A Jacobian Criterion for the Simultaneous Injectivity on Positive Variables of Linearly Parameterized Polynomial Maps

Gilles Gnacadja

Research and Development Information Systems, Amgen, Inc.
One Amgen Center Drive, Thousand Oaks, California 91320-1799, USA
gilles.gnacadja@gmail.com

Published in *Linear Algebra and its Applications*

DOI 10.1016/j.laa.2012.03.014

Preprint revision B.05 23 May 2012

Abstract

Consider a map $g : \mathbb{R}^r \times \mathbb{R}^n \to \mathbb{R}^p \times \mathbb{R}^m$ such that for $k \in \mathbb{R}^r$ and $x \in \mathbb{R}^n$, $g(k,x) = \big(L(x), f(k,x)\big)$, where $L : \mathbb{R}^n \to \mathbb{R}^p$ is a linear map and

$$f(k,x) \;=\; \sum_{i=1}^{r} k_i\, x^{a_i}\, v_i \;=\; \sum_{i=1}^{r} k_i\, x_1^{a_{i1}} \cdots x_n^{a_{in}}\, v_i \;;$$

$a_i \in \mathbb{Z}^n_{\geqslant 0}$ and $v_i \in \mathbb{R}^m$ are fixed for $i = 1, \ldots, r$. We prove that the partially evaluated map $g(k,\text{-}) : \mathbb{R}^n \to \mathbb{R}^p \times \mathbb{R}^m$ is injective on $\mathbb{R}^n_{>0}$ for every $k \in \mathbb{R}^r_{>0}$ if and only if for each $k \in \mathbb{R}^r_{>0}$ and $x \in \mathbb{R}^n_{>0}$, the (linear) derivative map $D(g,k,x) : \mathbb{R}^n \to \mathbb{R}^p \times \mathbb{R}^m$ of $g(k,\text{-})$ at x is injective. This result is useful for studying the uniqueness or multiplicity of equilibria in conservative systems of chemical reactions under mass action. A map such as f would represent the rates of change of concentrations of all or some judiciouly selected species. The linear map L would represent the time-invariant total concentrations. To illustrate this application, we prove the uniqueness of equilibria in a common pharmacological model of receptor-ligand interaction, without a customary assumption on rate constants that lets all equilibria be of a strong type known as detailed balance. Our result extends a theorem of Craciun and Feinberg applicable to maps of the kind of f. That earlier result is directly applicable to models of chemical reactions that include the outflow of all species.

Keywords. Jacobian Criterion; Polynomial Map; Injective Map; Reaction Network; Monostability; Multistability.

Mathematics Subject Classification (2010): 26B10, 11C08, 92C42.

1 Introduction

Just about any area of mathematical and computational modeling uses polynomial models. Some use variants of polynomials that restrict the sign of coefficients or variables, or extend

the collection of eligible exponents. The *Computer Algebra Handbook* [11] surveys several applications of polynomials. The types of problems include autonomous dynamical systems with polynomial maps as velocity fields, optimization problems with polynomial maps as objective functions, and systems of polynomial equations. In this latter case, valuable insight is gained from knowing whether solutions are unique, which is the case if the polynomial map is injective.

This paper is concerned with the injectivity problem for an interesting family of maps. The intended application is to study the uniqueness of equilibria in conservative systems of chemical reactions under mass action. So the maps we consider are essentially the species formation functions, i.e. the rates of change of species concentrations, parameterized by the reaction rate constants. Theorem 3.2 states that the simultaneous injectivity of such maps is equivalent to the simultaneous injectivity of their derivatives at all points. This result was established by Craciun and Feinberg [2, Theorem 3.1]. It is directly applicable to chemical systems in which all species are subject to outflow. Here we augment the result with two localized forms of the equivalent conditions. They make the theorem easier to use in practice.

Theorem 4.2 is the main result of this paper. It also states that the simultaneous injectivity of maps in a certain family is equivalent to that of their derivatives at all points. The maps considered have two parts which have direct interpretations in the intended applications. The first part is linear and free of parameters. It will represent the invariants of the system. The second part is polynomial and parameterized. It will represent the species formation for all or some suitably selected species. This theorem can be used to study the uniqueness of equilibria in conservative chemical systems and in fact, a formulation of the theorem in the context of reaction networks is found in Feliu and Wiuf [5]. We illustrate this application in Section 5 by proving the uniqueness of equilibria for the ternary allosteric complex model. This is a biochemical model frequently used in pharmacology. The uniqueness result is already known when the reaction rate constants satisfy a certain assumption that results in all equilibria being detailed-balanced. The work presented here shows that the uniqueness of equilibria is not an algebraic singularity requiring this assumption. This is important because the assumption, an exact equality condition, cannot be verified experimentally or enforced in finite-precision numerical computations. We anticipate that this uniqueness result is merely an instance of a more general property of a class of explicitly-reversibly constructive chemical reaction networks, as defined in Gnacadja [10]. It is also our hope that the generality of Theorem 4.2 will make it useful in areas other than chemical reaction network theory.

Another approach in injectivity problems is to use the Theorem of Gale and Nikaidô [6, Theorem 4 and Remark 4.3]. The theorem says that a differentiable function on a rectangular domain is injective provided the Jacobian matrix at every point is a P-matrix, i.e. all its principal minors are positive. It is used most frequently in mathematical economics. With regard to reaction networks, an interesting question is whether there are conditions on the network structure

and/or the kinetics that ensure that the relevant Jacobian matrices are P-matrices, and thus enable the use of the Theorem of Gale and Nikaidô. Our work in Gnacadja [8] is a contribution in that direction. Banaji, Donnell and Baigent [1] consider the problem in greater generality and discuss structural conditions that allow the use of the Theorem of Gale and Nikaidô. To our knowledge however, physical conditions to fulfill these structural conditions remain to be found. Also, the reaction networks in their work include outflowing species, whereas the networks in our work just cited and in Section 5 herein are conservative.

2 Utility Material

We collect in this section some notations and definitions for convenient use in the paper. We begin with notations for a number of vector operations. Let $x, y, \alpha \in \mathbb{R}^n$.

$$\begin{array}{rcl} x \odot y & = & (x_1 y_1, \ldots, x_n y_n) \\ x \oslash y & = & (x_1/y_1, \ldots, x_n/y_n) \quad \text{if } y_1, \ldots, y_n \in \mathbb{R}_{\neq 0} \\ \langle x, y \rangle & = & x_1 y_1 + \cdots + x_n y_n \\ x^\alpha & = & x_1^{\alpha_1} \cdots x_n^{\alpha_n} \quad \text{if defined} \\ \mathrm{e}^x & = & (\mathrm{e}^{x_1}, \ldots, \mathrm{e}^{x_n}) \\ \ln x & = & (\ln x_1, \ldots, \ln x_n) \quad \text{if } x_1, \ldots, x_n \in \mathbb{R}_{>0} \end{array}$$

To ensure that x^α is defined, we can require $\alpha_i \in \mathbb{Z}_{\geqslant 0}$ or $x_i \in \mathbb{R}_{>0}$.

With ∇ denoting the gradient operator, we note that

$$x \odot \nabla(x^\alpha) \quad = \quad x^\alpha \alpha \; . \tag{2.1}$$

We set $0_n = (0, \ldots, 0) \in \mathbb{Z}^n$, $1_n = (1, \ldots, 1) \in \mathbb{Z}^n$, and $[\![1..n]\!] = \{1, \ldots, n\}$.

Next we define some maps. First is the map $\eta : \mathbb{R} \to \mathbb{R}_{>0}$ given by

$$\eta(t) = \frac{\mathrm{e}^t - 1}{t} \text{ for } t \in \mathbb{R}_{\neq 0} \quad \text{and} \quad \eta(0) = 1 \; . \tag{2.2}$$

Then we have the maps $\mu = (\mu_i)_{1 \leqslant i \leqslant r} : \mathbb{R}^n \times \mathbb{R}^n \times \mathbb{R}^n_{\neq 0} \to \mathbb{R}^r$ and $\nu = (\nu_i)_{1 \leqslant i \leqslant r} : \mathbb{R}^n_{\neq 0} \times \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}^r$ such that

$$\mu_i(x, y, z) \; = \; \frac{(x \oslash z)^{a_i}}{\eta(\langle a_i, y \rangle)} \quad \text{and} \quad \nu_i(x, y, z) \; = \; \eta(\langle a_i, y \rangle)\, (z \oslash x)^{a_i} \; . \tag{2.3}$$

Note that $\mu(x, y, z) \odot \nu(x, y, z) = 1_r$ for $(x, y, z) \in \mathbb{R}^n_{\neq 0} \times \mathbb{R}^n \times \mathbb{R}^n_{\neq 0}$.

Finally, we define injectivity of a map at a point in a natural way.

Definition 2.1. Consider a map $f : X \to Y$, a subset $A \subseteq X$, and a point $a \in A$. We say that f *injective at* a *on* A if a is the only preimage under f in A of $f(a)$, i.e. if $A \cap f^{-1}(f(a)) = \{a\}$. □

Clearly, f is injective on A if and only if for every $a \in A$, f is injective at a on A.

3 First Injectivity Theorem

Let $m, n, r \in \mathbb{Z}_{>0}$. We fix two r-tuples $a = (a_i)_{1 \leqslant i \leqslant r}$ and $v = (v_i)_{1 \leqslant i \leqslant r}$ with $a_i = (a_{i1}, \ldots, a_{in}) \in \mathbb{Z}^n_{\geqslant 0}$ and $v_i = (v_{i1}, \ldots, v_{im}) \in \mathbb{R}^m$ for each $i \in [1..r]$. Then we define the linearly parameterized polynomial map $f : \mathbb{R}^r \times \mathbb{R}^n \to \mathbb{R}^m$ such that for $k = (k_1, \ldots, k_r) \in \mathbb{R}^r$ and $x = (x_1, \ldots, x_n) \in \mathbb{R}^n$,

$$f(k, x) \;=\; \sum_{i=1}^{r} k_i \, x^{a_i} \, v_i \;=\; \sum_{i=1}^{r} k_i \, x_1^{a_{i1}} \cdots x_n^{a_{in}} \, v_i \; . \tag{3.1}$$

Note that every polynomial map $\mathbb{R}^n \to \mathbb{R}^m$ may be expressed as $f(k, \text{-})$ with $k = 1_r$ for suitable r-tuples a and v. This particular parameterization is motivated by the applications of the results in chemical reaction network theory, a field of Mathematics concerned with studying systems of chemical reactions and infering their dynamic and static properties from their structure. Classical references include Horn and Jackson [14], Feinberg [4] and Gunawardena [13]. When a reaction network is governed by the Law of Mass Action, its evolution is described by an autonomous dynamical system in which the velocity field is naturally of the form $f(k, \text{-}) : \mathbb{R}^n \to \mathbb{R}^m, x \mapsto f(k, x)$, with $n = m$ the number of chemical species and k the vector of reaction rate constants.

We write $D(f, k, x)$ for the linear map of $\mathbb{R}^n \to \mathbb{R}^m$ which is the derivative at x of the partially evaluated map $f(k, \text{-}) : \mathbb{R}^n \to \mathbb{R}^m$. From the very definition of f in Equation (3.1), we get

$$\big(D(f, k, x)\big)(u) \;=\; \sum_{i=1}^{r} k_i \, \langle \nabla(x^{a_i}), u \rangle \, v_i \; .$$

And from Equation (2.1), we get

$$\langle \nabla(x^{a_i}), x \odot y \rangle = \langle x \odot \nabla(x^{a_i}), y \rangle = \langle x^{a_i} a_i, y \rangle = x^{a_i} \, \langle a_i, y \rangle \; .$$

Therefore,

$$\big(D(f, k, x)\big)(x \odot y) \;=\; \sum_{i=1}^{r} k_i \, x^{a_i} \, \langle a_i, y \rangle \, v_i \; . \tag{3.2}$$

As is well known, there is no Multidimensional Mean Value Theorem. But Equation (3.2) gets us close in the context of this paper with the rather explicit analogue of Proposition 3.1.

Proposition 3.1. *Let $k \in \mathbb{R}^r$ and $x, y, z \in \mathbb{R}^n$.*

If $z \in \mathbb{R}^n_{\neq 0}$, then

$$\big(D(f,k,x)\big)(x \odot y) \;=\; f\big(k \odot \mu(x,y,z), \mathrm{e}^y \odot z\big) - f\big(k \odot \mu(x,y,z), z\big)\;. \tag{3.3}$$

If $x \in \mathbb{R}^n_{\neq 0}$, then

$$f\big(k, \mathrm{e}^y \odot z\big) - f\big(k, z\big) \;=\; \big(D\big(f, k \odot \nu(x,y,z), x\big)\big)(x \odot y)\;. \tag{3.4}$$

Proof. First we prove Equation (3.3). We have

$$(\mathrm{e}^y \odot z)^{a_i} - z^{a_i} = \mathrm{e}^{\langle a_i, y\rangle} z^{a_i} - z^{a_i} = \Big(\mathrm{e}^{\langle a_i, y\rangle} - 1\Big)\, z^{a_i} = \langle a_i, y\rangle\, \eta(\langle a_i, y\rangle)\, z^{a_i}$$

and it follows that

$$x^{a_i} \langle a_i, y\rangle \;=\; x^{a_i} \frac{\big(\mathrm{e}^y \odot z\big)^{a_i} - z^{a_i}}{\eta(\langle a_i, y\rangle)\, z^{a_i}} \;=\; \mu_i(x,y,z)\Big(\big(\mathrm{e}^y \odot z\big)^{a_i} - z^{a_i}\Big)\;.$$

Then, with Equation (3.2),

$$\begin{aligned}
\big(D(f,k,x)\big)(x \odot y) &= \sum_{i=1}^{r} k_i\, x^{a_i} \langle a_i, y\rangle\, v_i \\
&= \sum_{i=1}^{r} k_i\, \mu_i(x,y,z)\Big(\big(\mathrm{e}^y \odot z\big)^{a_i} - z^{a_i}\Big)\, v_i \\
&= \sum_{i=1}^{r} k_i\, \mu_i(x,y,z)\big(\mathrm{e}^y \odot z\big)^{a_i}\, v_i - \sum_{i=1}^{r} k_i\, \mu_i(x,y,z) z^{a_i}\, v_i \\
&= f\big(k \odot \mu(x,y,z), \mathrm{e}^y \odot z\big) - f\big(k \odot \mu(x,y,z), z\big)\;.
\end{aligned}$$

Equation (3.3) is thus proved. We obtain Equation (3.4), first for $z \in \mathbb{R}^n_{\neq 0}$ by substituting k with $k \odot \nu(x,y,z)$ in Equation (3.3), and then for $z \in \mathbb{R}^n$ by continuity. □

The following theorem fundamentally is Theorem 3.1 from the work of Craciun and Feinberg [2] on multistability in continuous-flow stirred-tank reactors; the preceding proposition brings out some key details that underlie their proof. The result as formulated here adds a few features. First, the tuples a and v need not represent what they do for chemical systems; this has already been noted in Craciun, García-Puente and Sottile [3, Theorem 7] and in Pantea, Köppl and Craciun [16, Theorem 1]. Second, the input and output vector spaces need not have the same dimension. Finally, and this is the main novelty, we have equivalent conditions stating that it is sufficient to be concerned with injectivity at a selected point; see Definition 2.1 for the notion of injectivity at a point. These localized formulations make the theorem easier to use in practice. For our intended applications however, the directly relevant result is the more general Theorem 4.2.

Theorem 3.2. *Let $x^\star, z^\star \in \mathbb{R}^n_{>0}$. The following are equivalent.*

(a) *For every $k \in \mathbb{R}^r_{>0}$, the map $f(k,\text{-}) : \mathbb{R}^n \to \mathbb{R}^m$ is injective at $z^\star$ on $\mathbb{R}^n_{>0}$.*

(b) *For every $k \in \mathbb{R}^r_{>0}$, the derivative map $D(f,k,x^\star) : \mathbb{R}^n \to \mathbb{R}^m$ is injective.*

(1) *For every $k \in \mathbb{R}^r_{>0}$, the map $f(k,\text{-}) : \mathbb{R}^n \to \mathbb{R}^m$ is injective on $\mathbb{R}^n_{>0}$.*

(2) *For every $k \in \mathbb{R}^r_{>0}$ and $x \in \mathbb{R}^n_{>0}$, the derivative map $D(f,k,x) : \mathbb{R}^n \to \mathbb{R}^m$ is injective.*

Remark 3.3. Theorem 3.2 bears some resemblance with the much studied Jacobian Conjecture; see for instance van den Essen [18] and Pinchuk [17]. Theorem 3.2 is not as broad. It addresses injectivity only with respect to positive variables. Also, it does not claim that given a fixed $k \in \mathbb{R}^r_{>0}$, the injectivity on $\mathbb{R}^n_{>0}$ of $x \mapsto f(k,x)$ and of $D(f,k,x)$ for all $x \in \mathbb{R}^n_{>0}$ are equivalent. The fact that k ranges over $\mathbb{R}^r_{>0}$ is instrumental in the proof. □

Remark 3.4. In Theorem 3.2, Conditions (a) and (b) could be regarded as local forms of the global Conditions (1) and (2), respectively. Condition (1) is the conjunction of Condition (a) for all $z^\star \in \mathbb{R}^n_{>0}$, and Condition (2) is the conjunction of Condition (b) for all $x^\star \in \mathbb{R}^n_{>0}$. Therefore, if we assume that Conditions (a) and (b) are equivalent, it results that the four conditions are equivalent. Consequently, Theorem 3.2 will be proved when we show the equivalence of Conditions (a) and (b). □

Remark 3.5. Obviously, for Theorem 3.2 to be useful, we must have $m \geqslant n$. If $m = n$, the injectivity of the derivative map $D(f,k,x)$ may be expressed as the nonvanishing of the Jacobian determinant. In fact, by an argument on connectedness and continuity, the values of $\det\big(D(f,k,x)\big)$ form an interval of $\mathbb{R}$ as k ranges over $\mathbb{R}^r_{>0}$ and x is fixed or ranges $\mathbb{R}^n_{>0}$. Hence, with $m = n$, we have the following two additional equivalent conditions.

(c) *Either* $\det\big(D(f,k,x^\star)\big) > 0$ *for all* $k \in \mathbb{R}^r_{>0}$,
or (exclusively) $\det\big(D(f,k,x^\star)\big) < 0$ *for all* $k \in \mathbb{R}^r_{>0}$.

(3) *Either* $\det\big(D(f,k,x)\big) > 0$ *for all* $k \in \mathbb{R}^r_{>0}$ *and* $x \in \mathbb{R}^n_{>0}$,
or (exclusively) $\det\big(D(f,k,x)\big) < 0$ *for all* $k \in \mathbb{R}^r_{>0}$ *and* $x \in \mathbb{R}^n_{>0}$.

By using Condition (c) with $x^\star = 1_n$ or other judiciouly selected values of $x^\star$, the calculations of Jacobian determinants used to verify injectivity, as done in Craciun and Feinberg [2] and several subsequent publications, is greatly simplified. □

Remark 3.6. Theorem 3.2 remains true if the condition that k ranges over $\mathbb{R}^r_{>0}$ is replaced with the condition that k ranges over a set $\mathcal{K} \subseteq \mathbb{R}^r$ that is closed under *anisotropic scaling*, i.e. such that for every $\lambda \in \mathbb{R}^r_{>0}$ and $k \in \mathcal{K}$, $\lambda \odot k \in \mathcal{K}$. If $\mathcal{K} = \mathcal{K}_1 \times \cdots \times \mathcal{K}_r$ and $\mathcal{K}_i$ is either $\mathbb{R}_{>0}$, $\mathbb{R}_{\geqslant 0}$ or $\mathbb{R}$ for each $i = 1, \ldots, r$, then $\mathcal{K}$ is closed under anisotropic scaling. But note that if $\mathcal{K} = \mathbb{R}^r_{\geqslant 0}$ or $\mathcal{K} = \mathbb{R}^r$, or more generally if $\mathcal{K} \subseteq \mathbb{R}^r$ is closed under anisotropic scaling and contains 0_r, then Theorem 3.2 becomes a uninformative tautology. □

Remark 3.7. Theorem 3.2 remains true if the exponent vectors $a_1, \ldots, a_r$ are taken from $\mathbb{R}^n$, not necessarily $\mathbb{Z}^n_{\geqslant 0}$. But then one has to require $x, y, z \in \mathbb{R}^n_{>0}$ in Proposition 3.1. □

Proof (Proof of Theorem 3.2). Thanks to Remark 3.4, we just need to show that Conditions 3.2.(a) and 3.2.(b) are equivalent.

Suppose that $f(h,\text{-})$ is injective at $z^\star$ on $\mathbb{R}^n_{>0}$ for every $h \in \mathbb{R}^r_{>0}$. Let $k \in \mathbb{R}^r_{>0}$ and let $y' \in \operatorname{Ker}\big(D(f,k,x^\star)\big)$. Then let $y = y' \oslash x^\star$, so that $y' = x^\star \odot y$. Let $h = k \odot \mu(x^\star, y, z^\star)$. With Equation (3.3), we have

$$0_m \;=\; \big(D(f,k,x^\star)\big)(y') \;=\; \big(D(f,k,x^\star)\big)(x^\star \odot y) \;=\; f\big(h, \mathrm{e}^y \odot z^\star\big) - f\big(h, z^\star\big)\,.$$

Therefore, we successively have $\mathrm{e}^y \odot z^\star = z^\star$, $\mathrm{e}^y = 1_n$, $y = 0_n$, and $y' = 0_n$. Thus, the map $D(f,k,x^\star)$ is injective.

Now suppose that the map $D(f,h,x^\star)$ is injective for every $h \in \mathbb{R}^r_{>0}$. Let $k \in \mathbb{R}^r_{>0}$ and let $z' \in \mathbb{R}^n_{>0}$ such that $f(k,z') = f(k,z^\star)$. Then let $y = \ln(z' \oslash z^\star)$, so that $z' = \mathrm{e}^y \odot z^\star$. Let $h = k \odot \nu(x^\star, y, z^\star)$. With Equation (3.4), we have

$$0_m \;=\; f(k,z') - f(k,z^\star) \;=\; f(k, \mathrm{e}^y \odot z^\star) - f(k,z^\star) \;=\; \big(D(f,h,x^\star)\big)(x^\star \odot y)\,.$$

Therefore, we successively have $x^\star \odot y = 0_n$, $y = 0_n$, and $z' = z^\star$. Thus, the map $f(k,\text{-})$ is injective at $z^\star$ on $\mathbb{R}^n_{>0}$. □

4 Second Injectivity Theorem

The main goal of this paper is to provide an injectivity result which can be used to study the uniqueness of equilibria in conservative chemical systems. Such study must proceed under the constraints of prescribed conservation relations, otherwise the uniqueness of equilibria should not be expected and fails in a trivial way. Conservation relations in chemical systems are expressed by linear forms which are independent of reaction rate constants. Because the map studied in Section 3 is fully parameterized, Theorem 3.2 is not readily applicable. We generalize it into the more relevant Theorem 4.2. In preparation for it, we first have in Proposition 4.1 the suitable analogue of Proposition 3.1.

Consider a linear map $L : \mathbb{R}^n \to \mathbb{R}^p$ and the linearly parameterized polynomial map $f : \mathbb{R}^r \times \mathbb{R}^n \to \mathbb{R}^m$ of Section 3. Then let the linearly parameterized polynomial map $g : \mathbb{R}^r \times \mathbb{R}^n \to \mathbb{R}^p \times \mathbb{R}^m$ be given for $k \in \mathbb{R}^r$ and $x \in \mathbb{R}^n$ by

$$g(k,x) \;=\; \big(L(x), f(k,x)\big) \;=\; \left(L(x)\,, \sum_{i=1}^{r} k_i\, x^{a_i}\, v_i\right)\,. \tag{4.1}$$

Proposition 4.1. *Let $k \in \mathbb{R}^r$, $x \in \mathbb{R}^n_{\neq 0}$, $y \in \mathbb{R}^n$, $z \in \mathbb{R}^n_{\neq 0}$. Suppose that $\mathrm{e}^y \odot z - z = x \odot y$. Then we have*

$$\big(D(g,k,x)\big)(x \odot y) \quad = \quad g\big(k \odot \mu(x,y,z), \mathrm{e}^y \odot z\big) - g\big(k \odot \mu(x,y,z), z\big) \tag{4.2}$$

and

$$g\big(k, \mathrm{e}^y \odot z\big) - g\big(k, z\big) \quad = \quad \big(D\big(g, k \odot \nu(x,y,z), x\big)\big)(x \odot y)\ . \tag{4.3}$$

Proof. We have $D(g,k,x) = \big(L, D(f,k,x)\big)$ and $L(\mathrm{e}^y \odot z) - L(z) = L(x \odot y)$. By combining this with Equation (3.3) (resp. Equation (3.4)), we obtain Equation (4.2) (resp. Equation (4.3)). □

We now state the main result of this paper. A version formulated in the context of reaction networks appears in Feliu and Wiuf [5].

Theorem 4.2. *The following are equivalent.*

(1) *For every $k \in \mathbb{R}^r_{>0}$, the partially evaluated map $g(k,\text{-}) : \mathbb{R}^n \to \mathbb{R}^p \times \mathbb{R}^m, x \mapsto g(k,x) = \big(L(x), f(k,x)\big)$ is injective on $\mathbb{R}^n_{>0}$.*

(2) *For every $k \in \mathbb{R}^r_{>0}$ and $x \in \mathbb{R}^n_{>0}$, the derivative map $D(g,k,x) = \big(L, D(f,k,x)\big) : \mathbb{R}^n \to \mathbb{R}^p \times \mathbb{R}^m$ is injective.*

Remark 4.3. In contrast with Theorem 3.2, Theorem 4.2 does not have local forms of its equivalent conditions. This is because, while the identities in Proposition 3.1 hold without constraints on x, y and z, the identities in Proposition 4.1 hold provided x, y and z are related (by $\mathrm{e}^y \odot z - z = x \odot y$) to accomodate the non-parameterized linear part L. □

Remark 4.4. This is the analogue of Remark 3.5 for g. Theorem 4.2 may be useful only if $p + m \geqslant n$. If $p + m = n$, the two conditions in Theorem 4.2 are equivalent to:

(3) *Either $\det\big(D(g,k,x)\big) > 0$ for all $k \in \mathbb{R}^r_{>0}$ and $x \in \mathbb{R}^n_{>0}$, or (exclusively) $\det\big(D(g,k,x)\big) < 0$ for all $k \in \mathbb{R}^r_{>0}$ and $x \in \mathbb{R}^n_{>0}$.* □

Remark 4.5. The hypotheses in Theorem 4.2 may be weakened in ways similar to those in Remarks 3.6 and 3.7. Specifically, Theorem 4.2 remains true if the condition that k ranges over $\mathbb{R}^r_{>0}$ is replaced with the condition that k ranges over a set $\mathcal{K} \subseteq \mathbb{R}^r$ that is closed under anisotropic scaling. Theorem 4.2 also remains true if the exponent vectors $a_1, \ldots, a_r$ are taken from $\mathbb{R}^n$, not necessarily $\mathbb{Z}^n_{\geqslant 0}$. This requires $x, y, z \in \mathbb{R}^n_{>0}$ in Proposition 4.1. □

Proof (Proof of Theorem 4.2).

Suppose that $g(h,\text{-})$ is injective on $\mathbb{R}^n_{>0}$ for every $h \in \mathbb{R}^r_{>0}$. Let $k \in \mathbb{R}^r_{>0}$ and $x \in \mathbb{R}^n_{>0}$, and let

$y' \in \mathrm{Ker}\big(D(f,k,x)\big)$. Then let $y = y' \oslash x$, so that $y' = x \odot y$. Furthermore let $z = x \oslash \eta^{\times n}(y) = \big(x_1/\eta(y_1), \ldots, x_n/\eta(y_n)\big)$, so that $\mathrm{e}^y \odot z - z = x \odot y$. Finally let $h = k \odot \mu(x,y,z)$. With Equation (4.2), we have

$$(0_p, 0_m) \;=\; \big(D(g,k,x)\big)(y') \;=\; \big(D(g,k,x)\big)(x \odot y) \;=\; g\big(h, \mathrm{e}^y \odot z\big) - g\big(h, z\big)\ .$$

Therefore, we successively have $\mathrm{e}^y \odot z = z$, $\mathrm{e}^y = 1_n$, $y = 0_n$, and $y' = 0_n$. Thus, the map $D(g,k,x)$ is injective.

Suppose that the map $D(g,h,x)$ is injective for every $h \in \mathbb{R}^r_{>0}$ and $x \in \mathbb{R}^n_{>0}$. Let $k \in \mathbb{R}^r_{>0}$ and let $z, z' \in \mathbb{R}^n_{>0}$ such that $g(k,z) = g(k,z')$. Then let $y = \ln(z' \oslash z)$, so that $z' = \mathrm{e}^y \odot z$. Furthermore let $x = \eta^{\times n}(y) \odot z = \big(\eta(y_1)z_1, \ldots, \eta(y_n)z_n\big)$, so that $\mathrm{e}^y \odot z - z = x \odot y$. Finally let $h = k \odot \nu(x,y,z)$. With Equation (4.3), we have

$$(0_p, 0_m) \;=\; g(k,z') - g(k,z) \;=\; g(k, \mathrm{e}^y \odot z) - g(k,z) \;=\; \big(D(g,h,x)\big)(x \odot y)\ .$$

Therefore, we successively have $x \odot y = 0_n$, $y = 0_n$, and $z = z'$. Thus, the map $g(k,\text{-})$ is injective on $\mathbb{R}^n_{>0}$. □

5 Application

One could think that Theorems 3.2 and 4.2 merely translate one difficult problem into another: proving the injectivity of linearly parameterized polynomial maps is challenging, but so is proving that (Jacobian) matrices with entries that themselves are linearly parameterized polynomials have full rank. However the work of Craciun and Feinberg [2] on equilibria in continuous-flow stirred-tank reactors shows that Theorem 3.2 can be used successfully. We present in this section an application of Theorem 4.2.

The allosteric ternary complex model is the following representation of the interaction of a receptor R with two ligands A and B.

$$\begin{array}{ccc} R & + A \rightleftharpoons & RA \\ + & & + \\ B & & B \\ \Updownarrow & & \Updownarrow \\ RB & + A \rightleftharpoons & RAB \end{array}$$

The model is frequently used in pharmacology. Receptors are cell surface molecules that transmit signals from outside cells to within them. Signals are caused by ligand molecules that bind to receptors from outside cells. Typically in the model considered here, one ligand is endogenous and pathogenic, and the other ligand is under consideration to serve as a therapeutic

agent that reduces the signal or the effect of the signal caused by the pathogenic ligand. This model is necessarily a simplification of the actual biochemistry. It has nevertheless long served as a useful approximation, e.g. to model certain in vitro experiments. For reference, see for instance Kenakin [15] and Gregory, Sexton and Christopoulos [12].

We denote x_R, x_A, x_B, x_{RA}, x_{RB}, x_{RAB} the (time-dependent) concentrations of R, A, B, RA, RB, RAB. The building units of the system are R, A, B. Let T_R, T_A, T_B be their *total concentrations*, i.e. their cummulated concentrations as free and bound chemical species. We have the following Conservation Equations.

$$\left\{\begin{array}{rcl} x_R + x_{RA} + x_{RB} + x_{RAB} &=& T_R \\ x_A + x_{RA} \qquad + x_{RAB} &=& T_A \\ x_B \qquad + x_{RB} + x_{RAB} &=& T_B \end{array}\right. \tag{5.1}$$

We make the usual assumption that the system is governed by the Law of Mass Action. Then each reaction has a *rate constant*, a positive number which we denote by k indexed by the reaction. For instance, $k_{R+A\to RA}$ and $k_{RAB\to RB+A}$ are the rate constants of the *binding reaction* $R + A \to RA$ and of the *dissociation reaction* $RAB \to RA + B$ respectively. In addition, to each pair of mutually reverse binding/dissociation reactions corresponds an *equilibrium binding constant* as follows.

$$K_{R+A,RA} = \frac{k_{R+A\to RA}}{k_{RA\to R+A}} \qquad K_{RA+B,RAB} = \frac{k_{RA+B\to RAB}}{k_{RAB\to RA+B}}$$

$$K_{R+B,RB} = \frac{k_{R+B\to RB}}{k_{RB\to R+B}} \qquad K_{RB+A,RA} = \frac{k_{RB+A\to RAB}}{k_{RAB\to RB+A}}$$

The ratios

$$\alpha_{AB} = \frac{K_{RA+B,RAB}}{K_{R+A,RA}} \qquad \text{and} \qquad \alpha_{BA} = \frac{K_{RB+A,RAB}}{K_{R+B,RB}}$$

are known as the *cooperativity factors*. The practice in pharmacology is to assume that $\alpha_{AB} = \alpha_{BA}$. We know not of a justification for this assumption, but as a consequence, equilibrium states are detailed-balanced: when the system is at equilibrium, so are the four subsystems of mutually reverse binding/dissociation reactions. With this condition, there exists for any nonnegative triple of total concentrations a unique (and globally asymptotically stable) nonnegative equilibrium state that satisfies the Conservation Equations (5.1). This fact is covered in the work of Gnacadja [8] and an easy method to calculate the equilibrium state is presented in Gnacadja [9]. Even if assuming the equality of the cooperativity factors is physically justified, it is important to know that the uniqueness of equilibrium state is not a algebraic singularity resulting from this assumption. Indeed, exact equality cannot be verified experimentally or enforced in finite-precision numerical computations. In this section, we apply Theorem 4.2 to prove the uniqueness result without requiring that the cooperativity factors be

equal.

Let k be the reactions-indexed 8-tuple of rate constants, and let $x = (x_R, x_A, x_B, x_{RA}, x_{RB}, x_{RAB})$. The mass-action species formation function is the parameterized polynomial function f such that the evolution of the system is governed by the following autonomous dynamical system.

$$\dot{x} \quad = \quad f(k,x) \tag{5.2}$$

We have $f = (f_R, f_A, f_B, f_{RA}, f_{RB}, f_{RAB})$ given as follows by the Law of Mass Action.

$$\begin{aligned}
&\big(f_R(k,x), f_A(k,x), f_B(k,x), f_{RA}(k,x), f_{RB}(k,x), f_{RAB}(k,x)\big) \\
= \quad & k_{R+A\to RA}\ x_R x_A\ (-1,-1,\ 0,\ 1,\ 0,\ 0\,) \\
+ \ & k_{RA\to R+A}\ x_{RA}\ (\ 1,\ 1,\ 0,-1,\ 0,\ 0\,) \\
+ \ & k_{R+B\to RB}\ x_R x_B\ (-1,\ 0,-1,\ 0,\ 1,\ 0\,) \\
+ \ & k_{RB\to R+B}\ x_{RB}\ (\ 1,\ 0,\ 1,\ 0,-1,\ 0\,) \\
+ \ & k_{RA+B\to RAB}\ x_{RA}x_B\ (\ 0,\ 0,-1,-1,\ 0,\ 1\,) \\
+ \ & k_{RAB\to RA+B}\ x_{RAB}\ (\ 0,\ 0,\ 1,\ 1,\ 0,-1\,) \\
+ \ & k_{RB+A\to RAB}\ x_{RB}x_A\ (\ 0,-1,\ 0,\ 0,-1,\ 1\,) \\
+ \ & k_{RAB\to RB+A}\ x_{RAB}\ (\ 0,\ 1,\ 0,\ 0,\ 1,-1\,)
\end{aligned}$$

This expression makes it apparent that f is indeed a map of the kind studied in Section 3 (with $n = m = 6$ and $r = 8$). The equilibria of the system are the nonnegative solutions x of the following polynomial equation.

$$f(k,x) \quad = \quad (0,0,0,0,0,0) \tag{5.3}$$

It should be expected from the Conservation Equations (5.1), and it can be verified, that

$$\begin{aligned}
-f_R(k,x) &= f_{RA}(k,x) + f_{RB}(k,x) + f_{RAB}(k,x)\ , \\
-f_A(k,x) &= f_{RA}(k,x) \qquad\qquad + f_{RAB}(k,x)\ , \\
-f_B(k,x) &= \qquad\qquad f_{RB}(k,x) + f_{RAB}(k,x)\ .
\end{aligned}$$

Therefore the equilibria of the system are the nonnegative solutions x of the following polynomial equation.

$$\big(f_{RA}(k,x), f_{RB}(k,x), f_{RAB}(k,x)\big) \quad = \quad (0,0,0) \tag{5.4}$$

Note that the map $(f_{RA}, f_{RB}, f_{RAB})$ is also of the kind studied in Section 3 (with $n = 6$, $m = 3$ and $r = 8$). Let the linear map $L = (L_R, L_A, L_B)$ be given as follows.

$$\left\{\begin{array}{lcl}
L_R(x) &=& x_R + x_{RA} + x_{RB} + x_{RAB} \\
L_A(x) &=& x_A + x_{RA} \qquad + x_{RAB} \\
L_B(x) &=& x_B \qquad + x_{RB} + x_{RAB}
\end{array}\right. \tag{5.5}$$

The system of Conservation Equations (5.1) is equivalent to the equation $L(x) = (T_R, T_A, T_B)$. Let the map g be given as follows.

$$g(k,x) \quad = \quad \big(L_R(x), L_A(x), L_B(x), f_{RA}(k,x), f_{RB}(k,x), f_{RAB}(k,x)\big) \tag{5.6}$$

The map g is of the kind studied in Section 4 (with $n = 6$, $p = m = 3$ and $r = 8$). The result on equilibrium we are seeking is that for any positive 8-tuple k and positive triple (T_R, T_A, T_B), there is a unique positive solution x for the following equation.

$$g(k,x) \quad = \quad (T_R, T_A, T_B, 0, 0, 0) \tag{5.7}$$

The existence part of the problem is not too difficult and would be a distraction from the purpose of this section. We elect to admit it and refer the concerned reader to Gnacadja [7]. We prove the uniqueness part by using Theorem 4.2 to show that, for any positive 8-tuple k, the map $g(k,\text{-})$ is injective on positive variables. Let

$$E \quad = \quad \begin{pmatrix} 1 & 1 & 1 \\ 1 & 0 & 1 \\ 0 & 1 & 1 \end{pmatrix} .$$

The derivative map $D(g,k,x)$ is represented by the Jacobian matrix $J(g,k,x)$.

$$J(g,k,x) \quad = \quad \left(\begin{array}{c|c} \mathrm{Id}_3 & E \\ \hline \dfrac{\partial(f_{RA}, f_{RB}, f_{RAB})}{\partial(x_R, x_A, x_B)}(k,x) & \dfrac{\partial(f_{RA}, f_{RB}, f_{RAB})}{\partial(x_{RA}, x_{RB}, x_{RAB})}(k,x) \end{array}\right)$$

In this presentation of $J(g,k,x)$ as a block matrix, we have a square of four blocks of the same size and the blocks in positions $(1,1)$ and $(1,2)$ commute. The applicable determinant identity yields $\det\big(J(g,k,x)\big) = \det\big(\bar{J}(f,k,x)\big)$, where

$$\bar{J}(f,k,x) \quad = \quad \frac{\partial(f_{RA}, f_{RB}, f_{RAB})}{\partial(x_{RA}, x_{RB}, x_{RAB})}(k,x) - \frac{\partial(f_{RA}, f_{RB}, f_{RAB})}{\partial(x_R, x_A, x_B)}(k,x)\, E \ .$$

Calculations yield $\bar{J}(f,k,x)$ explicitly as follows.

$$
-\bar{J}(f,k,x) \;=\; \begin{pmatrix}
k_{RA\to R+A} & & -k_{RAB\to RA+B} \\
+k_{R+A\to RA}\,x_R & k_{R+A\to RA}\,x_A & +k_{R+A\to RA}\,x_R \\
+k_{R+A\to RA}\,x_A & -k_{RA+B\to RAB}\,x_{RA} & +k_{R+A\to RA}\,x_A \\
+k_{RA+B\to RAB}\,x_B & & -k_{RA+B\to RAB}\,x_{RA} \\
 & k_{RB\to R+B} & -k_{RAB\to RB+A} \\
k_{R+B\to RB}\,x_B & +k_{R+B\to RB}\,x_R & +k_{R+B\to RB}\,x_R \\
-k_{RB+A\to RAB}\,x_{RB} & +k_{RB+A\to RAB}\,x_A & +k_{R+B\to RB}\,x_B \\
 & +k_{R+B\to RB}\,x_B & -k_{RB+A\to RAB}\,x_{RB} \\
 & & k_{RAB\to RA+B} \\
-k_{RA+B\to RAB}\,x_B & -k_{RB+A\to RAB}\,x_A & +k_{RAB\to RB+A} \\
+k_{RB+A\to RAB}\,x_{RB} & +k_{RA+B\to RAB}\,x_{RA} & +k_{RA+B\to RAB}\,x_{RA} \\
 & & +k_{RB+A\to RAB}\,x_{RB}
\end{pmatrix}
$$

With the help of a computer algebra system, specifically the Symbolic Math Toolbox™ in the MATLAB® (Release R2012a) technical computing environment, we obtain that $\det\big(-\bar{J}(f,k,x)\big)$, a polynomial in the 14-tuple (k,x), is the sum of 64 monic monomials. Thus, if k and x are positive, then $-\det\big(\bar{J}(f,k,x)\big) = \det\big(-\bar{J}(f,k,x)\big) > 0$, $\det\big(J(g,k,x)\big) < 0$, and the Jacobian matrix $J(g,k,x)$ is nonsingular. By Theorem 4.2, the map $g(k,\text{-})$ is injective on positive variables. Consequently, we do have the uniqueness of positive equilibrium for given positive total concentrations.

6 Prospects for Broader Application

The use of computer algebra systems to study the uniqueness of equilibria can be less than satisfying. A reaction network need not be too large for the process to be very tedious. But more importantly, there are networks studied in the applied sciences for which the existence and uniqueness (and global asymptotic stability) of equilibria are routinely and tacitly taken for granted. A readily applicable theorem rather than case-by-case computational verifications would seem to be in order. Ongoing work is aimed at addressing this concern. The goal is to apply the main (second) injectivity theorem proved here to establish the uniqueness of equilibria in a large class of conservative chemical systems. Note that since we used a computer algebra system in Section 5, we could have worked directly with the 6×6 matrix $J(g,k,x)$ instead of the smaller 3×3 matrix $\bar{J}(f,k,x)$. The transformation was intended to hint at some of the techniques we use as we seek a more general result. The idea is to use the formalism of species composition developed in Gnacadja [10] and exploit the structural features that become apparent in the Jacobian matrices. A basic idea in the species composition formalism is the partition of the species into elementary species and composite species. In the example

of Section 5, the elementary species are R, A, B and the composite species are RA, RB, RAB; it is not according to whether or not a species symbol consists of a single letter that the partition is made. The expected result, using terminology from Gnacadja [10], is that if a reaction network is explicitly-reversibly constructive and there is no isomerism among the elementary species, then we have the existence, uniqueness and global asymptotic stability of positive mass-action equilibria. (We already know from Theorem 6.9 of that prior work that such networks are vacuously persistent under mass action, a necessary condition.) In addition to providing a mathematical foundation for properties that are implicitly presupposed in applied fields of research, this result would justify the seldom-noticed fact that instances of multistationary conservative chemical reaction networks in the mathematical literature always involve isomerism.

References

[1] M. Banaji, P. Donnell, and S. Baigent, *P Matrix Properties, Injectivity, and Stability in Chemical Reaction Systems*, SIAM Journal on Applied Mathematics **67** (2007), no. 6, 1523–1547, DOI 10.1137/060673412.

[2] G. Craciun and M. Feinberg, *Multiple Equilibria in Complex Chemical Reaction Networks: I. The Injectivity Property*, SIAM Journal on Applied Mathematics **65** (2005), no. 5, 1526–1546, DOI 10.1137/S0036139904440278.

[3] G. Craciun, L. D. García-Puente, and F. Sottile, *Some Geometrical Aspects of Control Points for Toric Patches*, Mathematical Methods for Curves and Surfaces (M. Dæhlen, M. Floater, T. Lyche, J.-L. Merrien, K. Mørken, and L. L. Schumaker, eds.), Lecture Notes in Computer Science, vol. 5862, Springer, 2010, DOI 10.1007/978-3-642-11620-9_9, pp. 111–135.

[4] M. Feinberg, *Lectures on Chemical Reaction Networks*, http://www.che.eng.ohio-state.edu/~Feinberg/LecturesOnReactionNetworks/, 1980.

[5] E. Feliu and C. Wiuf, *Injectivity of Chemical Reaction Networks with Mass Action Kinetics Revisited*, http://arxiv.org/abs/1109.5149.

[6] D. Gale and H. Nikaidô, *The Jacobian Matrix and Global Univalence of Mappings*, Mathematische Annalen **159** (1965), no. 2, 81–93, DOI 10.1007/BF01360282.

[7] G. Gnacadja, *Equilibria Exist in Compact Convex Forward-Invariant Sets*, http://mathoverflow.net/questions/68174/equilibria-exist-in-compact-convex-forward-invariant-sets.

[8] ———, *Univalent Positive Polynomial Maps and the Equilibrium State of Chemical Networks of Reversible Binding Reactions*, Advances in Applied Mathematics **43** (2009), no. 4, 394–414, DOI 10.1016/j.aam.2009.05.001.

[9] ———, *A Method to Calculate Binding Equilibrium Concentrations in the Allosteric Ternary Complex Model that Supports Ligand Depletion*, Mathematical Biosciences **232** (2011), no. 2, 135–141, DOI 10.1016/j.mbs.2011.05.003.

[10] ———, *Reachability, Persistence, and Constructive Chemical Reaction Networks (Part II): A Formalism for Species Composition in Chemical Reaction Network Theory and Application to Persistence*, Journal of Mathematical Chemistry **49** (2011), no. 10, 2137–2157, DOI 10.1007/s10910-011-9896-2.

[11] J. Grabmeier, E. Kaltofen, and V. Weispfenning (eds.), *Computer Algebra Handbook – Foundations, Applications, Systems*, Springer, 2003, ISBN 978-3-540-65466-7.

[12] K. J. Gregory, P. M. Sexton, and A. Christopoulos, *Overview of Receptor Allosterism*, Current Protocols in Pharmacology **51** (2010), no. 21, 1–34, DOI 10.1002/0471141755.ph0121s51.

[13] J. Gunawardena, *Chemical Reaction Network Theory for In-Silico Biologists*, http://www.jeremy-gunawardena.com/papers/crnt.pdf, 2003.

[14] F. Horn and R. Jackson, *General Mass Action Kinetics*, Archive for Rational Mechanics and Analysis **47** (1972), no. 2, 81–116, DOI 10.1007/BF00251225.

[15] T. Kenakin, *A Pharmacology Primer: Theory, Applications, and Methods*, 3rd ed., Academic Press, 2009, ISBN 9780123745859.

[16] C. Pantea, H. Köppl, and G. Craciun, *Global Injectivity and Multiple Equilibria in Uni- and Bi-Molecular Reaction Networks*, Discrete and Continuous Dynamical Systems - Series B **17** (2012), no. 6, 2153–2170, DOI 10.3934/dcdsb.2012.17.2153.

[17] S. Pinchuk, *A Counterexample to the Strong Real Jacobian Conjecture*, Mathematische Zeitschrift **217** (1994), no. 1, 1–4, DOI 10.1007/BF02571929.

[18] A. van den Essen, *Polynomial Automorphisms and the Jacobian Conjecture*, Algèbre Non Commutative, Groupes Quantiques et Invariants (J. Alev and G. Cauchon, eds.), Séminaires et Congrès, vol. 2, Société Mathématique de France, 1997, http://smf4.emath.fr/Publications/SeminairesCongres/1997/2/pdf/smf_sem-cong_2_55-81.pdf, pp. 55–81.