of this chemical system, we define the functions $x_1(t), x_2(t), \ldots, x_6(t)$ to be the molar concentrations of the species $X_1, X_2, \ldots, X_6$ at time t. The chemical reactions in the network are responsible for changes in the concentrations; for instance, whenever the reaction $X_1 + X_2 \to X_4$ occurs, there is a net gain of a molecule of X_4, whereas one molecule of X_1 and one molecule of X_2 are lost. For each $i \in \{1, \ldots, 6\}$, the reaction $X_i \to 0$ is called an *outflow reaction* and it represents the fact that species X_i is continuously removed from the reactor, whereas $0 \to X_i$, called an *inflow reaction* represents the fact that species X_i is fed to the reactor at a constant rate.

We assume that the rate of change of the concentration of each species is governed by mass-action kinetics [17], i.e., that each reaction takes place at a rate that is proportional to the product of the concentrations of the species being consumed in that reaction. For example, under the mass-action kinetics assumption, the contribution of the reaction $X_1 + X_2 \to X_4$ to the rate of change of x_4 has the form $k_1x_1x_2$, where k_1 is a positive number called *reaction rate constant*. In the same way, this reaction contributes the negative value $-k_1x_1x_2$ to the rates of change of x_1 and x_2. Similarly, if the reaction rate constant of $X_4 \to X_1 + X_2$ is k_2, then this reaction contributes k_2x_4 to the rate of change of x_1 and $-k_2x_4$ to the rate of change of x_4. The outflow reaction $X_1 \to 0$ contributes the term $-k_9x_1$ to the rate of change of x_1, whereas the inflow reaction $0 \to X_1$ contributes the constant quantity k_{10} to the rate of change of X_1. Collecting these contributions from all the reactions, we obtain the system of differential equations (2) for $\boldsymbol{x} = (x_1, \dots, x_6) \in \mathbb{R}^6_{>0}$.

$$
\begin{aligned}
\frac{dx_1}{dt} &= -k_1x_1x_2 + k_2x_4 + 2k_5x_3 - 2k_6x_1^2 - k_9x_1 + k_{10} \\
\frac{dx_2}{dt} &= -k_1x_1x_2 + k_2x_4 - k_3x_2x_3 + k_4x_5 - k_{11}x_2 + k_{12} \\
\frac{dx_3}{dt} &= -k_3x_2x_3 + k_4x_5 - k_5x_3 + k_6x_1^2 - 2k_7x_3^2 + 2k_8x_6 - k_{13}x_3 + k_{14} \\
\frac{dx_4}{dt} &= k_1x_1x_2 - k_2x_4 - k_{15}x_4 + k_{16} \\
\frac{dx_5}{dt} &= k_3x_2x_3 - k_4x_5 - k_{17}x_5 + k_{18} \\
\frac{dx_6}{dt} &= k_7x_3^2 - k_8x_6 - k_{19}x_6 + k_{20}
\end{aligned} \tag{2}
$$

Consider the (vector-valued) rate function $r : \mathbb{R}^6_{>0} \times \mathbb{R}^{20}_{>0} \to \mathbb{R}^6$ given by the right-hand side of the system (2). Then (2) can be written

$$\frac{d\boldsymbol{x}}{dt} = r(\boldsymbol{x}, \boldsymbol{k}) \tag{3}$$

where $\boldsymbol{x} = (x_1, \ldots, x_6)$ is the vector of species concentrations and $\boldsymbol{k} = (k_1, \ldots, k_{20})$ is the vector of parameters (reaction rate constants).

We say that the system (3) admits two different equilibria for some vector of parameters $\boldsymbol{k}$ if there exist two distinct vectors of species concentrations $\boldsymbol{x}$ and $\boldsymbol{x}'$ such that $r(\boldsymbol{x}, \boldsymbol{k}) = r(\boldsymbol{x}', \boldsymbol{k}) = \boldsymbol{0}$. Therefore, if the function $r(\cdot, \boldsymbol{k})$ is injective (i.e., one-to-one) for some parameter vector $\boldsymbol{k}$, then the system (3) cannot admit multiple equilibria for that $\boldsymbol{k}$. This connection between global injectivity and capacity for multiple equilibria has been used before in the context of mass-action systems [5, 6, 7, 25], general chemical kinetics [1, 2, 10, 9], or even general models of interaction networks [3]. In this paper we focus on mass-action systems, so $r(\cdot, \boldsymbol{k})$ is a family of polynomial functions indexed by the parameter vector $\boldsymbol{k}$.

The following theorem regarding global injectivity of families of polynomial (or, more general, power-law) functions was proved in [5] (see also [8] for a formulation which is more similar to the one below). If $\boldsymbol{x} = (x_1, \ldots, x_n) \in \mathbb{R}^n_{>0}$ and $\boldsymbol{y} = (y_1, \ldots, y_n) \in \mathbb{R}^n$ we denote $\boldsymbol{x}^{\boldsymbol{y}} = \prod_{i=1}^n x_i^{y_i}$.

Theorem 1. *Consider a family of maps $p_{\boldsymbol{k}} : \mathbb{R}^n_{>0} \to \mathbb{R}^n$, given by*

$$p_{\boldsymbol{k}}(\boldsymbol{x}) = \sum_{i=1}^{m} k_i \boldsymbol{x}^{\boldsymbol{y}_i} \boldsymbol{z}_i,$$

where $\boldsymbol{k} = (k_1, ..., k_m) \in \mathbb{R}^m_{>0}$, and $\boldsymbol{y}_1, \ldots, \boldsymbol{y}_m, \boldsymbol{z}_1, \ldots, \boldsymbol{z}_m \in \mathbb{R}^n$. The maps $p_{\boldsymbol{k}}$ are injective for all $\boldsymbol{k} \in \mathbb{R}^m_{>0}$ if and only if $\det(\mathrm{Jac}(p_{\boldsymbol{k}}(\boldsymbol{x}))) \neq 0$ for all $\boldsymbol{x} \in \mathbb{R}^n_{>0}$ and all $\boldsymbol{k} \in \mathbb{R}^m_{>0}$, where $\mathrm{Jac}(p_{\boldsymbol{k}}(\boldsymbol{x}))$ is the Jacobian matrix of $p_{\boldsymbol{k}}$ at $\boldsymbol{x}$.

If a mass-action differential equation system associated to a reaction network has injective right-hand side for some values of $\boldsymbol{k}$, then we say that *the reaction network is injective for those values of $\boldsymbol{k}$*.

We may try to use Theorem 1 to analyze the capacity for multiple equilibria for the system (2) and calculate $\det(\mathrm{Jac}(r(\boldsymbol{x}, \boldsymbol{k}))) = \det\left((\partial r(\boldsymbol{x}, \boldsymbol{k})_i / \partial x_j)_{i,j \in \{1,\ldots,n\}}\right)$. Using the software package `BioNetX` [24] we obtain

$$
\begin{aligned}
(4)\qquad \det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k}))) \;=\;& k_5k_9k_{10}k_{17}k_{15}k_{19} + k_4k_8k_9k_{11}k_{13}k_{15} + 4k_6k_8k_{11}k_{13}k_{15}k_{17}\,x_1\\
+\;& k_2k_3k_8k_9k_{11}k_{17}\,x_2 + k_2k_3k_9k_{11}k_{17}k_{19}\,x_2 + k_1k_3k_8k_{11}k_{15}k_{17}\,x_2^2\\
+\;& k_1k_3k_{11}k_{15}k_{17}k_{19}\,x_2^2 + k_3k_8k_9k_{13}k_{15}k_{17}\,x_3 + k_3k_9k_{13}k_{15}k_{17}k_{19}\,x_3\\
+\;& 4k_3k_7k_9k_{15}k_{17}k_{19}\,x_3^2 + 4k_2k_3k_7k_9k_{17}k_{19}\,x_3^2 + 4k_1k_3k_7k_{15}k_{17}k_{19}\,x_2x_3^2\\
+\;& \dots\\
+\;& k_1k_3k_8k_{13}k_{15}k_{17}\,x_2x_3 + k_1k_3k_{13}k_{15}k_{17}k_{19}\,x_2x_3\\
+\;& 4k_1k_4k_7k_{11}k_{15}k_{19}\,x_2x_3 + 4k_1k_7k_{11}k_{15}k_{17}k_{19}\,x_2x_3\\
-\;& k_1k_3k_5k_8k_{15}k_{17}\,x_2x_3 - k_1k_3k_5k_{15}k_{17}k_{19}\,x_2x_3.
\end{aligned}
$$

The expansion (4) of $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k})))$ contains 93 terms, of which 91 are positive terms (only 16 of which are shown in (4)) and two are negative terms (both are shown on the last line of (4)). Exactly four positive terms and both negative terms of this expansion contain the $\boldsymbol{x}$-monomial x_2x_3. These terms are written explicitly on the last three lines of (4). For an analysis of the sparseness of the negative terms, see [19, 20].

Theorem 1 does *not* allow us to draw any conclusion about the capacity for multiple equilibria of the network (1), because the expansion of $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k})))$ above has some negative coefficients (see also Theorem 3.3 in [5]). [1]

Given the expression of $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k})))$ above, we conclude that for some values of the parameter vector $\boldsymbol{k}$ the function $r(\cdot,\boldsymbol{k})$ is injective on $\mathbb{R}^n_{>0}$, while for other values of $\boldsymbol{k}$ the function $r(\cdot,\boldsymbol{k})$ is not injective on $\mathbb{R}^n_{>0}$. Note though that, even if $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k}))) \neq 0$ for some $\boldsymbol{k}$, Theorem 1 does not guarantee that $r(\cdot,\boldsymbol{k})$ is injective for that value of $\boldsymbol{k}$.

Therefore, in this paper we address the following main questions:

Question 1. Given a reaction network, is it true that if $\det(\mathrm{Jac}(r(\cdot,\boldsymbol{k}))) \neq 0$ for some values [2] of $\boldsymbol{k}$, then $r(\cdot,\boldsymbol{k})$ is injective on $\mathbb{R}^n_{>0}$ for those values of $\boldsymbol{k}$?

[1] On the other hand, if we remove one or more reactions from network (1), i.e., set some of the k_i equal to zero, then $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k})))$ may become strictly positive on $\mathbb{R}^6_{>0}$ for all values of the new $\boldsymbol{k}$ and Theorem 1 applies. See [5] for many other examples where Theorem 1 does apply.

[2] by $\det(\mathrm{Jac}(r(\cdot,\boldsymbol{k})))$ we mean the polynomial $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k})))$ regarded as a function of $\boldsymbol{x} \in \mathbb{R}^n_{>0}$.

and

Question 2. Given a reaction network which is *not* injective for all values of the reaction rate vector $\boldsymbol{k} = (k_1, ..., k_m)$, are there any explicit conditions on $k_1, \dots, k_m$ which guarantee that $\det(\mathrm{Jac}(r(\cdot, \boldsymbol{k}))) \neq 0$ on $\mathbb{R}^n_{>0}$?

Note that Question 1 is similar to the Jacobian conjecture over the field of real numbers, which says that if a polynomial function $f : \mathbb{R}^n \to \mathbb{R}^n$ has nonsingular Jacobian everywhere, then f is injective. On the other hand, there is also an important difference, since in Question 1 the domain of the function $r(\cdot, \boldsymbol{k})$ is restricted to $\mathbb{R}^n_{>0}$.

While the real Jacobian conjecture has been shown to be false [26], we will see in Section 2 that a version of the real Jacobian conjecture holds for quadratic polynomial functions. Therefore, for all uni- and bi-molecular reaction networks, whenever we can show that $\det(\mathrm{Jac}(r(\cdot, \boldsymbol{k}))) \neq 0$ for some values of $\boldsymbol{k}$, it will follow that there cannot be any multiple equilibria for those values of $\boldsymbol{k}$.

In general, note that an affirmative answer to Question 1 makes Question 2 very relevant. Question 2 deals with global positivity of polynomials on the positive orthant and is significantly more difficult than Question 1. A large portion of this paper (Section 3) addresses Question 2 using methods from the field of geometric programming [30, 14, 15, 16]. Note also that even for networks for which the answer to Question 1 is negative or unknown, one can still take advantage of an affirmative answer to Question 2, by applying methods based on homotopy invariance of degree [10].

2. Global injectivity for quadratic polynomials

The vast majority of reaction networks encountered in applications contain only uni- and bi-molecular elementary reactions, since the collision of three or more molecules at the same place and time is very rare [29]. The class of uni- and bi-molecular reactions networks is therefore very important.[3] In this section we prove an equivalence between local and global injectivity for quadratic polynomial functions on a convex domain, which will imply that for the class of uni- and bi-molecular reaction networks, the answer to Question 1 is affirmative.

[3] By "uni- and bi-molecular reactions network" we mean a finite set of reactions where, for each reaction, the number of reactant molecules is 2 or less (while the number of product molecules can be any non-negative integer). For example, $2A \to 3B$ and $A + B \to C + 2D$ are such reactions.

Note that Theorem 2 applies for a single polynomial function g, while Theorem 1 only applies for families of functions.

Theorem 2. *Let $g = (g_1, \dots, g_n) : \mathbb{R}^n \to \mathbb{R}^n$ be a polynomial function such that the degree of each g_i is at most two. Then g is injective on some convex open set $\Omega \subset \mathbb{R}^n$ if and only if $\det(\mathrm{Jac}(g(\boldsymbol{x})) \neq 0$ for all $\boldsymbol{x} \in \Omega$.*

Proof. We show that g is not injective on Ω if and only if the determinant of the Jacobian of g vanishes on Ω. Suppose there exist two distinct points $\boldsymbol{x}', \boldsymbol{x}'' \in \Omega$ such that $g(\boldsymbol{x}') = g(\boldsymbol{x}'')$. Let $\boldsymbol{x} = (\boldsymbol{x}' + \boldsymbol{x}'')/2$ and let $\boldsymbol{v} = \boldsymbol{x}'' - \boldsymbol{x}'$. The vector-valued function $G(t) = g(\boldsymbol{x} + t\boldsymbol{v})$ defined for $t \in \mathbb{R}$ has coordinates $G_i(t) = g_i(\boldsymbol{x} + t\boldsymbol{v})$, $i \in \{1, \dots, n\}$, which are polynomials in t of degree at most two. By hypothesis, $g_i(\boldsymbol{x}') = g_i(\boldsymbol{x}'')$ for all $i \in \{1, \dots, n\}$ and it follows that $G_i(-1/2) = G_i(1/2)$ for all $i \in \{1, \dots, n\}$. Since $\deg(G_i) \leq 2$, it follows that the graph of G_i is either an horizontal line or a parabola with symmetry axis $t = 0$. This implies that $dG_i/dt|_{t=0} = 0$ and therefore

$$\mathbf{0} = \left.\frac{dG}{dt}\right|_{t=0} = \mathrm{Jac}(g)\big|_{\boldsymbol{x}}\, \boldsymbol{v}. \tag{5}$$

Since $\boldsymbol{v} \neq 0$ we conclude that $\det(\mathrm{Jac}(g)\big|_{\boldsymbol{x}}) = 0$.

The reverse implication is shown similarly. If $\det(\mathrm{Jac}(g)\big|_{\boldsymbol{x}}) = 0$ for some $\boldsymbol{x} \in \Omega$ then there exists $\boldsymbol{v} \in \mathbb{R}^n$ such that $\mathrm{Jac}(g)\big|_{\boldsymbol{x}}\, \boldsymbol{v} = \mathbf{0}$. Defining $G(t) = g(\boldsymbol{x} + t\boldsymbol{v})$ as above, we see from (5) that for each coordinate G_i, $i = \{1, \dots, n\}$ of G we have $dG_i/dt\ |_{t=0}= 0$. Since each G_i is a polynomial in t of degree at most two, its graph must be symmetric about the vertical line $t = 0$ and we have $G(t) = G(-t)$ for all $t \in \mathbb{R}$. Since Ω is open, we may choose $t > 0$ small enough such that $\boldsymbol{x}' = \boldsymbol{x} - t\boldsymbol{v}$ and $\boldsymbol{x}'' = \boldsymbol{x} + t\boldsymbol{v}$ are also in Ω. We then have $g(\boldsymbol{x}') = g(\boldsymbol{x}'')$ and therefore g is not injective on Ω. ☐

Remark 1. From Theorem 2 it follows by looking at the last three lines of (4) that if

$$\begin{aligned} & k_1k_3k_8k_{13}k_{15}k_{17} + k_1k_3k_{13}k_{15}k_{17}k_{19} + 4k_1k_4k_7k_{11}k_{15}k_{19} + 4k_1k_7k_{11}k_{15}k_{17}k_{19} \\ \geq\ & k_1k_3k_5k_8k_{15}k_{17} + k_1k_3k_5k_{15}k_{17}k_{19} \end{aligned} \tag{6}$$

then the system (2) has an injective right-hand side, so it cannot have multiple equilibria on $\mathbb{R}^6_{>0}$.

In general, given some quadratic rate function $r(\boldsymbol{x}, \boldsymbol{k})$, let us denote

$$f_{\boldsymbol{k}}(\boldsymbol{x}) = \det(\mathrm{Jac}(r(\boldsymbol{x}, \boldsymbol{k}))). \tag{7}$$

We regard $f_{\boldsymbol{k}}(\boldsymbol{x})$ as a polynomial function of $\boldsymbol{x} \in \mathbb{R}^n_{>0}$ and depending on the vector of parameters $\boldsymbol{k} \in \mathbb{R}^m_{>0}$.

According to Theorem 2, whenever we can prove that $f_{\boldsymbol{k}} \neq 0$ on $\mathbb{R}^n_{>0}$ for some $\boldsymbol{k}$, it follows that the dynamical system $d\boldsymbol{x}/dt = r(\boldsymbol{x}, \boldsymbol{k})$ cannot have multiple equilibria for that $\boldsymbol{k}$.

The inequality (6) shows a trivial example where we have been able to show that $f_{\boldsymbol{k}} \neq 0$ on $\mathbb{R}^n_{>0}$, because, if (6) is satisfied, then the negative terms in $f_{\boldsymbol{k}}$ are being dominated by the sum of the positive terms corresponding to *the same* $\boldsymbol{x}$-monomial, x_2x_3.

In the next sections we will see that there are several non-trivial ways for the sum of the positive terms of $f_{\boldsymbol{k}}$ to dominate the negative terms of $f_{\boldsymbol{k}}$. For example, we will see that appropriate linear combinations of the monomials x_2^2, x_3 and $x_2x_3^2$ dominate the monomial x_2x_3 for all $x_2, x_3 > 0$.

In general, we will focus on finding explicit conditions for a positive linear combination of monomials to dominate another monomial on the whole positive orthant.

3. Polynomial inequalities on the positive orthant

Establishing the positivity of a polynomial on the positive orthant is an important problem with numerous applications in engineering, economy or biology [4, 16]. In what follows we focus on polynomials that are positive on the positive orthant and contain a single negative coefficient. More precisely, if n is a positive integer, $\boldsymbol{x} = (x_1, \ldots, x_n)$, $f \in \mathbb{R}[\boldsymbol{x}]$ is a polynomial with positive coefficients and $h(\boldsymbol{x}) = x_1^{\gamma_1} \ldots x_n^{\gamma_n}$, we ask whether $f(\boldsymbol{x}) - h(\boldsymbol{x}) \geq 0$ for all $\boldsymbol{x} \in \mathbb{R}^n_{>0}$.

We will consider the more general case when the exponents of f and h are arbitrary real numbers, and not necessarily positive integers. A *power function* $h : \mathbb{R}^n_{>0} \to \mathbb{R}$ is given by $h(\boldsymbol{x}) = \boldsymbol{x}^{\boldsymbol{\alpha}}$ for some $\boldsymbol{\alpha} = (\alpha_1, \ldots, \alpha_n) \in \mathbb{R}^n$, where we use the notation $\boldsymbol{x}^{\boldsymbol{\alpha}} = \prod_{i=1}^n x_i^{\alpha_i}$. To simplify the exposition, we slightly abuse the terminology and call power functions *monomials*, keeping in mind that the exponents $\boldsymbol{\alpha}$ are allowed to have real (positive, negative, or zero) coordinates instead of the usual non-negative integer coordinates.

A finite nonnegative linear combination of monomials is called a *posynomial* [16, 15]. The precise statement of the problem we consider is the following:

Let $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\gamma} \in \mathbb{R}^n$, *be fixed vectors. For a given* $\boldsymbol{a} = (a_0, \ldots, a_m) \in \mathbb{R}^{m+1}_{\geq 0}$, *check whether*

$$f(\boldsymbol{x}) = \sum_{i=0}^{m} a_i \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} \geq \boldsymbol{x}^{\gamma} \text{ for all } \boldsymbol{x} \in \mathbb{R}^n_{>0}. \tag{8}$$

What can be said about the set $\mathcal{M}$ of nonnegative vectors $\boldsymbol{a} \in \mathbb{R}^{m+1}_{\geq 0}$ for which (8) holds?

While an explicit (closed-form) necessary and sufficient condition for a generic vector $\boldsymbol{a}$ to belong to $\mathcal{M}$ is possible only in special cases (see Proposition 3), the problem of verifying (8) for a given $\boldsymbol{a} \in \mathbb{R}^{m+1}_{\geq 0}$ enjoys nice mathematical properties that make it amenable to numerical approaches.

3.1. **Monomials dominated by posynomials.** In the next subsection we consider inequality (8) and we introduce a couple of simplifying assumptions that can be made without loss of generality.

3.1.1. *Preliminary assumptions.* Inequality (8) holds for some $\boldsymbol{a} \in \mathbb{R}^{m+1}_{\geq 0}$ if and only if $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\gamma}$ satisfy a geometric condition, as stated in the next proposition.

Proposition 1. *Let $\boldsymbol{\alpha}^{(0)}, \boldsymbol{\alpha}^{(1)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\gamma} \in \mathbb{R}^n$ and $a_0, a_1, \ldots, a_m \in \mathbb{R}_{>0}$ such that*

$$f(\boldsymbol{x}) = \sum_{i=0}^{m} a_i \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} \geq \boldsymbol{x}^{\boldsymbol{\gamma}} \tag{9}$$

for all $\boldsymbol{x} \in \mathbb{R}^n_{>0}$. Then $\boldsymbol{\gamma}$ lies in the convex hull of $\boldsymbol{\alpha}^{(0)}, \boldsymbol{\alpha}^{(1)}, \ldots, \boldsymbol{\alpha}^{(m)}$, denoted by $\mathrm{conv}(\boldsymbol{\alpha}^{(0)}, \boldsymbol{\alpha}^{(1)}, \ldots, \boldsymbol{\alpha}^{(m)})$. Conversely, if $\boldsymbol{\gamma} \in \mathrm{conv}(\boldsymbol{\alpha}^{(0)}, \boldsymbol{\alpha}^{(1)}, \ldots, \boldsymbol{\alpha}^{(m)})$ then there exist $a_0, a_1, \ldots, a_m \in \mathbb{R}_{>0}$ such that (9) is satisfied for all $\boldsymbol{x} \in \mathbb{R}^n_{>0}$.

Proof. Suppose $\boldsymbol{\gamma} \notin \mathrm{conv}(\boldsymbol{\alpha}^{(0)}, \boldsymbol{\alpha}^{(1)}, \ldots, \boldsymbol{\alpha}^{(m)})$. We show that there exists $\boldsymbol{x} \in \mathbb{R}^n_{>0}$ for which inequality (9) is false. Let $M > 0$. First we prove that there exists $\boldsymbol{x} \in \mathbb{R}^n_{>0}$ such that for all $j \in \{0, 1, \ldots, m\}$,

$$M \boldsymbol{x}^{\boldsymbol{\alpha}^{(j)}} < \boldsymbol{x}^{\boldsymbol{\gamma}}, \tag{10}$$

or equivalently (taking logarithms and letting $\boldsymbol{X} = \log \boldsymbol{x}$), that there exists $\boldsymbol{X} \in \mathbb{R}^n$ such that

$$\langle \boldsymbol{\alpha}^{(j)} - \boldsymbol{\gamma}, \boldsymbol{X} \rangle < -\log M \tag{11}$$

for all $j \in \{0, 1, \ldots, m\}$.

Since $\boldsymbol{\gamma}$ is not in the convex hull of $\{\boldsymbol{\alpha}^{(0)}, \boldsymbol{\alpha}^{(1)}, \ldots, \boldsymbol{\alpha}^{(m)}\}$, the convex cone $\mathcal{C}$ with vertex at $\boldsymbol{\gamma}$ generated by the vectors $\boldsymbol{\alpha}^{(0)} - \boldsymbol{\gamma}, \ldots, \boldsymbol{\alpha}^{(m)} - \boldsymbol{\gamma}$ is not equal to $\mathbb{R}^n$. Then the normal cone $\mathcal{N}$ of $\mathcal{C}$ at $\boldsymbol{\gamma}$ is not equal to $\mathbf{0}$, and therefore there exists $\bar{\boldsymbol{X}}$ such that

$$\langle \boldsymbol{\alpha}^{(j)} - \boldsymbol{\gamma}, \bar{\boldsymbol{X}} \rangle < -\epsilon$$

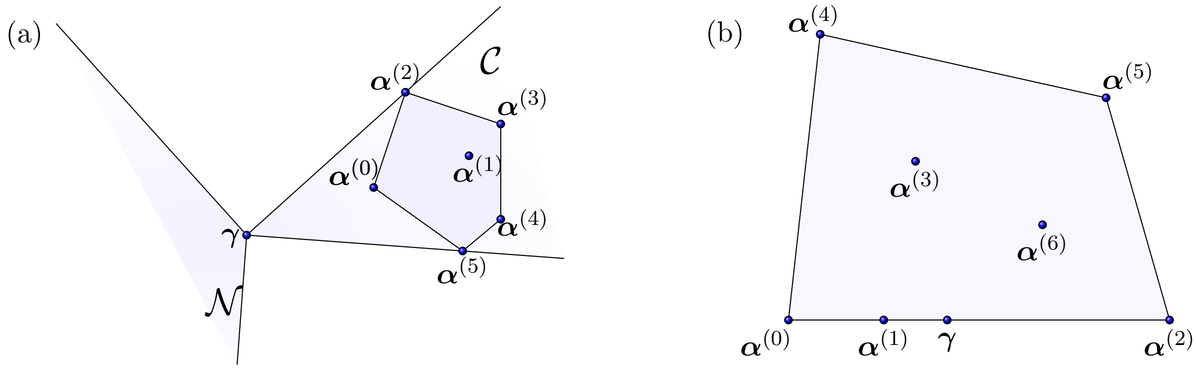

FIGURE 1. (a) Illustration of the proof of Proposition 1; (b) An example configuration for Lemma 2.

for some $\epsilon > 0$ and for all $j \in \{0, \ldots, m\}$ (see Figure 1(a)). If we choose $\boldsymbol{X}$ to be equal to $\bar{\boldsymbol{X}}$ multiplied by a sufficiently large constant, inequality (11) is true.

Finally, setting $M = m \cdot \max\{a_0, \ldots, a_m\}$ and summing (10) over all j one obtains the contradiction

$$\sum_{i=0}^{m} a_i \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} < \boldsymbol{x}^{\boldsymbol{\gamma}}.$$

For the converse we use the weighted arithmetic and geometric means inequality (see [27]): if $\sum_{i=1}^{m} \lambda_i = 1$ for some nonnegative numbers λ_i, then

$$\sum_{i=1}^{m} \lambda_i y_i \geq \prod_{i=1}^{m} y_i^{\lambda_i}$$

for all $y_1, \ldots, y_m > 0$.

We let $\lambda_1, \ldots, \lambda_m$ be nonnegative numbers such that $\sum_{i=1}^{m} \lambda_i = 1$ and $\boldsymbol{\gamma} = \sum_{i=1}^{m} \lambda_i \boldsymbol{\alpha}^{(i)}$. We permute the indices such that for some $k \leq m$ we have $\lambda_1, \ldots, \lambda_k > 0$ and $\lambda_{k+1} = 0, \ldots, \lambda_m = 0$. Then we have

$$\sum_{i=0}^{m} \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} \geq \sum_{i=0}^{k} \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} = \sum_{i=0}^{k} \lambda_i \left(\frac{1}{\lambda_i} \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} \right) \geq \prod_{i=1}^{k} \left(\frac{1}{\lambda_i} \right)^{\lambda_i} \boldsymbol{x}^{\sum_{i=0}^{k} \lambda_i \boldsymbol{\alpha}^{(i)}} = \prod_{i=1}^{k} \left(\frac{1}{\lambda_i} \right)^{\lambda_i} \boldsymbol{x}^{\boldsymbol{\gamma}}$$

and therefore inequality (9) is satisfied for $a_1 = \ldots = a_m = \prod_{i=1}^{k} \lambda_i^{\lambda_i}$. □

Motivated by Proposition 1 we focus on exponents $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}$ and $\boldsymbol{\gamma}$ such that $\boldsymbol{\gamma} \in \operatorname{conv}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$ and we consider the set of nonnegative linear combinations of $\boldsymbol{x}^{\boldsymbol{\alpha}^{(0)}}, \ldots, \boldsymbol{x}^{\boldsymbol{\alpha}^{(m)}}$ that dominate $\boldsymbol{x}^{\boldsymbol{\gamma}}$ on $\mathbb{R}^n_{>0}$.

Definition 1. *Let* $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)} \in \mathbb{R}^n$ *and* $\boldsymbol{\lambda} \in \mathbb{R}^{m+1}_{\geq 0}$ *such that* $\sum_{j=0}^m \lambda_j = 1$*, and denote* $\boldsymbol{\gamma} = \sum_{j=0}^m \lambda_j \boldsymbol{\alpha}^{(j)}$*. Then*

$$\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$$

is defined as the set of vectors $\boldsymbol{a} = (a_0, a_1, \ldots, a_m) \in \mathbb{R}^{m+1}_{\geq 0}$ *such that*

$$\sum_{i=0}^m a_i \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} \geq \boldsymbol{x}^{\boldsymbol{\gamma}} \text{ for all } \boldsymbol{x} \in \mathbb{R}^n_{>0}. \tag{12}$$

Note that, by letting $\ln \boldsymbol{x} = \boldsymbol{X}$, $\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$ is also defined as the set of $\boldsymbol{a} = (a_0, \ldots, a_m)$ such that

$$\sum_{i=0}^m a_i e^{\langle \boldsymbol{\alpha}^{(i)}, \boldsymbol{X} \rangle} \geq e^{\langle \boldsymbol{\gamma}, \boldsymbol{X} \rangle} \text{ for all } \boldsymbol{X} \in \mathbb{R}^n, \tag{13}$$

where $\langle \cdot, \cdot \rangle$ represents the usual dot product on $\mathbb{R}^n$.

A couple of simplifying assumptions on $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\gamma}$ can be made as consequences of the following lemmas. In what follows, if $\mathcal{V}$ is a set of vectors, then $\operatorname{affspan}(\mathcal{V})$ will denote the affine span of $\mathcal{V}$.

Lemma 1. *If* $L : \operatorname{affspan}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda}) \to \mathbb{R}^{n'}$ *is an affine transformation then*

$$\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda}) \subseteq \mathcal{M}(L(\boldsymbol{\alpha}^{(0)}), \ldots, L(\boldsymbol{\alpha}^{(m)}), \boldsymbol{\lambda}).$$

If L *is one-to-one, then the inclusion becomes equality.*

Proof. Let $L = L' + \boldsymbol{\sigma}$ where L' is some linear transformation and $\boldsymbol{\sigma} \in \mathbb{R}^{n'}$, let $\boldsymbol{a} = (a_1, \ldots, a_m) \in \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$ and let $\boldsymbol{X} \in \mathbb{R}^{n'}$ be chosen arbitrarily. If we denote $\boldsymbol{\gamma} = \sum_{i=0}^m \lambda_i \boldsymbol{\alpha}^{(i)}$ then (13) yields

$$\sum_{i=0}^m a_i e^{\langle \boldsymbol{\alpha}^{(i)}, L'^t(\boldsymbol{X}) \rangle} \geq e^{\langle \boldsymbol{\gamma}, L'^t(\boldsymbol{X}) \rangle}$$

or equivalently

$$\sum_{i=0}^m a_i e^{\langle L'(\boldsymbol{\alpha}^{(i)}), \boldsymbol{X} \rangle} \geq e^{\langle L'(\boldsymbol{\gamma}), \boldsymbol{X} \rangle},$$

which implies

$$e^{\langle \boldsymbol{\sigma}, \boldsymbol{X}\rangle} \sum_{i=0}^{m} a_i e^{\langle L'(\boldsymbol{\alpha}^{(i)}), \boldsymbol{X}\rangle} \geq e^{\langle \boldsymbol{\sigma}, \boldsymbol{X}\rangle} e^{\langle L'(\boldsymbol{\gamma}), \boldsymbol{X}\rangle},$$

or equivalently

$$\sum_{i=0}^{m} a_i e^{\langle L(\boldsymbol{\alpha}^{(i)}), \boldsymbol{X}\rangle} \geq e^{\langle L(\boldsymbol{\gamma}), \boldsymbol{X}\rangle}.$$

Since $L(\boldsymbol{\gamma}) = \sum_{i=0}^{m} \lambda_i (L(\boldsymbol{\alpha}^{(i)}))$, we conclude that $\boldsymbol{a} \in \mathcal{M}(L(\boldsymbol{\alpha}^{(0)}), \ldots, L(\boldsymbol{\alpha}^{(m)}), \boldsymbol{\lambda})$. □

Lemma 2. *Suppose* $\boldsymbol{\gamma} = \sum_{i=0}^{m} \lambda_i \boldsymbol{\alpha}^{(i)}$ *lies on the boundary of* $\operatorname{conv}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$ *and suppose, without loss of generality, that for some* $k < m$, $\operatorname{conv}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)})$ *is the smallest face of the convex polytope* $\operatorname{conv}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$ *that contains* $\boldsymbol{\gamma}$*, and that* $\boldsymbol{\alpha}^{(k+1)}, \ldots, \boldsymbol{\alpha}^{(m)}$ *do not belong to this face. Then*

$$\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda}) = \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)}, \tilde{\boldsymbol{\lambda}}) \times \mathbb{R}_{\geq 0}^{m-k},$$

where $\tilde{\boldsymbol{\lambda}} = (\lambda_1, \ldots, \lambda_k)$.

Proof. Figure 1(b) depicts a set of exponents $\boldsymbol{\alpha}^{(i)}$ as in the hypothesis of Lemma 1. The inclusion

$$\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda}) \supseteq \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)}, \tilde{\boldsymbol{\lambda}}) \times \mathbb{R}_{\geq 0}^{m-k}$$

is clear. For the reverse inclusion, let $\boldsymbol{a} = (a_1, \ldots, a_m) \in \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$ and let $\boldsymbol{X} \in \mathbb{R}^n$ be chosen arbitrarily. The hypothesis implies that there is a supporting hyperplane H of $\operatorname{conv}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$ that contains $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)}, \boldsymbol{\gamma}$, and $\boldsymbol{\alpha}^{(k+1)}, \ldots, \boldsymbol{\alpha}^{(m)}$ lie on the same side of H. If H has normal vector $\boldsymbol{n}$ then we have

$$\langle \boldsymbol{\alpha}^{(i)} - \boldsymbol{\gamma}, \boldsymbol{n}\rangle = 0 \text{ for } i \in \{0, \ldots, k\} \tag{14}$$

$$\langle \boldsymbol{\alpha}^{(i)} - \boldsymbol{\gamma}, \boldsymbol{n}\rangle < 0 \text{ for } i \in \{k+1, \ldots, m\}. \tag{15}$$

Using (13), for any $t > 0$ we have

$$\sum_{i=0}^{m} a_i e^{\langle \boldsymbol{\alpha}^{(i)} - \boldsymbol{\gamma}, \boldsymbol{X} + t\boldsymbol{n}\rangle} \geq 1,$$

or, taking into account (14),

$$\sum_{i=0}^{k} a_i e^{\langle \boldsymbol{\alpha}^{(i)} - \boldsymbol{\gamma}, \boldsymbol{X}\rangle} + \sum_{i=k+1}^{m} a_i e^{\langle \boldsymbol{\alpha}^{(i)} - \boldsymbol{\gamma}, \boldsymbol{X}\rangle} e^{t\langle \boldsymbol{\alpha}^{(i)} - \boldsymbol{\gamma}, \boldsymbol{n}\rangle} \geq 1.$$

Using (15) and making $t \to \infty$ we obtain $\sum_{i=0}^{k} a_i e^{\langle \boldsymbol{\alpha}^{(i)} - \boldsymbol{\gamma}, \boldsymbol{X} \rangle} \geq 1$, or $\sum_{i=0}^{k} a_i e^{\langle \boldsymbol{\alpha}^{(i)}, \boldsymbol{X} \rangle} \geq e^{\langle \boldsymbol{\gamma}, \boldsymbol{X} \rangle}$. Since $\boldsymbol{X}$ was chosen arbitrarily, we have $(a_0, \ldots, a_k) \in \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)}, \tilde{\boldsymbol{\lambda}})$, as desired. □

Remark 2. In the inequality (12) that defines the set $\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$, the dimension of $\boldsymbol{x}$ is n. Lemma 1 implies that, in fact, $\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$ can be defined by a similar inequality where the dimension of $\boldsymbol{x}$ is equal to the dimension of affspan$(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$. Therefore, without loss of generality we can assume that the dimension of affspan$(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$ equals the dimension n of $\boldsymbol{x}$.

For example, since $(2,2) = 0(0,-2) + (1/2)(3/2,1) + (1/2)(5/2,3)$, the set $\mathcal{M}((0,-2),(3/2,1),(5/2,3),(0,1/2,1/2))$ consists of vectors $\boldsymbol{a} = (a_0, a_1, a_2)$ such that

$$a_0 y^{-2} + a_1 x^{3/2} y + a_2 x^{5/2} y^3 \geq x^2 y^2 \text{ for all } (x,y) \in \mathbb{R}^2_{>0},$$

or equivalently

$$a_0 x^{-1} y^{-2} + a_1 x^{1/2} y + a_2 x^{3/2} y^3 \geq x y^2 \text{ for all } (x,y) \in \mathbb{R}^2_{>0}.$$

Making $t = x^{1/2} y$, the inequality above is equivalent to

$$a_0 t^{-2} + a_1 t + a_2 t^3 \geq t^{0\cdot(-2)+(1/2)\cdot 1+(1/2)\cdot 3} = t^2 \text{ for all } t \in \mathbb{R}^2_{>0},$$

and therefore $\mathcal{M}((-1,2),(1/2,1),(3/2,3),(0,1/2,1/2)) = \mathcal{M}(-2,1,3,(0,1/2,1/2))$. Note that $\dim(\text{affspan}\{(0,-2),(3/2,1),(5/2,3)\}) = 1$.

Remark 3. Lemma 2 states that the monomials whose exponents $\boldsymbol{\alpha}^{(i)}$ do not lie on the face of conv$(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$ that contains γ do not play any useful role in satisfying inequality (8), i.e. if we remove them from the left-hand side of (8) , the inequality is still true. We can take advantage of this fact and assume that no such monomial exists, or in other words, that γ is contained in the interior of conv$(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$.

In the light of these remarks, for the remainder of this section we will consider the inequality (8) (or the set $\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$) for exponents that satisfy the following constraints:

(16) *(i) the affine span of* $\{\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}\}$ *is full dimensional,*

(ii) γ *is contained in the interior of* conv$(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)})$.

3.1.2. *Geometric programming approach.* With the notation introduced so far, recall that $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)} \in \mathbb{R}^n$, $\boldsymbol{\lambda} \in \mathbb{R}^{m+1}_{\geq 0}$ such that $\sum_{i=0}^m \lambda_i = 1$, and $\boldsymbol{\gamma} = \sum_{i=0}^m \lambda_i \boldsymbol{\alpha}^{(i)}$. Denoting $\overline{\boldsymbol{\alpha}}^{(0)} = \boldsymbol{\alpha}^{(0)} - \boldsymbol{\gamma}, \ldots, \overline{\boldsymbol{\alpha}}^{(m)} = \boldsymbol{\alpha}^{(m)} - \boldsymbol{\gamma}$, inequality (8) can be written equivalently

$$\overline{f}(\boldsymbol{x}) = f(\boldsymbol{x})\boldsymbol{x}^{-\gamma} = \sum_{i=0}^m a_i \boldsymbol{x}^{\overline{\boldsymbol{\alpha}}^{(i)}} \geq 1 \text{ for all } \boldsymbol{x} \in \mathbb{R}^n_{>0}, \tag{17}$$

and it follows that $\boldsymbol{a} = (a_1, \ldots, a_m) \in \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$ if and only if

$$\inf_{\boldsymbol{x} \in \mathbb{R}^n_{>0}} \sum_{i=0}^m a_i \boldsymbol{x}^{\overline{\boldsymbol{\alpha}}^{(i)}} \geq 1 \tag{18}$$

Finding the infimum of a posynomial on the positive orthant is a special case of a class of optimization problems called *geometric programs* ([30, 14, 15, 16]). Classical (and more general) results in geometric programming imply that the geometric program (18) has a unique positive solution. For completeness, we provide a short proof of this fact in Theorem 3 below. Recall that we have made simplifying assumptions on the posynomial $\overline{f}$, which we restate in Theorem 3.

Theorem 3. *If a posynomial* $\overline{f}(\boldsymbol{x}) = \sum_{i=0}^m a_i \boldsymbol{x}^{\overline{\boldsymbol{\alpha}}^{(i)}}$ *with* $a_i > 0$ *for all* $i \in \{0, \ldots, m\}$ *is such that*

(i) the span of $\{\overline{\boldsymbol{\alpha}}^{(0)}, \ldots, \overline{\boldsymbol{\alpha}}^{(m)}\}$ *is full dimensional,*

(ii) the origin is contained in the interior of $\operatorname{conv}(\overline{\boldsymbol{\alpha}}^{(0)}, \ldots, \overline{\boldsymbol{\alpha}}^{(m)})$;

then $\inf_{\boldsymbol{x} \in \mathbb{R}^n_{>0}} \overline{f}(\boldsymbol{x})$ *is attained for a unique* $\boldsymbol{x}$ *in the positive orthant.*

Proof. Let $[0, \infty]$ be the standard compactification of the positive real line. We may extend $\overline{f}$ continuously to a function $F : [0, \infty]^n \to [0, \infty]$. Indeed, let $\boldsymbol{y} = (y_1, \ldots, y_n) \in \partial[0, \infty]^n$. Since $\boldsymbol{0} \in \operatorname{conv}(\overline{\boldsymbol{\alpha}}^{(0)}, \ldots, \overline{\boldsymbol{\alpha}}^{(m)})$, there exists $\boldsymbol{\epsilon} = (\epsilon_1, \ldots, \epsilon_n)$ in the interior of $\operatorname{conv}(\overline{\boldsymbol{\alpha}}^{(0)}, \ldots, \overline{\boldsymbol{\alpha}}^{(m)})$ such that $\epsilon_i > 0$ if $y_i = \infty$ and $\epsilon_i < 0$ if $y_i = 0$. Let $(\delta_0, \ldots, \delta_m) \in \mathbb{R}^{m+1}_{>0}$ such that $\sum_{i=0}^m \delta_i = 1$ and $\boldsymbol{\epsilon} = \sum_{i=0}^m \delta_i \overline{\boldsymbol{\alpha}}^{(i)}$. The weighted arithmetic and geometric means inequality [27] yields

$$\overline{f}(\boldsymbol{x}) = \sum_{i=0}^m a_i \boldsymbol{x}^{\overline{\boldsymbol{\alpha}}^{(i)}} = \sum_{i=0}^m \delta_i \left(\frac{a_i}{\delta_i} \boldsymbol{x}^{\overline{\boldsymbol{\alpha}}^{(i)}} \right) \geq \prod_{i=1}^m \left(\frac{a_i}{\delta_i} \right)^{\delta_i} \boldsymbol{x}^{\sum_{i=0}^m \delta_i \overline{\boldsymbol{\alpha}}^{(i)}} = \prod_{i=1}^m \left(\frac{a_i}{\delta_i} \right)^{\delta_i} \boldsymbol{x}^{\boldsymbol{\epsilon}}.$$

Our choice of $\boldsymbol{\epsilon}$ implies that $\lim_{\boldsymbol{x} \to \boldsymbol{y}} \overline{f}(\boldsymbol{x}) \geq \prod_{i=1}^m \left(\frac{a_i}{\delta_i} \right)^{\delta_i} \lim_{\boldsymbol{x} \to \boldsymbol{y}} \boldsymbol{x}^{\boldsymbol{\epsilon}} = \infty$. Defining $F(\partial[0, \infty]^n) = \infty$ produces the desired extension of $\overline{f}$. Let $M > 0$ be such that $[0, M] \cap \overline{f}(\mathbb{R}^n_{>0}) \neq \emptyset$. Since F is continuous we have $F^{-1}([0, M]) \subset [0, \infty]^n$ is closed. Since $F(\partial[0, \infty]^n) = \infty$, we have $F^{-1}([0, M]) \subset [a, b]^n$ for some $a, b \in (0, \infty)$. Therefore $\inf_{\mathbb{R}^n_{>0}} \overline{f} = \inf_{[a,b]^n} \overline{f} = \overline{f}(\boldsymbol{x}^{min})$ for some $\boldsymbol{x}^{min} \in [a, b]^n$.

It remans to show that the minimum point $\boldsymbol{x}^{min}$ is unique. Letting $\boldsymbol{X} = \ln \boldsymbol{x}$, this is equivalent to proving that

$$g(\boldsymbol{X}) = \sum_{i=0}^{m} e^{\langle \overline{\boldsymbol{\alpha}}^{(i)}, \boldsymbol{X} \rangle}$$

has a unique minimum on $\mathbb{R}^n$. We show that this is the case by proving that g is strictly convex. Indeed, a short computation shows that the Hessian of g is

$$H_g(\boldsymbol{X}) = \sum_{i=0}^{m} e^{\langle \overline{\boldsymbol{\alpha}}^{(i)}, \boldsymbol{X} \rangle} \overline{\boldsymbol{\alpha}}^{(i)} \otimes \overline{\boldsymbol{\alpha}}^{(i)t}$$

where we assume that $\overline{\boldsymbol{\alpha}}^{(i)}$ is a column vector, $\overline{\boldsymbol{\alpha}}^{(i)t}$ denotes the transpose of $\overline{\boldsymbol{\alpha}}^{(i)}$ and "$\otimes$" represents the Kronecker product of two matrices [21]. To check that $H_g(\boldsymbol{X})$ is positive definite, we let $\boldsymbol{Y} \in \mathbb{R}^n$ be an arbitrary row vector and we have

$$\boldsymbol{Y} H_g(\boldsymbol{X}) \boldsymbol{Y}^t = \sum_{i=0}^{m} e^{\langle \overline{\boldsymbol{\alpha}}^{(i)}, \boldsymbol{X} \rangle} \boldsymbol{Y} (\overline{\boldsymbol{\alpha}}^{(i)} \otimes \overline{\boldsymbol{\alpha}}^{(i)t}) \boldsymbol{Y}^t = \sum_{i=0}^{m} e^{\langle \overline{\boldsymbol{\alpha}}^{(i)}, \boldsymbol{X} \rangle} \langle \overline{\boldsymbol{\alpha}}^{(i)}, \boldsymbol{Y} \rangle^2 \tag{19}$$

where the last equality is a consequence of the mixed-product property of the Kronecker product [21]:

$$\boldsymbol{Y}(\overline{\boldsymbol{\alpha}}^{(i)} \otimes \overline{\boldsymbol{\alpha}}^{(i)t})\boldsymbol{Y}^t = \boldsymbol{Y}(\overline{\boldsymbol{\alpha}}^{(i)} \otimes \overline{\boldsymbol{\alpha}}^{(i)t})(1 \otimes \boldsymbol{Y}^t) = \boldsymbol{Y}(\overline{\boldsymbol{\alpha}}^{(i)} 1 \otimes \overline{\boldsymbol{\alpha}}^{(i)t} \boldsymbol{Y}^t) = (\boldsymbol{Y}\overline{\boldsymbol{\alpha}}^{(i)})(\overline{\boldsymbol{\alpha}}^{(i)t}\boldsymbol{Y}^t) = \langle \overline{\boldsymbol{\alpha}}^{(i)}, \boldsymbol{Y} \rangle^2.$$

It follows from (19) that $\boldsymbol{Y} H_g(\boldsymbol{X}) \boldsymbol{Y}^t \geq 0$, with equality if only if $\boldsymbol{Y}$ is orthogonal to all $\overline{\boldsymbol{\alpha}}^{(i)}$, $i \in \{0, \ldots, m\}$. Since $\overline{\boldsymbol{\alpha}}^{(0)}, \ldots, \overline{\boldsymbol{\alpha}}^{(m)}$ span the whole $\mathbb{R}^n$, no such nonzero $\boldsymbol{Y}$ exists. □

Remark 4. A geometric program is not necessarily a convex optimization problem, since a posynomial is not necessarily a convex function. However, making the change of variable $\boldsymbol{X} = \ln \boldsymbol{x}$, as we have done in the proof of Theorem 3, leads to a convex optimization problem, which can be solved numerically.

3.2. **The case of affinely independent exponents.**

Proposition 2. *Consider* affinely independent $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)} \in \mathbb{R}^n$ *and* $\boldsymbol{\lambda} \in \mathbb{R}^{m+1}_{\geq 0}$ *such that* $\sum_{i=0}^{m} \lambda_i = 1$. *Then the set* $\mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda})$ *does not depend on the particular choice of* $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}$, *or on the number* n.

Proof. Let $\boldsymbol{\beta}^{(0)}, \ldots, \boldsymbol{\beta}^{(m)} \in \mathbb{R}^{n'}$ be another affinely independent $(m+1)$-tuple of dimension n'. Then there exists an invertible affine transformation $L : \text{affspan}\{\alpha^{(0)}, \ldots, \alpha^{(m)}\}$ such that $\boldsymbol{\beta}^{(i)} = L(\boldsymbol{\alpha}^{(i)})$ for all $i \in \{1, \ldots, m\}$ and the conclusion of the proposition follows from Lemma 1. □

In view of Proposition 1 we may state the following definition.

Definition 2. *For any affinely independent* $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)} \in \mathbb{R}^n$ *and for* $\boldsymbol{\lambda} \in \mathbb{R}^{m+1}_{\geq 0}$ *such that* $\sum_{i=0}^{m} \lambda_i = 1$ *we denote*

$$\mathcal{M}(\boldsymbol{\lambda}) = \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda}).$$

Remark 5. If τ is a permutation of $\{0, \ldots, m\}$ and $\tau(\boldsymbol{\lambda})$ denotes the vector $(\lambda_{\tau(0)}, \ldots, \lambda_{\tau(m)})$ then

$$\mathcal{M}(\boldsymbol{\lambda}) = \mathcal{M}(\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}, \boldsymbol{\lambda}) = \mathcal{M}(\boldsymbol{\alpha}^{(\tau(0))}, \ldots, \boldsymbol{\alpha}^{(\tau(m))}, \tau(\boldsymbol{\lambda})) = \mathcal{M}(\tau(\boldsymbol{\lambda})).$$

Remark 6. Let $\{\boldsymbol{e}_1, \ldots, \boldsymbol{e}_m\}$ denote the standard basis of $\mathbb{R}^m$. The set $\{\boldsymbol{0}, \boldsymbol{e}_1, \ldots, \boldsymbol{e}_m\}$ is affinely independent and therefore

$$\mathcal{M}(\boldsymbol{\lambda}) = \{(a_0, \ldots, a_m) \in \mathbb{R}^{m+1} \mid F_{\boldsymbol{\lambda}}(\boldsymbol{x}) \geq 0 \textit{ for all } \boldsymbol{x} = (x_1, \ldots, x_m) \in \mathbb{R}^m_{>0}\},$$

where $F_{\boldsymbol{\lambda}} : \mathbb{R}^m_{>0} \to \mathbb{R}$, $F_{\boldsymbol{\lambda}}(\boldsymbol{x}) = a_0 + a_1 x_1 + \ldots + a_m x_m - x_1^{\lambda_1} x_2^{\lambda_2} \ldots x_m^{\lambda_m}$.

If $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}$ are affinely independent, the following result gives an explicit necessary and sufficient condition for a linear combination of monomials $\boldsymbol{x}^{\boldsymbol{\alpha}^{(0)}}, \ldots, \boldsymbol{x}^{\boldsymbol{\alpha}^{(m)}}$ to dominate $x^{\boldsymbol{\gamma}}$ on the whole positive orthant $\mathbb{R}^n_{>0}$, given that $\boldsymbol{\gamma}$ is in the convex hull of $\{\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(m)}\}$.

Proposition 3. *For any* $\boldsymbol{\lambda} \in \mathbb{R}^{m+1}_{\geq 0}$ *such that* $\sum_{j=0}^{m} \lambda_i = 1$ *we have:*

$$\mathcal{M}(\boldsymbol{\lambda}) = \{(a_0, a_1, \ldots, a_m) \in \mathbb{R}^{m+1}_{\geq 0} \mid \prod_{i=0}^{m} \left(\frac{\lambda_i}{a_i}\right)^{\lambda_i} \leq 1\}.$$

Proof. From Remark 3, we may permute the coordinates of $\boldsymbol{\lambda}$ such that, for some $k \leq m$, $\lambda_0, \ldots, \lambda_k$ are positive and $\lambda_{k+1}, \ldots, \lambda_m$ are zero. Let $\tilde{\boldsymbol{\lambda}} = (\lambda_0, \ldots, \lambda_k) \in \mathbb{R}^{k+1}_{>0}$.

Lemma 2 implies that $\mathcal{M}(\boldsymbol{\lambda}) = \mathcal{M}(\tilde{\boldsymbol{\lambda}}) \times \mathbb{R}^{m-k}$. Since by convention we have $0/0 = 0^0 = 1$, it follows that $(\lambda_i/a)^{\lambda_i} = 1$ for all $i \in \{k+1, \ldots, m\}$ and for all $a \in \mathbb{R}$. Therefore the conclusion of the proposition is equivalent to

$$\mathcal{M}(\tilde{\boldsymbol{\lambda}}) = \{(a_0, a_1, \ldots, a_k) \in \mathbb{R}^{k+1}_{\geq 0} \mid \prod_{i=0}^{k} \left(\frac{\lambda_i}{a_i}\right)^{\lambda_i} \leq 1\}.$$

Let $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)}$ be affinely independent vectors and let $\boldsymbol{\gamma} = \sum_{i=1}^{k} \lambda_i \boldsymbol{\alpha}^{(i)}$. The weighted arithmetic and geometric means inequality yields

$$\sum_{i=0}^{k} a_i \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} = \sum_{i=0}^{k} \lambda_i \left(\frac{a_i}{\lambda_i} \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} \right) \geq \prod_{i=1}^{k} \left(\frac{a_i}{\lambda_i} \right)^{\lambda_i} \boldsymbol{x}^{\sum_{i=0}^{m} \lambda_i \boldsymbol{\alpha}^{(i)}} = \prod_{i=1}^{k} \left(\frac{a_i}{\lambda_i} \right)^{\lambda_i} \boldsymbol{x}^{\boldsymbol{\gamma}}. \tag{20}$$

It follows that if $\prod_{i=0}^{k} \left(\frac{\lambda_i}{a_i} \right)^{\lambda_i} \leq 1$, then $\sum_{i=0}^{m} a_i \boldsymbol{x}^{\boldsymbol{\alpha}^{(i)}} \geq \boldsymbol{x}^{\boldsymbol{\gamma}}$ and therefore $\{(a_0, a_1, \ldots, a_k) \in \mathbb{R}_{\geq 0}^{k+1} \mid \prod_{i=0}^{k} \left(\frac{\lambda_i}{a_i} \right)^{\lambda_i} \leq 1\} \subset \mathcal{M}(\tilde{\boldsymbol{\lambda}})$.

For the reverse inclusion let $(a_0, a_1, \ldots, a_k) \in \mathcal{M}(\tilde{\lambda})$ and note that, since $\boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)}$ are affinely independent, $\boldsymbol{\alpha}^{(1)} - \boldsymbol{\alpha}^{(0)}, \ldots, \boldsymbol{\alpha}^{(k)} - \boldsymbol{\alpha}^{(0)}$ are linearly independent and there exists $\boldsymbol{x}_0 \in \mathbb{R}_{>0}^{n}$ such that for all $i \in \{1, \ldots, k\}$ we have

$$(\boldsymbol{\alpha}^{(i)} - \boldsymbol{\alpha}^{(0)}) \cdot \ln \boldsymbol{x}_0 = \ln \left(\frac{a_i}{\lambda_i} \cdot \frac{\lambda_0}{a_0} \right), \text{ or equivalently } \frac{a_i}{\lambda_i} {\boldsymbol{x}_0}^{\boldsymbol{\alpha}^{(i)}} = \frac{a_0}{\lambda_0} {\boldsymbol{x}_0}^{\boldsymbol{\alpha}^{(0)}}.$$

Then the inequality in (20) becomes equality for $\boldsymbol{x}_0$ and, since $(a_0, a_1, \ldots, a_k) \in \mathcal{M}(\tilde{\lambda})$, we have

$$\prod_{i=1}^{k} \left(\frac{a_i}{\lambda_i} \right)^{\lambda_i} {\boldsymbol{x}_0}^{\boldsymbol{\gamma}} = \sum_{i=0}^{k} a_i {\boldsymbol{x}_0}^{\boldsymbol{\alpha}^{(i)}} \geq {\boldsymbol{x}_0}^{\boldsymbol{\gamma}}$$

and therefore $\prod_{i=1}^{k} \left(\frac{\lambda_i}{a_i} \right)^{\lambda_i} \leq 1$. □

4. Examples

While the results discussed in the previous section apply to general polynomial inequalities, in this section we discuss some examples of how one can use them to study the capacity for multiple equilibria of reaction networks. We revisit network (1) and we let $r(\boldsymbol{x}, \boldsymbol{k})$ denote the right-hand side of the corresponding mass-action differential equations (2). Since the only $\boldsymbol{x}$-monomial contained in negative terms of the expansion (4) of $\det(\text{Jac}(r(\boldsymbol{x}, \boldsymbol{k})))$ is $x_2 x_3$, we collect $\boldsymbol{x}$-monomials in (4) and write

$$\begin{aligned} \det(\text{Jac}(r(\boldsymbol{x}, \boldsymbol{k}))) &= K_{0,0} + K_{1,0} x_2 + K_{0,1} x_3 + K_{2,0} x_2^2 + K_{1,1} x_2 x_3 + K_{0,2} x_3^2 + K_{1,2} x_2 x_3^2 \\ &+ \text{ terms containing } \boldsymbol{x}\text{-variables other than } x_2 \text{ and } x_3. \end{aligned} \tag{21}$$

Here $K_{i,j}$ is the coefficient of $x_2^i x_3^j$ within the $\boldsymbol{x}$-polynomial $\det(\text{Jac}(r(\boldsymbol{x}, \boldsymbol{k})))$. The $K_{i,j}$'s are $\boldsymbol{k}$-polynomials which can be computed easily using the software package `BioNetX`. If we assume that all the outflow rates $k_9, k_{11}, k_{13}, k_{15}, k_{17}, k_{19}$ are equal (which is a common assumption in a chemostat

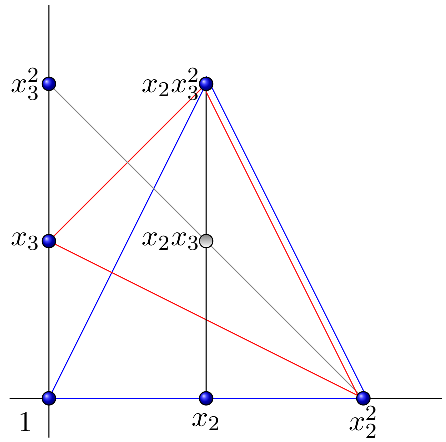

FIGURE 2. Monomials relevant in the positivity analysis of polynomial (4).

[13] or a continuous stirred-tank reactor (CSTR) [5]), then, by changing units, we may also assume that this constant equals 1. Then we have

$$
\begin{aligned}
K_{0,0} &= (1+k_2)(1+k_4)(1+k_5)(1+k_8) \\
K_{1,0} &= (1+k_8)(k_1+k_3+k_1k_4+k_1k_5+k_2k_3+k_1k_4k_5) \\
K_{0,1} &= (1+k_2)(k_3+4k_7+k_3k_5+k_3k_8+4k_4k_7+k_3k_5k_8) \\
K_{2,0} &= k_1k_3(1+k_8) \\
K_{1,1} &= k_1(k_3+4k_7+k_3k_8+4k_4k_7-k_3k_5-k_3k_5k_8) \\
K_{0,2} &= 4k_3k_7(1+k_2) \\
K_{1,2} &= 4k_1k_3k_7.
\end{aligned} \tag{22}
$$

Example 1. If $k_5 = 10$ and $k_i = 1$ for all $i \neq 5$ then we obtain $K_{1,1} = -10$ and (21) becomes

$$
\begin{aligned}
\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k}))) &= 88+48x_2+60x_3+2x_2^2-10x_2x_3+8x_3^2+4x_2x_3^2 \\
&+ \text{ terms containing } \boldsymbol{x}\text{-variables other than } x_2 \text{ and } x_3.
\end{aligned} \tag{23}
$$

Then, according to Proposition 3, it follows that

$$4x_2x_3^2 + 48x_2 > 10x_2x_3 \text{ for all } x_2, x_3 > 0 \tag{24}$$

since we have $\left(\frac{1/2}{4/10}\right)^{1/2}\left(\frac{1/2}{48/10}\right)^{1/2} < 1$.

Also, note that, as shown in Figure 2, there are several other possible choices of positive monomials that dominate the negative monomial $K_{1,1}x_2x_3$ (shown using different colors in Figure 2), such as

$$60x_3 + 2x_2^2 + 4x_2x_3^2 > 10x_2x_3 \text{ for all } x_2, x_3 > 0 \tag{25}$$

since we have $\left(\frac{1/3}{60/10}\right)^{1/3}\left(\frac{1/3}{2/10}\right)^{1/3}\left(\frac{1/3}{4/10}\right)^{1/3} < 1$.

In general, if a negative monomial is contained in the interior of the convex hull of a *single* set of positive monomials then Proposition 3 provides a necessary and sufficient condition for injectivity, in terms of a single inequality between the monomial coefficients.

Also, if a negative monomial is contained in the interior of the convex hull of *several* sets of positive monomials (as is the case in Figure 2) then we can obtain sufficient conditions for injectivity by combining several inequalities between monomial coefficients.

On the other hand, note that we cannot simply add the inequalities (24) and (25) to conclude injectivity for larger values of k_5 (corresponding to larger absolute values of $K_{1,1}$), since they contain the common term $4x_2x_3^2$. In future work we intend to study optimal methods of combining such inequalities, and also consider the case of two or more negative monomials.

Example 2. Suppose we are interested in conditions on $\boldsymbol{k}$ that imply that $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k}))) \neq 0$ for all $\boldsymbol{x} \in \mathbb{R}^6_{>0}$. Then, according to Theorem 2, it will follow that $r(\cdot,\boldsymbol{k})$ is injective on $\mathbb{R}^6_{>0}$ for those values of $\boldsymbol{k}$, and, as we noted in the introduction, this rules out the capacity for multiple equilibria of (2) for those values of $\boldsymbol{k}$. Note that both of the negative terms in (4) contain the $\boldsymbol{x}$-monomial x_2x_3. Moreover, according to Figure 2, the exponent of the monomial x_2x_3 is in the convex hull of the exponents of other monomials in $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k})))$. Then, according to Proposition 1, this monomial may be dominated by a linear combination of other monomials in $\det(\mathrm{Jac}(r(\boldsymbol{x},\boldsymbol{k})))$. For example, a sufficient condition for injectivity of $r(\cdot,\boldsymbol{k})$ is

$$\left(\frac{1/2}{K_{2,0}/K_{1,1}}\right)^{1/2}\left(\frac{1/2}{K_{0,2}/K_{1,1}}\right)^{1/2} < 1, \tag{26}$$

i.e., $4K_{2,0}K_{0,2} > K_{1,1}^2$. In terms of the reaction rates k_i this inequality becomes

$$16k_1k_3^2k_7(1+k_2)(1+k_8) > k_1^2(k_3 + 4k_7 + k_3k_8 + 4k_4k_7 - k_3k_5 - k_3k_5k_8)^2. \tag{27}$$

Since we only need to dominate the negative summands in the coefficient $K_{1,1}$ of x_2x_3 (whose sum is $k_3k_5 + k_3k_5k_8 = k_3k_5(1 + k_8)$), a simpler sufficient condition for the injectivity of $r(\cdot, \boldsymbol{k})$ is

$$16k_1k_3^2k_7(1 + k_2)(1 + k_8) > k_1^2k_3^2k_5^2(1 + k_8)^2, \tag{28}$$

i.e.,

$$16k_2k_7 > k_1k_5^2(1 + k_8). \tag{29}$$

On the other hand, since $(1, 1) = \frac{1}{4}(0, 0) + \frac{1}{4}(2, 0) + \frac{1}{2}(1, 2)$, then, according to Proposition 3, another sufficient condition for injectivity of $r(\cdot, \boldsymbol{k})$ is

$$\left(\frac{1/4}{K_{0,0}/K_{1,1}}\right)^{1/4}\left(\frac{1/4}{K_{2,0}/K_{1,1}}\right)^{1/4}\left(\frac{1/2}{K_{1,2}/K_{1,1}}\right)^{1/2} < 1, \tag{30}$$

i.e.,

$$\frac{1}{64} < \frac{K_{0,0}K_{2,0}K_{1,2}^2}{K_{1,1}^4}$$

or $K_{1,1}^4 < 64K_{0,0}K_{2,0}K_{1,2}^2$. As above, since we only need to dominate the negative summands in $K_{1,1}x_2x_3$, another condition for injectivity of $r(\cdot, \boldsymbol{k})$ in terms of the coordinates of $\boldsymbol{k}$ is

$$k_1^4k_3^4k_5^4(1 + k_8)^4 < 64(1 + k_2)(1 + k_4)(1 + k_5)(1 + k_8)k_1k_3(1 + k_8)\,16k_1^2k_3^2k_7^2,$$

or equivalently,

$$k_1k_3k_5^4(1 + k_8)^2 < 1024(1 + k_2)(1 + k_4)(1 + k_5)k_7^2.$$

There are two more similar inequalities that represent sufficient conditions for injectivity of $r(\cdot, \boldsymbol{k})$, corresponding to the two other ways of choosing exponents that may dominate x_2x_3 shown in Figure 2. Note also that, while the sufficient conditions for injectivity in terms of $K_{i,j}$ are relatively simple, they may become complicated when written in terms of k_i's, because the $K_{i,j}$'s are in general high degree polynomials in k_i's.

Example 3. Finally, suppose we are trying to create a multistable system based on the reaction network (1) and, in a setting often encountered in synthetic biology [23, 28], we have some freedom in choosing the size (i.e., order of magnitude) of some parameter k_j in the system (2). Then we need to make sure that such a choice of $\boldsymbol{k}$ leads to a reaction rate function $r(\cdot, \boldsymbol{k})$ which is *not* injective, i.e., $\det(\mathrm{Jac}(r(\cdot, \boldsymbol{k})))$ *does* change its sign on $\mathbb{R}^6_{>0}$ for this value of $\boldsymbol{k}$. For example, suppose that we know that $k_i = O(1)$ for $i \neq 5$, and that we have biochemical tools that allow us to assume that

$k_5 \gg 1$. Then, by looking at the equations (22) we conclude that, under these assumptions, we will have $K_{1,1} < 0$, and that there will be no terms in the expansion of $\det(\mathrm{Jac}(r(\boldsymbol{x}, \boldsymbol{k})))$ that can dominate $K_{1,1}x_2x_3$ on the whole positive orthant $\mathbb{R}^6_{>0}$, because k_5 does not appear in any set of $K_{i,j}$'s corresponding to a set of monomials that may dominate the monomial x_2x_3. On the other hand, $K_{1,1}x_2x_3$ also cannot dominate all other terms in the expansion of $\det(\mathrm{Jac}(r(\boldsymbol{x}, \boldsymbol{k})))$. Then it follows that $\det(\mathrm{Jac}(r(\cdot, \boldsymbol{k})))$ has both positive and negative values on $\mathbb{R}^6_{>0}$, so it must vanish somewhere on $\mathbb{R}^6_{>0}$. Therefore, $r(\cdot, \boldsymbol{k})$ is not injective on $\mathbb{R}^6_{>0}$.

This is *not* the case if we consider the same scenario with k_3 instead of k_5, because k_3 does appear in a set of $K_{i,j}$'s corresponding to monomials that may dominate the monomial x_2x_3 (see (22) and Figure 2). In other words, it follows that if we are trying to create a multistable system based on the reaction network (1) and we have the biochemical means to increase either k_3 or k_5, we must choose k_5.

5. Discussion

The global inequalities discussed in this paper may also be used for designing sufficient conditions for injectivity and uniqueness of equilibria using the P-matrix criteria developed in [1, 3]. These methods can also be used in the design of Lyapunov functions for the study of boundedness and persistence [11] and global stability [12] of mass action systems. We have also described how one can use methods developed in this paper for the design of functional modules in systems biology and synthetic biology.

Note also that Theorem 2 may be used even if such inequalities do *not* actually hold on the whole positive orthant $\mathbb{R}^n_{>0}$, but only on some set $\Omega \subset \mathbb{R}^n_{>0}$, where n is the number of species. Then, it follows that $r(\cdot, \boldsymbol{k})$ is injective on any convex open set $\Omega' \subset \Omega$, so the system (2) cannot have multiple equilibria on any such domain Ω'. In particular, these methods are amenable to the use of interval analysis [18, 22], and may allow us to derive information about the dynamics of a mass-action system given only approximate measurements of parameter values.

Acknowledgments. This work was partially supported by the National Institutes of Health grant R01GM086881.

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Department of Mathematics and Department of Biomolecular Chemistry, University of Wisconsin-Madison, pantea@math.wisc.edu

Automatic Control Laboratory, Department of Information Technology and Electrical Engineering, Swiss Federal Institute of Technology (ETH) Zürich, koeppl@ethz.ch

Department of Mathematics and Department of Biomolecular Chemistry, University of Wisconsin-Madison, craciun@math.wisc.edu