

Power-Law Kinetics and Determinant Criteria for the Preclusion of Multistationarity in Networks of Interacting Species*

Carsten Wiuf[†] and Elisenda Feliu[†]

Abstract. We present determinant criteria for the preclusion of nondegenerate multiple steady states in networks of interacting species. A network is modeled as a system of ordinary differential equations in which the form of the species formation rate function is restricted by the reactions of the network and how the species influence each reaction. We characterize families of so-called power-law kinetics for which the associated species formation rate function is injective within each stoichiometric class and thus the network cannot exhibit multistationarity. The criterion for power-law kinetics is derived from the determinant of the Jacobian of the species formation rate function. Using this characterization, we further derive similar determinant criteria applicable to general sets of kinetics. The criteria are conceptually simple, computationally tractable, and easily implemented. Our approach embraces and extends previous work on multistationarity, such as work in relation to chemical reaction networks with dynamics defined by mass-action or noncatalytic kinetics, and also work based on graphical analysis of the interaction graph associated with the system. Further, we interpret the criteria in terms of circuits in the so-called DSR-graph.

Key words. influence specification, reaction network, monotone kinetics, Jacobian, degenerate, power-law

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1. Introduction. Networks of interacting species are used in many areas of science to represent the structural form of a dynamical system. This is particularly the case in systems biology and biochemistry, where biochemical reactions are represented in the form of a network. However, similar network structures are also used in ecology, cell biology, and epidemics, as well as outside the natural sciences, to describe the possible interactions between some species of interest. Common to these networks is that they consist of a set of species and a set of interactions among the species. The state of the system is given by the concentration (or abundance) of each species, and each interaction represents a transformation of the state of the system. An example is the chemical reaction $A + B \rightarrow 2C$, where one molecule of A and one molecule of B form two molecules of C .

Typically, a system of ordinary differential equations (ODEs) is used to describe how species concentrations change over time. The species formation rate function of the system describes the instantaneous change in the concentrations when considering simultaneously the

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[†]Department of Mathematical Sciences, University of Copenhagen, Universitetsparken 5, 2100 Copenhagen, Denmark (wiuf@math.ku.dk, efeliu@math.ku.dk). The work of the first author was supported by the Lundbeck Foundation, Denmark, the Danish Research Councils, and the Leverhulme Trust, UK. The work of the second author was supported by the postdoctoral grant “Beatriu de Pinós” from the Generalitat de Catalunya, and by project MTM2012-38122-C03-01 from the Ministerio de Economía y Competitividad of the Spanish government.

individual rates of all reactions in the network. Reaction rates are generally unknown, but some qualitative aspects might be assumed or inferred. For instance, the presence of the species on the left side of a reaction (A, B in the above example) might be a prerequisite for the reaction to take place, and higher concentrations of these species typically lead to higher reaction rates. In some cases, reaction rates are fixed to follow a specific functional form that might depend on parameters to be inferred from experimental observations, in addition to the concentrations of the species. In other cases, only weak assumptions are imposed on the reaction rates and functions. We consider restrictions given by a so-called influence specification [38], which specifies how each species affects (positively, negatively, or neutrally) the reaction rates with increasing concentration. As pointed out by other authors [2], the full structure of the network (in particular, the reactions) is not required to develop the theory. We will, however, keep the terminology of reaction networks, as they provide the main source of inspiration and examples.

For many networks the structure of the interactions and the influence specification alone determine dynamical and steady-state properties of the system (for example, multistationarity, persistence, or oscillations). That is to say, irrespective of the rates and the parameters quantifying them, taken together with the initial species concentrations, the system shows qualitatively the same type of behavior. This is perhaps surprising, as the network structure itself does not encode any information about the specific rate functions and abundances. Even small networks might have many parameters which potentially could give rise to a rich and varied dynamics as well as differences in the long-term behavior of the system.

Of particular interest has been determining whether a system allows for multiple positive steady states, also known as multistationarity. Multistationarity provides a mechanism for switching (rapidly) between different responses and confers robustness to the steady-state values of the system [23, 29]. One way to address whether a system exhibits multistationarity is by finding the positive solutions to the steady-state equations of the system. Solving the equations might prove difficult, if not impossible, depending on the assumptions about the reactions rates and the number of parameters. Here we take a more conceptual route and focus on understanding the characteristics of networks that cannot exhibit multistationarity, irrespective of the specific choices of reaction rates.

Various criteria have been developed to preclude the existence of multiple positive steady states for general classes of reaction functions, also called kinetics, such as mass-action kinetics [16, 10, 9, 17, 15, 6, 7], noncatalytic kinetics [4], and weakly monotonic kinetics [38]. These criteria typically utilize the structure of the system together with some assumptions about the form of the rate functions. For example, for mass-action kinetics the rate functions are polynomials and the steady-state equations become a system of polynomial equations. Capitalizing on the polynomial form of the equations has led to specific conditions to preclude multistationarity [10, 9, 17, 32].

The aim of this paper is to provide a computationally tractable determinant criterion for *injectivity* of a network for different classes of kinetics. Injectivity refers to injectivity of the species formation rate function that governs the dynamical behavior of the system. If this function is injective for the allowed kinetics, then the system does not have the capacity for multiple positive steady states. The idea of injectivity was introduced by Craciun and Feinberg [9], but it also underlies previous work on the preclusion of multistationarity [40].

We show that injectivity of a network is closely related to injectivity of a network taken with *power-law kinetics* [22, 5]. Power-law kinetics generalize mass-action kinetics and confer greater flexibility to the form of the rate functions than do mass-action kinetics. Savageau [34] emphasizes the importance of power-law kinetics in biochemistry, but their importance outside biology for modeling purposes is also well documented [1, 41]. It can be argued that power-law kinetics provide approximations to kinetics in general [34], which is also exemplified in our work.

Power-law kinetics share common features with mass-action kinetics, and parallel results can be derived for the two types of kinetics. We derive necessary and sufficient *determinant criteria* for a network to be injective over different classes of power-law kinetics. The determinant refers to the determinant of a *modified* version of the species formation rate function (Definition 6.1 in this paper). We show that the determinant of the Jacobian of the modified function is nonzero for all concentration vectors and kinetics in one of the classes if and only if the network is injective over the particular class. For power-law kinetics our results extend parallel results for mass-action kinetics [17]. We proceed to show that injectivity over the class of all power-law kinetics compatible with an influence specification is equivalent to injectivity over the class of all kinetics that respect the same influence specification. Therefore, we obtain determinant criteria to preclude the existence of multiple steady states for all kinetics that respect the influence specification *independently of the specific functional form of the kinetics* (Theorem 10.1). The criteria depend in part on the network structure and in part on the influence specification.

The criteria are easily implemented using symbolic software packages, such as Mathematica, Maple, or SAGE, and thus they are of practical use. We present two equivalent criteria: one involving the computation of a symbolic determinant, and the other involving the computation of minors of numerical matrices. For moderately sized networks the criteria are computationally efficient, and the first is usually faster. For larger networks memory restrictions might constrain the computation of the symbolic determinant, and time restrictions might constrain the computation using the minors. Being based on the computation of determinants, the criteria can be reformulated in terms of circuits in a variant of the DSR-graph [3]. This might allow for the development of visual approaches to injectivity, in the style of [3, 2, 11, 39].

Our work extends and embraces previous determinant criteria developed for networks taken with mass-action kinetics [10, 9, 17, 12]. Further, it closely relates to recent work by Shinar and Feinberg [38], where a characterization of injective networks is provided for classes of kinetics defined by an influence specification (these networks are called concordant networks). Their definition of influence specification differs from the one adopted here, but it can be recovered in our context (section 12). Specifically, their definition corresponds to considering the union of certain classes of kinetics, rather than the classes individually. Instead of being determinant-based, the criteria in [38] are based on computing the signs of vectors in different sets, and hence the two approaches differ in nature. Further, the present work clarifies the role played by power-law kinetics in deciding injectivity.

In a series of papers [4, 3, 2], the authors study injectivity of a certain class of kinetics (called noncatalytic kinetics) and of dynamical systems more generally. These articles tackle injectivity of so-called open networks (which contain all reactions of the form $S \rightarrow 0$, where

S is a species). We provide a discussion in section 13 of the relationship between our results and those in [4, 3, 2]. Finally, this work also relates to a criterion for multistationarity based on the interaction graph given by Kaufman, Soulé, and Thomas [27] and by Soulé [40]. The interaction graph records the sign of the entries in the Jacobian of a dynamical system. In section 14, we relate our determinant criterion to that of [27, 40].

The structure of the paper is the following. In section 2 we introduce some notation, in section 3 we introduce the basic concepts of networks and kinetics, and section 4 presents the general form of the dynamical systems we consider. Section 5 is concerned with some useful theoretical matrix results, and section 6 introduces the notion of degeneracy and injectivity, two key concepts. Sections 7 and 8 focus on power-law kinetics and derive a determinant criterion for injectivity. In section 9, we discuss influence specifications, give examples from the literature, and derive further results on injectivity for families of power-law kinetics. These results are extended in section 10 to broader and more general classes of kinetics. In section 11 we develop a graph-theoretical interpretation of our criteria. Sections 12, 13, and 14 are devoted to the relationship between our work and previous work [38, 4, 2, 27]. Finally, in section 15, we show that other types of kinetics could be used in place of power-law kinetics. To keep the exposition clear in the main text, all proofs are in the appendix.

2. Notation. Let \mathbb{R}_+ denote the set of positive real numbers (without zero), and $\overline{\mathbb{R}}_+$ the set of nonnegative real numbers (with zero). Similarly, let $\overline{\mathbb{N}}$ be the set of nonnegative integers. Given a finite set \mathcal{E} , the ring of polynomials in \mathcal{E} is denoted $\mathbb{R}[\mathcal{E}]$. The total degree of a monomial $\prod_{E \in \mathcal{E}} E^{n_E}$, with n_E a nonnegative integer for all E , is the sum of the degrees of the variables, $\sum_{E \in \mathcal{E}} n_E$. The degree of a polynomial is the maximum of the total degrees of its monomials.

If a polynomial p vanishes for all assignments $a: \mathcal{E} \rightarrow \mathbb{R}_+$, then $p = 0$ identically. Further, if p is a nonzero polynomial in $\mathbb{R}[\mathcal{E}]$ such that the degree of each variable in each monomial is either 1 or zero, then all the coefficients of p are nonnegative if and only if $p(a(\mathcal{E})) > 0$ for any assignment $a: \mathcal{E} \rightarrow \mathbb{R}_+$. If this is not the case, then there is an assignment such that $p(a(\mathcal{E})) = 0$.

For vectors $u = (u_1, \dots, u_m) \in \mathbb{R}^m$ and $v = (v_1, \dots, v_m) \in \mathbb{R}^m$, we let $u \wedge v$ be the componentwise minimum, $(u \wedge v)_i = \min(u_i, v_i)$, and let

$$v_+ = (\max(v_1, 0), \dots, \max(v_m, 0)) \quad \text{and} \quad v_- = (\min(v_1, 0), \dots, \min(v_m, 0))$$

be the positive and negative parts of v . The support of v is defined as the set of indices for which v is nonzero, $\text{supp}(v) = \{i | v_i \neq 0\}$. The positive support of v is $\text{supp}^+(v) = \text{supp}(v_+)$, and the negative support is $\text{supp}^-(v) = \text{supp}(v_-)$. Let v^t denote the transpose of v , and $u \cdot v$ the usual scalar product in \mathbb{R}^n .

For every $x \in \mathbb{R}$, we let $\text{sign}(x) \in \{-, 0, +\}$ be defined as

$$\text{sign}(x) = \begin{cases} - & \text{if } x < 0, \\ 0 & \text{if } x = 0, \\ + & \text{if } x > 0. \end{cases}$$

Signs are multiplied using the usual rules. If σ is a sign and $x \in \mathbb{R}$, then $\sigma \cdot x$ is 0 if $\sigma = 0$ and $\pm x$ if $\sigma = \pm$, respectively.

We let $\#B$ denote the cardinality of a finite set B .

3. Motivation: Networks as dynamical systems. In this section we introduce networks and kinetics, and associate a dynamical system with a network and a kinetics. The definition of a network is identical to that of a chemical reaction network, which is used mainly in (bio)chemistry to describe networks of (bio)chemical reactions [14]. In general we use the nomenclature that is standard for chemical reaction networks. See, for instance, [22, 14, 16] for background and extended discussions.

Definition 3.1. A network \mathcal{N} consists of three finite sets:

- (1) A set $\mathcal{S} = \{S_1, \dots, S_n\}$ of species.
- (2) A set $\mathcal{C} \subset \overline{\mathbb{N}}^n$ of complexes.
- (3) A set $\mathcal{R} = \{r_1, \dots, r_m\} \subset \mathcal{C} \times \mathcal{C}$ of reactions such that $(y, y) \notin \mathcal{R}$ for all $y \in \mathcal{C}$ and if $y \in \mathcal{C}$, then there exists $y' \in \mathcal{C}$ such that either $(y, y') \in \mathcal{R}$ or $(y', y) \in \mathcal{R}$. A network is denoted by $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$.

We use the convention that an element $r_j = (y_j, y'_j) \in \mathcal{R}$ is denoted by $r_j: y_j \rightarrow y'_j$. The *reactant* and the *product* (complexes) of a reaction $r_j: y_j \rightarrow y'_j$ are y_j and y'_j , respectively. By definition, any complex is either the reactant or the product of some reaction. The zero complex $0 \in \mathcal{C}$ is allowed by definition. A reaction $S_i \rightarrow 0$, $S_i \in \mathcal{S}$, is called an *outflow reaction*.

Throughout the paper, we use n to denote the number of species in \mathcal{S} . The species S_i is identified with the i th canonical n -tuple of $\overline{\mathbb{N}}^n$ with 1 in the i th position and zeroes elsewhere. Accordingly, a complex $y \in \mathcal{C}$ is given as $y = \sum_{i=1}^n y_i S_i$ or (y_1, \dots, y_n) . We assume that $y \in \overline{\mathbb{N}}^n$, as reactions typically involve integer numbers of species. However, the results presented in this paper hold generally for $y \in \overline{\mathbb{R}}^n$. In examples we will often use other letters than S_i for species to ease the presentation. Generally, we use i to denote a species index, and j to denote a reaction index.

Example 3.2. Enzyme biology provides a rich source of examples. For instance, consider the network with set of biochemical species $\mathcal{S} = \{S_1, S_2, S_3, S_4\}$, set of complexes $\{S_1 + S_2, S_1 + S_3, S_2, S_3, S_4\}$, and reactions



That is, the reactions are $r_1: S_1 + S_2 \rightarrow S_4$, $r_2: S_4 \rightarrow S_1 + S_3$, $r_3: S_4 \rightarrow S_1 + S_3$, and $r_4: S_3 \rightarrow S_2$. This network assumes the Michaelis–Menten enzyme mechanism, in which a substrate S_2 is modified into a substrate S_3 through the formation of an intermediate S_4 [8]. The reaction is catalyzed by an enzyme S_1 . The modification can be reversed via a direct demodification reaction.

Reactions in a network are schematic representations of dynamical processes. Over time the concentrations or abundances of the species in the network change as a consequence of the reactions. In order to describe the dynamical properties of the network, we introduce a kinetics (Definition 3.3) and the species formation rate function (Definition 3.6). The kinetics provides the reaction rate for given species concentrations, and the species formation rate function the instantaneous change in the concentrations when considering simultaneously the rate of all reactions.

Definition 3.3. A kinetics for a network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is an assignment to each reaction $r_j \in \mathcal{R}$ of a rate function $K_j: \Omega_K \rightarrow \overline{\mathbb{R}}_+$, where Ω_K is a set such that $\mathbb{R}_+^n \subseteq \Omega_K \subseteq \overline{\mathbb{R}}_+^n$,

$c \wedge d \in \Omega_K$ whenever $c, d \in \Omega_K$, and

$$K_j(c) \geq 0 \quad \text{for all } c \in \Omega_K.$$

A kinetics for a network \mathcal{N} is denoted by $K = (K_1, \dots, K_m): \Omega_K \rightarrow \overline{\mathbb{R}}_+^m$. If K_j is differentiable for all $j = 1, \dots, m$ and $c \in \mathbb{R}_+^n$, then K is said to be a differentiable kinetics.

Example 3.4. Let $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be the network with $\mathcal{S} = \{S_1, S_2, S_3\}$, $\mathcal{C} = \{S_1 + S_2, S_3\}$, and \mathcal{R} given by the reaction $r_1: S_1 + S_2 \rightarrow S_3$. The kinetics $K \in \mathcal{K}(\mathcal{N})$ defined by $K_1(c) = kc_1/((\beta + c_1)c_2^\alpha)$, where k, α, β are positive constants, has $\Omega_K = \overline{\mathbb{R}} \times \mathbb{R}_+ \times \overline{\mathbb{R}}_+$.

Example 3.5. Kinetics commonly used in chemistry and biology are the so-called mass-action kinetics. These were introduced by Guldberg and Waage in the 19th century based on the ideal assumption that the rate of a reaction is proportional to the product of the concentrations of the reactant species [8]. Specifically, each reaction $r_j: y_j \rightarrow y'_j$ is assigned a positive constant $k_j \in \mathbb{R}_+$, and the rate function for the reaction is given by

$$K_j(c) = k_j \prod_{i=1}^n c_i^{y_{j,i}}$$

with $\Omega_K = \overline{\mathbb{R}}_+^n$, $K = (K_1, \dots, K_m)$. We adopt the convention that $0^0 = 1$. Under in vivo conditions, however, the use of mass-action kinetics might not be fully justified. Reactant species might not form a homogeneous mixture, for instance because they appear in insufficient concentrations or because their distribution depends on spatial constraints. In situations in which the use of mass-action is not justified, the use of other types of kinetics such as *power-law kinetics* or *Hill-type kinetics* is often preferred. These will be introduced later. Note that $K_j(c)$ is an increasing function in c_i and does not depend on species other than those involved in y_j .

The *stoichiometric matrix* A is defined as the $n \times m$ matrix whose j th column is $y'_j - y_j$.

Definition 3.6. The species formation rate function for a network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with kinetics K and stoichiometric matrix A is the map $f_{A,K}: \Omega_K \rightarrow \Gamma$ defined by

$$f_{A,K}(c) = AK(c) = A \begin{pmatrix} K_1(c) \\ \vdots \\ K_m(c) \end{pmatrix} = \sum_{j=1}^m K_j(c)(y'_j - y_j).$$

The dynamics of a network \mathcal{N} with kinetics K and stoichiometric matrix A is described by a set of ODEs given by the species formation rate function:

$$(3.1) \quad \dot{c} = f_{A,K}(c),$$

where $\dot{c} = \dot{c}(t)$ denotes the derivative of $c(t)$ with respect to t . Observe that the image of $f_{A,K}$ is contained in $\text{Im}(A)$, and hence the dynamics of the system is confined to invariant linear spaces of the form $c + \text{Im}(A)$. In other words, for any $\omega \in \text{Im}(A)^\perp$ we have that $\omega \cdot \dot{c} = 0$. Therefore, $\omega \cdot c$ is independent of time and determined by the initial concentrations of the system. The value of $\omega \cdot c$ is called a *conserved amount*.

In this context, $\text{Im}(A)$ is called the *stoichiometric space*. Two vectors $c, c' \in \mathbb{R}^n$ are called *stoichiometrically compatible* if $\omega \cdot c = \omega \cdot c'$ for all $\omega \in \text{Im}(A)^\perp$, and c, c' are said to be in the

same *stoichiometric class*, $c + \text{Im}(A)$. We let s be the rank of A , and thus the dimension of $\text{Im}(A)^\perp$ is $d = n - s$.

The *steady states* of the network are the solutions to the system of equations in c_1, \dots, c_n obtained by setting the derivatives of the concentrations to zero:

$$0 = f_{A,K}(c).$$

This system of equations is referred to as the steady-state equations. In particular, we are interested in the positive steady states, that is, the solutions c to the steady-state equations such that all concentrations are positive, $c \in \mathbb{R}_+^n$.

Example 3.7. The stoichiometric matrix of Example 3.2 is

$$(3.2) \quad A = \begin{pmatrix} -1 & 1 & 1 & 0 \\ -1 & 1 & 0 & 1 \\ 0 & 0 & 1 & -1 \\ 1 & -1 & -1 & 0 \end{pmatrix}$$

and has rank $s = 2$. A basis of $\text{Im}(A)^\perp$ is $\{\omega^1, \omega^2\}$ with

$$(3.3) \quad \omega^1 = (1, 0, 0, 1), \quad \omega^2 = (0, 1, 1, 1).$$

If K is any kinetics, then the corresponding system of ODEs is

$$\begin{pmatrix} \dot{c}_1 \\ \dot{c}_2 \\ \dot{c}_3 \\ \dot{c}_4 \end{pmatrix} = \begin{pmatrix} -1 & 1 & 1 & 0 \\ -1 & 1 & 0 & 1 \\ 0 & 0 & 1 & -1 \\ 1 & -1 & -1 & 0 \end{pmatrix} \begin{pmatrix} K_1(c) \\ K_2(c) \\ K_3(c) \\ K_4(c) \end{pmatrix} = \begin{pmatrix} -K_1(c) + K_2(c) + K_3(c) \\ -K_1(c) + K_2(c) + K_4(c) \\ K_3(c) - K_4(c) \\ K_1(c) - K_2(c) - K_3(c) \end{pmatrix}.$$

Observe that $\dot{c}_1 + \dot{c}_4 = \dot{c}_2 + \dot{c}_3 + \dot{c}_4 = 0$ for any kinetics K .

4. Dynamical systems admitting a factorization. Dynamical systems arising from reaction networks in the way specified above have a specific form; that is, the species formation rate function factors as the product of a matrix A and a function vector $K: \Omega_K \rightarrow \overline{\mathbb{R}}_+^m$.

Any dynamical system $\dot{c} = f(c)$ such that $f(c)$ admits a factorization of the same form, $f(c) = AK(c)$, can be interpreted as arising from a network with stoichiometric matrix A . The reactions are, however, not uniquely given by A and might not have a physical interpretation.

Example 4.1. Savageau [33] considers a model of microbial growth with ODE system

$$\begin{aligned} \dot{c}_1 &= \alpha_1 c_1 c_2 c_3^{-1} - c_1, & \dot{c}_2 &= c_4 - \beta_2 c_1 c_2 c_3^{-1}, \\ \dot{c}_3 &= c_4 - \beta_2 c_1 c_2 c_3^{-1}, & \dot{c}_4 &= \beta_2 c_1 c_2 c_3^{-1} - c_4, \end{aligned}$$

where $\alpha_1, \beta_2 > 0$. It can be written as

$$\begin{pmatrix} \dot{c}_1 \\ \dot{c}_2 \\ \dot{c}_3 \\ \dot{c}_4 \end{pmatrix} = \begin{pmatrix} 0 & 0 & 1 & -1 \\ -1 & 1 & 0 & 0 \\ -1 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \end{pmatrix} \begin{pmatrix} \beta_2 c_1 c_2 c_3^{-1} \\ c_4 \\ \alpha_1 c_1 c_2 c_3^{-1} \\ c_1 \end{pmatrix}.$$

It can, for example, be interpreted as a network with reactions $S_2 + S_3 \rightleftharpoons S_4, 0 \rightleftharpoons S_1$.

We study the steady states of dynamical systems of the form $\dot{c} = AK(c)$ for a fixed $n \times m$ matrix A but with a variable kinetics $K(c)$. In order to simplify the notation, we use f_K to denote $f_{A,K}$ whenever there is no confusion. The dynamics of the system $\dot{c} = AK(c)$ takes place in an invariant stoichiometric class given by the initial concentrations of the system. Hence, the relevant dynamical properties, such as multistationarity, need to be inspected inside each stoichiometric class.

The main examples come from reaction networks, and we keep the nomenclature introduced in the previous section. Even though the physical interpretation might be vague, we call K a kinetics, call A the stoichiometric matrix, and use the definitions introduced in the previous section. We let $\mathcal{K}_{m,n}$ denote the set of kinetics $K: \Omega_K \rightarrow \overline{\mathbb{R}}_+^m$ for some $\Omega_K \subseteq \overline{\mathbb{R}}_+^n$ and let $\mathcal{K}_{m,n}^d \subset \mathcal{K}_{m,n}$ be the set kinetics that are continuous on Ω_K and differentiable on \mathbb{R}_+^n .

For any differentiable function $f = (f_1, \dots, f_q): \Omega \rightarrow \mathbb{R}^q$ defined on a set Ω including \mathbb{R}_+^m , we let $J_c(f)$ denote the Jacobian of f at $c \in \mathbb{R}_+^m$, that is, the $q \times m$ matrix with entry (j, i) being $\partial f_j(c)/\partial c_i$. If K is a differentiable kinetics, then the Jacobian matrix $J_c(f_K)$ factorizes as the product of two matrices:

$$(4.1) \quad J_c(f_K) = A(\partial K),$$

where $(\partial K) = (\partial K)(c)$ is the $m \times n$ matrix such that $(\partial K)_{j,i} = \partial K_j(c)/\partial c_i$.

Graphical conditions on the preclusion of multistationarity for dynamical systems for which the Jacobian can be decomposed as the product of two matrices (not necessarily of the form given here) have been studied in [3].

5. Some matrix-theoretical results. Let M be an $n \times n$ matrix, and let F be an s -dimensional vector space that contains the space generated by the columns of M . Let F^\perp be the space orthogonal to F , which has dimension $d = n - s$.

Definition 5.1. A basis $\{\omega^1, \dots, \omega^d\}$ of F^\perp with $\omega^i = (\lambda_1^i, \dots, \lambda_n^i)$ is said to be reduced if $\lambda_i^i = 1$ for all i and $\lambda_j^i = 0$ for all $j = 1, \dots, \hat{i}, \dots, d$.

After reordering of the coordinates of \mathbb{R}^n , if necessary, such a basis always exists and is unique. Let \widetilde{M} be the $n \times n$ matrix whose top d rows are $\omega^1, \dots, \omega^d$ and whose bottom s rows agree with the bottom s rows of M . We view M as a linear map from \mathbb{R}^n to \mathbb{R}^n and let $\ker(M)$ be the kernel of this map.

Proposition 5.2. Let M, F be as above. Let $\{\omega^1, \dots, \omega^d\}$ be a reduced basis of F^\perp , and \widetilde{M} the corresponding matrix. Then

$$\ker(M) \cap F = \{0\} \quad \text{if and only if} \quad \det(\widetilde{M}) \neq 0.$$

For any $n \times m$ matrix B , and sets $I \subseteq \{1, \dots, n\}$ and $J \subseteq \{1, \dots, m\}$, we let $B_{I,J}$ denote the submatrix of B with entries of B with indices (i, j) in (I, J) .

Proposition 5.3. Let M be an $n \times n$ matrix. Using the notation above, we have

$$\det(\widetilde{M}) = \sum_{I \subseteq \{1, \dots, n\}, \#I=s} \det(M_{I,I}).$$

If $M \not\subseteq F$, then both sides of the equality are zero, because the rank of M is strictly smaller than s . In our applications, F will be $\text{Im}(A)$, and M will be $J_c(f_K) = A(\partial K)$. In this

case, using the Cauchy–Binet formula on the minors of a product of matrices, we have that

$$(5.1) \quad \det(\widetilde{M}) = \sum_{I, J \subseteq \{1, \dots, n\}, \#I = \#J = s} \det(A_{I, J}) \det((\partial K)_{J, I}).$$

6. Degenerate steady states and injectivity. In this section some key concepts and definitions are introduced, namely those of degeneracy of a steady state and injectivity of a matrix. Denote the components of the species formation rate function by $f_K = (f_{K,1}, \dots, f_{K,n})$. Note that after reordering of the rows of a matrix A , if necessary, a reduced basis of $\text{Im}(A)^\perp$ always exists and is unique. Therefore, from now on, we assume that the rows of A are ordered such that a reduced basis exists.

Definition 6.1. Let A be an $n \times m$ matrix of rank s , and $\{\omega^1, \dots, \omega^d\}$ the reduced basis of $\text{Im}(A)^\perp$. If $K \in \mathcal{K}_{m,n}$ is a kinetics, then the associated extended rate function $\widetilde{f}_K: \Omega_K \rightarrow \mathbb{R}^n$ is the function defined by

$$\widetilde{f}_K(c) = (\omega^1 \cdot c, \dots, \omega^d \cdot c, f_{K,d+1}(c), \dots, f_{K,n}(c)).$$

Example 6.2. The basis of $\text{Im}(A)^\perp$ provided for Example 3.2 in (3.3) is reduced. The associated extended rate function $\widetilde{f}_K: \Omega_K \rightarrow \mathbb{R}^4$ for any kinetics K is

$$\widetilde{f}_K(c) = (c_1 + c_4, c_2 + c_3 + c_4, K_3(c) - K_4(c), K_1(c) - K_2(c) - K_3(c)).$$

Definition 6.3. Let $\dot{c} = AK(c)$ be a dynamical system such that K is a differentiable kinetics. A steady state $c \in \mathbb{R}_+^n$ of the system is degenerate if $\ker(J_c(f_K)) \cap \text{Im}(A) \neq \{0\}$.

That is, a steady state is degenerate if the Jacobian restricted to the stoichiometric subspace $\text{Im}(A)$ is nonsingular. Using the constructions in section 5 with $F = \text{Im}(A)^\perp$, we have that

$$(6.1) \quad \ker(J_c(f_K)) \cap \Gamma = \{0\} \quad \text{if and only if} \quad \det(J_c(\widetilde{f}_K)) \neq 0.$$

It follows that a steady state $c \in \mathbb{R}_+^n$ is degenerate if and only if $\det(J_c(\widetilde{f}_K)) = 0$. The Jacobian of \widetilde{f}_K has a natural interpretation as the flow of the dynamical system projected onto the stoichiometric space [21].

Finally, we introduce the notion of injectivity.

Definition 6.4. Let A be an $n \times m$ matrix and $\mathcal{K}_0 \subseteq \mathcal{K}_{m,n}$.

- (i) We say that A is injective over \mathcal{K}_0 if for any pair of distinct stoichiometrically compatible vectors $a, b \in \mathbb{R}_+^n$ we have $AK(a) \neq AK(b)$ for all $K \in \mathcal{K}_0$.
- (ii) The matrix A is said to have the capacity for multiple positive steady states over \mathcal{K}_0 if there exists a kinetics $K \in \mathcal{K}_0$ and distinct stoichiometrically compatible vectors $a, b \in \mathbb{R}_+^n$ such that $AK(a) = AK(b) = 0$.

Note that being injective is equivalent to requiring that the function \widetilde{f}_K be injective over \mathbb{R}_+^n for all $K \in \mathcal{K}_0$. Clearly, if A is injective over \mathcal{K}_0 , then A does not have the capacity for multiple steady states over \mathcal{K}_0 and, thus, (i) implies (ii) in Definition 6.4.

Remark 6.5. If A is the stoichiometric matrix of a network \mathcal{N} , we say that the network \mathcal{N} is injective, and also that the network \mathcal{N} has the capacity for multiple steady states if it is the case for A .

The aim is to provide a criterion for a matrix A to be injective over a set of kinetics \mathcal{K}_0 in terms of computationally tractable quantities. To this end we introduce the class of power-law kinetics (defined in section 7) and derive some injectivity results for classes of power-law kinetics using techniques introduced in [17].

7. Power-law kinetics. Power-law kinetics form a large family of kinetics [22]. They are generalizations of mass-action kinetics and are based on a power-law formalism. Their general form makes them flexible for modeling purposes in many areas of science such as chemistry, ecology, and epidemics. Furthermore, these kinetics are important in the study of injectivity in that they, in some sense, are “dense” in the set of kinetics that are strictly monotonic or constant in each concentration (to be made precise in section 10). That is to say, injectivity of a matrix A over certain sets of kinetics can be determined on the basis of injectivity of A over suitable sets of power-law kinetics.

In this section we introduce power-law kinetics. Dynamical systems with power-law kinetics have properties that are very similar to those with mass-action kinetics, and similar results regarding injectivity can be derived for power-law kinetics as for mass-action kinetics themselves.

With a concentration vector c and $v \in \mathbb{R}^n$ we associate the power law $c^v = \prod_{i=1}^n c_i^{v_i}$. For example, if $v = (2.1, 0.72, 0, -1) \in \mathbb{R}^4$, then the associated power law is $c^v = c_1^{2.1} c_2^{0.72} c_4^{-1}$. A power law is well defined for all $c \in \overline{\mathbb{R}}_+^n$ such that $c_i > 0$ if $v_i < 0$.

Definition 7.1. A kinetics $K \in \mathcal{K}_{m,n}$ is a power-law kinetics if

$$K_j(c) = k_j c^{v_j} \quad \text{for } j = 1, \dots, m,$$

with $k_j \in \mathbb{R}_+$ and $v_j \in \mathbb{R}^n$. Here Ω_K is the maximal common domain of definition of the power laws c^{v_j} , $j = 1, \dots, m$, in the positive orthant.

Thus, a power-law kinetics is defined by an $m \times n$ matrix V with rows v_j , $j = 1, \dots, m$. The matrix V is called the kinetic order, and $\kappa = (k_1, \dots, k_m)$ the rate vector. The scalar k_j is the rate constant of reaction j . For simplicity, we identify the pair (κ, V) with the kinetics K . We let $\mathcal{K}_{m,n}^g[V]$ denote the set of power-law kinetics (κ, V) with arbitrary κ but fixed V .

Note that k_j is a scalar while v_j is a vector. By definition, power-law kinetics are differentiable kinetics. Given a network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with n species and m reactions, mass-action kinetics are special types of power-law kinetics obtained by considering the kinetic order with $v_j = y_j$ for all j . Therefore, if we let $Y = (y_1, \dots, y_m)$, then the set of mass-action kinetics for a network \mathcal{N} is $\mathcal{K}_{m,n}^g[Y]$.

Example 7.2. Consider Example 3.2 with the reduced basis given in (3.3). A kinetic order is given as

$$(7.1) \quad V = \begin{pmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ v & 0 & 1 & 0 \end{pmatrix}, \quad v \geq 0.$$

When $v = 0$, the kinetic order corresponds to mass-action. If $v > 0$, then the kinetic order V accounts for the hypothetical fact that the concentration of the modification enzyme S_1 acts

as an enhancer or inhibitor of the demodification of S_3 to S_2 , that is, of reaction r_4 . In the latter case, the kinetics is

$$K_1(c) = k_1 c_1 c_2, \quad K_2(c) = k_2 c_4, \quad K_3(c) = k_3 c_4, \quad K_4(c) = k_4 c_1^v c_3.$$

If, for instance, $v = 0.5$, then $K_4(c) = k_4 c_1^{0.5} c_3$, while if $v = -0.5$, then $K_4(c) = k_4 c_1^{-0.5} c_3$.

Example 7.3. After a suitable change of coordinates, ODE models of electrocatalytic oxidation of formic acid exhibit a power-law structure with a negative exponent. See, for instance, [37, Examples 1,2].

Example 7.4. S-systems provide a rich source of examples of modeling with power-law kinetics. Consider the model of the lac gene circuit developed by Savageau [35]. The model has five variables, c_1, \dots, c_5 , and the ODEs take the form

$$\begin{aligned} \dot{c}_1 &= \alpha_1 c_4^{v_1} - \beta_1 c_1^{v_2}, & \dot{c}_2 &= \alpha_2 c_1^{v_3} - \beta_2 c_2^{v_4}, & \dot{c}_3 &= \alpha_3 c_2^{v_5} - \alpha_4 c_2^{v_6} c_3^{v_7}, \\ \dot{c}_4 &= \alpha_4 c_2^{v_6} c_3^{v_7} - \alpha_5 c_2^{v_8} c_4^{v_9}, & \dot{c}_5 &= \alpha_5 c_2^{v_8} c_4^{v_9} - \alpha_7 c_5^{v_{10}} \end{aligned}$$

for some positive exponents v_* and positive constants α_*, β_* (see equation (1) in [35]). Similarly to Example 4.1, this ODE system factorizes as AK (see also Example 8.6).

Example 7.5. So-called SIR (S = susceptible, I = infected, R = recovered) models are standard in epidemiology to describe the outbreak of an epidemic in a population. One particular SIR model [1] considers the network with set of species $\{S, I, R\}$ and reactions



The first reaction says that a susceptible individual might become infected in the presence of an infected one. The second reaction says that infected individuals eventually recover. The SIR dynamics can be expressed in different ways. One possibility is the following set of differential equations [41]:

$$\dot{c}_1 = -k_1 c_1^\nu c_2, \quad \dot{c}_2 = k_1 c_1^\nu c_2 - k_2 c_2, \quad \dot{c}_3 = k_2 c_2,$$

where c_1, c_2, c_3 are the concentrations of the species S, I, R , respectively, and $k_1, k_2 > 0$, $\nu > 0$ are the parameters of the model. That is, $K_1(c) = k_1 c_1^\nu c_2$, and $K_2(c) = k_2 c_2$. The parameter ν accounts for inhomogeneity in population mixing. If $\nu = 1$, then the population is homogenous and the disease spreads according to the law of mass-action, whereas if $\nu \neq 1$, then the population is inhomogenous and the kinetics is a power-law kinetics. If ν is allowed to be negative, then susceptible individuals are repelled by infected individuals. Further, if we allow $\nu = 0$, then the spread of the disease would be independent of the number of infected individuals.

8. Injectivity for networks taken with power-law kinetics. In this section we provide criteria for a matrix to be injective with respect to the set of power-law kinetics with fixed kinetic order. If $K = (\kappa, V) \in \mathcal{K}_{m,n}$ is a power-law kinetics, then the species formation rate function is denoted by $f_K = f_{\kappa,V}$. If κ is not fixed, then the function $f_{\kappa,V}(c)$ can be seen as a polynomial function in the variables k_j for all j .

Theorem 8.1. *Let A be an $n \times m$ matrix and V an $m \times n$ kinetic order. Then the following are equivalent:*

- (i) A is injective over $\mathcal{K}_{m,n}^g[V]$.
- (ii) $\det(J_c(\tilde{f}_{\kappa,V})) \neq 0$ for all $c \in \mathbb{R}_+^n$ and $\kappa \in \mathbb{R}_+^m$.

The proof is similar to the one given in [17, Thm. 5.6] for mass-action kinetics and is thus omitted here. The following proposition provides an explicit description of $\det(J_c(\tilde{f}_{\kappa,V}))$. It is proven for mass-action kinetics in [17] using a different approach. The current proof is based on the general matrix results explained in section 5.

Proposition 8.2. *Let A be an $n \times m$ matrix of rank s , and V an $m \times n$ kinetic order. The determinant $\det(J_c(\tilde{f}_{\kappa,V}))$ is a homogeneous polynomial in $\kappa = (k_1, \dots, k_m)$ of total degree s and linear in each rate constant k_j .*

Further, let $J \subseteq \{1, \dots, n\}$ of cardinality s . The coefficient of the monomial $\prod_{j \in J} k_j$ in $\det(J_c(\tilde{f}_{\kappa,V}))$ for $c \in \mathbb{R}_+^n$ is

$$c^{-1 + \sum_{j \in J} v_j} \sum_{I \in \{1, \dots, n\}, \#I=s} \det(A_{I,J}) \det(V_{J,I}) \prod_{i \notin I} c_i.$$

Remark 8.3. The determinant is in general *not* a polynomial in V or in c because the coordinates of V enter the expressions as exponents of c . However, the determinant $\det(V_{J,I})$ is a polynomial function in the nonzero coordinates of v_j , $j \in J$, excluding the entries with indices not in I .

Proposition 8.4. *Let A be an $n \times m$ matrix of rank s , and V an $m \times n$ kinetic order. The following are equivalent:*

- (i) A is injective over $\mathcal{K}_{m,n}^g[V]$.
- (ii) The nonzero products $\det(A_{I,J}) \det(V_{J,I})$ have the same sign for all sets $I, J \subseteq \{1, \dots, n\}$ of cardinality s . Further, $\det(A_{I,J}) \det(V_{J,I}) \neq 0$ for at least one choice of I and J .

Example 8.5. Consider Example 3.2 and the kinetic order introduced in Example 7.2. We have

$$\det(J_c(\tilde{f}_{\kappa,V})) = (k_2 + k_3)k_4c_1^v c_4 + k_1k_3c_1c_4 + k_1k_4c_1^v(c_1 + vc_3 + c_2).$$

If $v \geq 0$, then all the terms of the determinant expansion have the same sign, and by Theorem 8.1 the network is injective over $\mathcal{K}_{m,n}^g[V]$. If, on the contrary, $v < 0$, then the term $t = vk_1k_4c_1^v c_3$ has sign opposite to the rest of the terms. It follows that the network is not injective over $\mathcal{K}_{m,n}^g[V]$ if $v < 0$. The term t corresponds to the sets $J = \{1, 4\}$ and $I = \{1, 2\}$. Indeed, for these sets we have (see (3.2) and (7.1))

$$V_{J,I} = \begin{pmatrix} 1 & 1 \\ v & 0 \end{pmatrix}, \quad A_{I,J} = \begin{pmatrix} -1 & 0 \\ -1 & 1 \end{pmatrix},$$

so that $\det(V_{J,I}) = -v$, $\det(A_{I,J}) = -1$, and $c^{-1 + \sum_{j \in J} v_j} \prod_{i \notin I} c_i = (c_1^v c_4^{-1})(c_3 c_4) = c_1^v c_3$. The sign of t depends on that of v , unless $v = 0$, in which case the term vanishes.

Example 8.6. Consider Example 7.4. The matrices A and V are

$$A = \begin{pmatrix} 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 \end{pmatrix}, \quad V = \begin{pmatrix} 0 & 0 & 0 & v_1 & 0 \\ v_2 & 0 & 0 & 0 & 0 \\ v_3 & 0 & 0 & 0 & 0 \\ 0 & v_4 & 0 & 0 & 0 \\ 0 & v_5 & 0 & 0 & 0 \\ 0 & v_6 & v_7 & 0 & 0 \\ 0 & v_8 & 0 & v_9 & 0 \\ 0 & 0 & 0 & 0 & v_{10} \end{pmatrix}.$$

The matrix A has maximal rank. The products $\det(A_{I,J}) \det(V_{J,I})$ are nonzero for the pairs (I, J) with $I = \{1, 2, 3, 4, 5\}$ and $J = \{1, 3, 5, 6, 8\}$, $\{1, 3, 6, 7, 8\}$, or $\{2, 4, 6, 7, 8\}$. For these pairs, the determinant products are

$$-v_1 v_3 v_7 v_8 v_{10}, \quad v_1 v_3 v_5 v_7 v_{10}, \quad -v_2 v_4 v_7 v_9 v_{10},$$

respectively. Since the terms do not have the same sign, it follows that for any choice of positive exponents v_ℓ the network is not injective.

9. Influence specifications. In the previous section we studied injectivity of the system $\dot{c} = AK(c)$, where K is a power-law kinetics with fixed kinetic order and varying rate constants. In the following sections we will study injectivity when K is not fixed but belongs to a general family of kinetics. The family is given by requiring that K fulfill certain monotonicity constraints, which are encoded by the sign-pattern of a matrix. When K is differentiable, the sign-pattern agrees with the sign-pattern of the Jacobian of K .

Definition 9.1. An $m \times n$ influence specification is a sign matrix $Z = (z_{j,i})$, that is, a matrix whose entries are the signs $+, -, 0$.

Let Z be an $m \times n$ influence specification. For $j = 1, \dots, m$, define

$$z_j^+ = \{i \mid z_{j,i} = +\}, \quad z_j^- = \{i \mid z_{j,i} = -\}, \quad z_j^0 = \{i \mid z_{j,i} = 0\}.$$

Two concentration vectors $a, b \in \overline{\mathbb{R}}_+^n$ are said to be *nonoverlapping with respect to Z*

$$\text{if } z_j^+ \not\subseteq \text{supp}(a) \text{ implies } z_j^+ \subseteq \text{supp}(b) \text{ for all } j.$$

That is, the coordinates a_i, b_ℓ (potentially with $i = \ell$) cannot both be zero if i, ℓ are both in z_j^+ for some j . When it is clear from the context what influence specification we are referring to, we omit “with respect to Z ” and just say that a, b are nonoverlapping. Nonoverlapping is a concept that specifies how two concentration vectors on the boundary of the positive orthant are positioned with respect to each other in relation to an influence specification Z . In particular, if one or both of the concentration vectors a, b are positive, then they are nonoverlapping.

9.1. Strictly monotone kinetics. We start with a definition.

Definition 9.2. A kinetics $K \in \mathcal{K}_{m,n}$ respects an $m \times n$ influence specification Z if, for all $c \in \Omega_K$,

$$K_j(c) > 0 \text{ if and only if } z_j^+ \subseteq \text{supp}(c) \text{ for all } j.$$

Let $\Omega_K(z_j^+) := \{c \in \Omega_K \mid z_j^+ \subseteq \text{supp}(c)\} = \{c \in \Omega_K \mid K_j(c) \neq 0\}$ denote the set of concentration vectors for which the kinetics K_j does not vanish.

Definition 9.3. Let $K \in \mathcal{K}_{m,n}$ be a kinetics that respects an $m \times n$ influence specification Z . We say that K is strictly monotonic with respect to Z if for all $j = 1, \dots, m$ and $i = 1, \dots, n$, the restriction of the function $K_j(\cdot)$ to $\Omega_K(z_j^+)$ is

- (i) strictly increasing in c_i if $i \in z_j^+$,
- (ii) strictly decreasing in c_i if $i \in z_j^-$,
- (iii) constant in c_i if $i \in z_j^0$.

Let $\mathcal{K}_{m,n}(Z)$ denote the set of kinetics that are strictly monotonic with respect to the influence specification Z .

The definition says that the rate functions K_j are strictly monotonic or constant in the coordinate c_i whenever the remaining coordinates take positive values for the species with positive influence. Strictly monotonic refers to the kinetics, but this does not imply that the species formation rate function is monotone.

Example 9.4. The length of a larvae is often assumed to increase linearly with a slow-down in the growth rate as the length increases. Denoting by c the length of the larvae, one model of the length is $\dot{c} = \alpha_1(\alpha_2 + c)$, where α_1, α_2 are positive constants. In this system, $n = m = 1$ and $A = (1)$. The kinetics $K_1(c) = \alpha_1/(\alpha_2 + c)$ is strictly monotonic with respect to the influence specification given by $Z = (-)$.

The following lemma shows how Definition 9.3 can be stated in the terminology of [38]. We will use this characterization again in section 12.

Lemma 9.5. *Let $K \in \mathcal{K}_{m,n}$ be a kinetics that respects an $m \times n$ influence specification Z . Then, K is strictly monotonic with respect to Z if and only if for each pair of nonoverlapping concentration vectors $a, b \in \Omega_K$, the following implications hold for all j :*

- (i) *if $K_j(a) > K_j(b)$, then $\text{sign}(a_i - b_i) = z_{j,i} \neq 0$ for some i ;*
- (ii) *if $K_j(a) = K_j(b)$, then either $a_i = b_i$ for all $i \in z_j^+ \cup z_j^-$ or $\text{sign}(a_i - b_i) = z_{j,i} \neq 0$ and $\text{sign}(a_\ell - b_\ell) = -z_{j,\ell} \neq 0$ for some distinct i, ℓ .*

Example 9.6. A standard model of population growth [30] is

$$(9.1) \quad \dot{c} = rc \left(1 - \frac{c}{D}\right),$$

where c denotes the size of a population S and r, D are positive constants. The system factorizes as AK with $A = (1, -1)$ and $K = (rc, rc^2/D)$. The kinetics is strictly monotonic with respect to $Z = (+, +)^t$. The system has a stable steady state at $c = K$ and an unstable steady state at $c = 0$. The two steady states are nonoverlapping with respect to Z .

Definition 9.7. *A kinetics $K \in \mathcal{K}_{m,n}$ is differentiable with respect to an $m \times n$ influence specification Z if K respects Z and, for every j , $K_j(\cdot)$ is continuous at $c \in \Omega_K$, differentiable at $c \in \mathbb{R}_+^n$, and for each index i the partial derivative $\frac{\partial K_j}{\partial c_i}(c)$ has constant sign*

$$z_{j,i} = \text{sign} \left(\frac{\partial K_j}{\partial c_i}(c) \right)$$

in \mathbb{R}_+^n . Let $\mathcal{K}_{m,n}^d(Z)$ denote the set of kinetics that are differentiable with respect to the influence specification Z .

Note that $\mathcal{K}_{m,n}^d(Z)$ is not the intersection of $\mathcal{K}_{m,n}(Z)$ with $\mathcal{K}_{m,n}^d$, as we require the sign of the partial derivatives to be constant in Definition 9.7, which is not implied by being strictly monotonic and differentiable. We state the following result without proof.

Lemma 9.8. *If $K \in \mathcal{K}_{m,n}^d(Z)$, then $K \in \mathcal{K}_{m,n}(Z)$.*

Example 9.9. Consider Example 4.1. The kinetics is strictly monotone with respect to the influence specification given by

$$Z = \begin{pmatrix} + & + & - & 0 \\ 0 & 0 & 0 & + \\ + & + & - & 0 \\ + & 0 & 0 & 0 \end{pmatrix}.$$

The matrix Z is simply the sign pattern of the Jacobian of K .

Example 9.10. Jacob and Monod [24] proposed a model for bacterial uptake of nutrients in microbial ecology. The modeling equations are

$$\dot{c}_1 = \frac{\alpha c_1 c_2}{\beta + c_2} \quad \text{and} \quad \dot{c}_2 = -\frac{\alpha c_1 c_2}{\gamma(\beta + c_2)},$$

where α, β, γ are positive parameters and c_1, c_2 are the concentrations of two species, S_1, S_2 . The species S_1 is a bacterium that feeds on a (chemical) nutrient S_2 . The species formation rate function factorizes as $AK(c)$ with

$$A = \begin{pmatrix} 0 & -1 \\ 1 & 0 \end{pmatrix} \quad \text{and} \quad K = \left(\frac{\alpha c_1 c_2}{\beta + c_2}, \frac{\alpha c_1 c_2}{\gamma(\beta + c_2)} \right).$$

The kinetics is strictly monotonic with respect to the influence specification Z with $+$ in all entries. All steady states have $c_1 = 0$ or $c_2 = 0$. Hence two steady states are nonoverlapping with respect to Z if at least one of them is strictly positive. Further, all steady states are degenerate.

9.2. Networks and influence specifications. The term ‘‘influence specification’’ comes from interpreting a dynamical system as a network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with species S_i and reactions r_j . Since the influence specification indicates the behavior of K_j with respect to each variable, the species S_i with $z_{j,i} \neq 0$ influence the reaction r_j . The species with $z_{j,i} = +$ are assumed to have positive influence or enhance the reaction, while those with $z_{j,i} = -$ are assumed to have negative influence and an inhibitory effect on the reaction. Those with $z_{j,i} = 0$ have neutral influence. A reaction can only occur if all species with positive influence on the reaction are present (that is, they are in positive concentrations). If one species is not present, then the reaction cannot occur. Absence of species with negative or neutral influence does not prevent the reaction from taking place.

Given a network, we define the following special influence specifications:

- The *complex dependent influence specification*, denoted by $Z_{\mathcal{C}}$, is defined as the influence specification with $z_{j,i} = +$ for $i \in \text{supp}(y_j)$ and zero otherwise.
- The *reaction dependent influence specification*, denoted by $Z_{\mathcal{R}}$, is defined as the influence specification with $z_{j,i} = \text{sign}(y_{j,i} - y'_{j,i})$.

Note that any mass-action kinetics K belongs to $\mathcal{K}_{m,n}^d(Z_{\mathcal{C}})$.

It is sometimes useful to illustrate an influence specification with a labeled bipartite graph with node set $\mathcal{S} \cup \mathcal{R}$. We draw a positive edge between a species and a reaction if the species has positive influence over the reaction. We draw a negative edge if the species has negative influence on the reaction. Example 3.2 is illustrated in Figure 1(a), assuming a reaction dependent influence specification.

Example 9.11. Common examples in the literature are gene regulatory networks [26]. These are typically represented by diagrams such as the one shown in Figure 1(b). The diagram represents three genes, each transcribing a protein. The proteins mutually affect the transcription rates of the genes such that the genes influence each other. The diagram corresponds to the network with production reactions



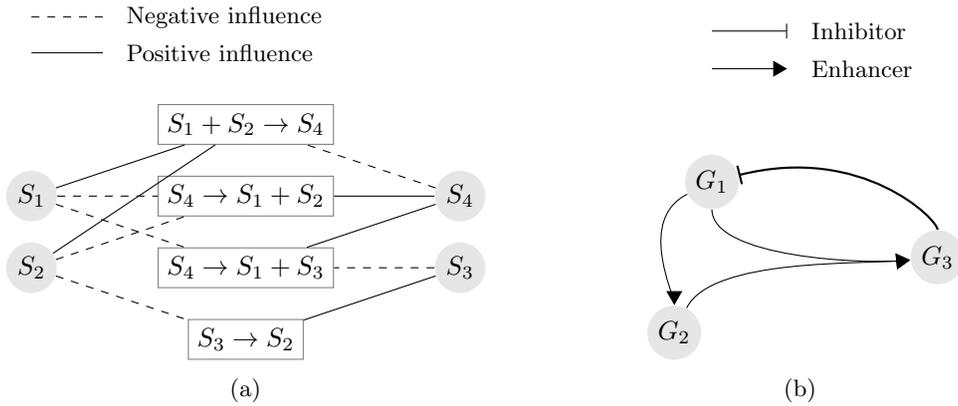


Figure 1. Graphical representation of a network with an influence specification. (a) Reaction dependent influence specification for Example 3.2, drawn as a bipartite graph. There is an edge between a species and a reaction if the species has nonzero influence on the reaction. If the influence is positive, the edge is solid. If the influence is negative, we draw a dashed edge. The complex dependent influence specification is obtained by removing the dashed edges. The species interacting in a reaction, for example $S_4 \rightarrow S_1 + S_3$, cannot be read off from the edges. (b) The influence specifications for the transcription of the three genes in Example 9.11 are shown. The presence of G_3 reduces the production of G_1 , whereas the presence of G_1 and G_2 cooperatively induces the production of G_3 . Likewise G_1 induces the production of G_2 .

and influence specification Z with $z_{1,3} = -$, $z_{2,1} = z_{3,1} = z_{3,2} = +$, and zero otherwise.

Example 9.12. An example from ecology is given by the Lotka–Volterra equations for modeling predator-prey dynamics or competing populations [30, 31]. The modeling equations are

$$\dot{c}_1 = c_1(\alpha - \beta c_2) \quad \text{and} \quad \dot{c}_2 = -c_2(\gamma - \beta c_1),$$

where c_1 and c_2 are the abundance of two species S_1 (prey) and S_2 (predator). The system comes from a network with reaction set $\mathcal{R} = \{S_1 \rightarrow 2S_1, S_1 + S_2 \rightarrow 2S_2, S_2 \rightarrow 0\}$ and kinetics

$$K_1(c_1, c_2) = \alpha c_1, \quad K_2(c_1, c_2) = \beta c_1 c_2, \quad \text{and} \quad K_3(c_1, c_2) = \gamma c_2,$$

with $\alpha, \beta, \gamma > 0$. The kinetics is mass-action and thus belongs to $\mathcal{K}_{3,2}(Z_C)$. The model has been proposed independently in epidemics [28, 1] as well as in physical chemistry as a model of H_2O_2 combustion [36].

9.3. Kinetic orders and influence specification. A kinetic order for a power-law kinetics is intimately related to an influence specification. If V is a kinetic order, define an influence specification $Z(V)$ by

$$Z(V)_{j,i} = \text{sign}(v_{j,i}).$$

In this case we say that $Z(V)$ is the influence specification associated with the kinetic order V . Reciprocally, if Z is an influence specification, let $V(Z)$ be the kinetic order defined by

$$V(Z)_{j,i} = z_{j,i} \cdot 1.$$

Note that $Z(V(Z)) = Z$.

Example 9.13. Consider Example 3.2 and the kinetic order V introduced in Example 7.2. Then we have

$$Z(V) = \begin{pmatrix} + & + & 0 & 0 \\ 0 & 0 & 0 & + \\ 0 & 0 & 0 & + \\ \text{sign}(v) & 0 & + & 0 \end{pmatrix} \quad \text{and} \quad V(Z(V)) = \begin{pmatrix} 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 \\ \text{sign}(v) \cdot 1 & 0 & 1 & 0 \end{pmatrix}.$$

For an influence specification Z , let $\mathcal{K}_{m,n}^g(Z) \subseteq \mathcal{K}_{m,n}(Z)$ be the set of power-law kinetics that are strictly monotonic with respect to Z . If V is a kinetic order, then it is straightforward to see that any power-law kinetics (κ, V) is differentiable with respect to the associated influence specification $Z(V)$. Therefore, $\mathcal{K}_{m,n}^g(Z) \subseteq \mathcal{K}_{m,n}^d(Z)$. Likewise any kinetics (κ, V) that is strictly monotonic with respect to an influence specification Z fulfills $Z = Z(V)$. Hence, we have the following lemma.

Lemma 9.14. *For any kinetic order V we have $\mathcal{K}_{m,n}^g[V] \subseteq \mathcal{K}_{m,n}^g(Z(V))$. A kinetics (κ, V) belongs to $\mathcal{K}_{m,n}^g(Z)$ if and only if $Z(V) = Z$. Further,*

$$\mathcal{K}_{m,n}^g(Z) = \bigcup_{V|Z(V)=Z} \mathcal{K}_{m,n}^g[V].$$

9.4. Z -injectivity. In this subsection we introduce the notion of Z -injectivity.

Definition 9.15. *Let A be an $n \times m$ matrix, Z an $m \times n$ influence specification, and $\mathcal{K}_0 \subseteq \mathcal{K}_{m,n}(Z)$. We say that A is Z -injective over \mathcal{K}_0 if for any $K \in \mathcal{K}_0$ and any pair of stoichiometrically compatible vectors $a, b \in \Omega_K$, which are nonoverlapping with respect to Z , we have $f_K(a) \neq f_K(b)$.*

If A is Z -injective, then the existence of pairs of distinct nonoverlapping stoichiometrically compatible steady states $a, b \in \Omega_K$ is precluded. In particular, some types of multiple steady states at the boundary of Ω_K are excluded. Since pairs of positive concentration vectors are nonoverlapping for any influence specification Z , Z -injectivity implies injectivity. Shinar and Feinberg [38] exclude the occurrence of pairs of distinct stoichiometrically compatible steady states a, b such that at least one of them is in the interior of $\Omega_K = \overline{\mathbb{R}_+^n}$ (in their setting). As noticed above, such pairs are nonoverlapping and hence covered by our approach. In [17], the condition of nonoverlapping is applied to networks with mass-action kinetics and influence specification Z_C . It is possible to have $f_K(\tilde{a}) = f_K(\tilde{b})$ for a pair of *not* nonoverlapping vectors and at the same time $f_K(a) \neq f_K(b)$ for all nonoverlapping pairs [17].

The rest of the paper is devoted to characterizing the matrices that are Z -injective for different families of kinetics and that consequently cannot have the capacity for multiple positive steady states. The aim is to provide a determinant criterion for an $n \times m$ matrix to be Z -injective over a set of kinetics $\mathcal{K}_0 \subseteq \mathcal{K}_{m,n}(Z)$ in terms of computational tractable quantities (Theorem 10.1). To this end we relate injectivity for power-law kinetics to Z -injectivity for kinetics that are strictly monotonic with respect to Z .

9.5. Kinetic orders with common influence specification. In section 8 we studied injectivity of matrices for a fixed kinetic order V and arbitrary rate vector κ . Here we are concerned about injectivity of matrices over a set of power-law kinetics for which the kinetic orders are related through their associated influence specifications.

To proceed we need some additional notation and definitions. We first introduce a partial order on the set of $m \times n$ influence specifications. One influence specification \tilde{Z} is said to be smaller than another influence specification Z if $\tilde{z}_j^+ \subseteq z_j^+$ and $\tilde{z}_j^- \subseteq z_j^-$ for all $j = 1, \dots, m$. If this is the case, then we write $\tilde{Z} \preceq Z$. The minimal element in this order is the zero influence specification; that is, the influence specification is zero for all reactions on all species. There is not a unique maximal element in this order, and all maximal elements must fulfill $z_j^+ \cup z_j^- = \{1, \dots, n\}$.

Definition 9.16. Let A be an $n \times m$ matrix of rank s , Z be an $m \times n$ influence specification, and $\Sigma(Z) := \{V \mid Z(V) = Z\}$. We say that Z has a signed A -determinant if the function

$$\delta: \Sigma(Z) \rightarrow \{-, 0, +\}, \quad V \mapsto \text{sign}(\det(\widetilde{AV}))$$

is constant. If, further, the image of δ is not zero, then Z is called A -sign-nonsingular (A -SNS).

If A is fixed, we simply say that Z has a signed determinant. According to the definition, Z has a signed determinant if the signs of $\det(\widetilde{AV})$ and $\det(\widetilde{AV}')$ agree for any two kinetic orders V, V' with influence specification Z . The kinetic orders in $\Sigma(Z)$ have the same sign-pattern; hence a kinetic order V in $\Sigma(Z)$ is uniquely identified by the absolute values $|v_{j,i}|$ of the nonzero entries of V . Let $|V|$ denote the matrix obtained from V by considering the absolute value componentwise. Then $V = Z * |V|$ (where $*$ denotes componentwise sign-number product). It follows that $\Sigma(Z)$ admits a positive parameterization.

Let $X = \{x_{*,*}\}$ be a generic symbolic $m \times n$ matrix and $Z_X := Z * X$. Let $p_Z(X) := \det(\widetilde{AZ_X})$. Then $p_Z(X)$ is a polynomial in the entries of X for which $z_{j,i} \neq 0$ such that

$$(9.2) \quad \det(\widetilde{AV}) = p_Z(|V|).$$

In fact, $p_Z(X)$ is either the zero polynomial or a homogeneous polynomial of degree s in $x_{j,i}$. Further, the degree of each monomial in each variable $x_{j,i}$ is either zero or one.

If Z' satisfies $Z' \preceq Z$, then $p_{Z'}(X)$ is obtained from $p_Z(X)$ by setting some variables $x_{j,i}$ to zero.

Lemma 9.17. Let A be an $n \times m$ matrix.

- (i) Z has a signed A -determinant if and only if either p_Z is the zero polynomial or the nonzero coefficients of the monomials of p_Z have common signs.
- (ii) Let Z' be such that $Z' \preceq Z$.
 - (a) If Z has a signed A -determinant, then Z' has a signed A -determinant.
 - (b) If Z and Z' are both A -SNS, then $\delta(Z) = \delta(Z')$.
 - (c) If Z' is A -SNS and Z has a signed A -determinant, then Z is A -SNS.

Using (5.1), we have the decomposition

$$(9.3) \quad \det(\widetilde{AZ_X}) = \sum_{I, J \subseteq \{1, \dots, n\}, \#I = \#J = s} \det(A_{I, J}) \det((Z_X)_{J, I}).$$

The product $\det(A_{I, J}) \det((Z_X)_{J, I})$ is a polynomial, $p_{Z, I, J}$, in the entries of X , such that

$$(9.4) \quad p_Z(X) = \sum_{I, J \subseteq \{1, \dots, n\}, \#I = \#J = s} p_{Z, I, J}(X).$$

Each polynomial $p_{Z,I,J}$ involves different variables, and hence none of the terms cancel out in the sum over I, J (unless they are zero). We say that $p_{Z,I,J}$ is *sign-nonzero* if it is nonzero and the coefficients of the nonzero terms in the polynomial have the same sign. The sign of any of the coefficients is then the sign of $p_{Z,I,J}$. Consequently, we have the following result.

Corollary 9.18. *Let A be an $n \times m$ matrix, and Z be an $m \times n$ influence specification. Then Z is A -SNS if and only if the nonzero terms $p_{Z,I,J}$ in (9.4) are sign-nonzero, have the same sign, and at least one of the terms is nonzero.*

An $n \times m$ matrix A is injective over $\mathcal{K}_{m,n}^g(Z)$ if and only if A is injective over $\mathcal{K}_{m,n}^g[V]$ for all kinetic orders with $Z(V) = Z$ (Lemma 9.14). Hence, we can use Proposition 8.4 and Lemma 9.17 to derive a determinant criterion valid for $\mathcal{K}_{m,n}^g(Z)$. Similarly, if Z_1, Z_2 are influence specifications such that $Z_1 \preceq Z_2$, then we can use Proposition 8.4 and Lemma 9.17 to derive a determinant criterion for A to be injective over $\bigcup_{Z|Z_1 \preceq Z \preceq Z_2} \mathcal{K}_{m,n}^g(Z)$.

Proposition 9.19. *Let A be an $n \times m$ matrix, and Z an $m \times n$ influence specification. Then A is injective over $\mathcal{K}_{m,n}^g(Z)$ if and only if Z is A -SNS.*

Using (5.1), we can rephrase the previous proposition as follows.

Corollary 9.20. *Let A be an $n \times m$ matrix of rank s , and Z an $m \times n$ influence specification. Then A is injective over $\mathcal{K}_{m,n}^g(Z)$ if and only if the following two statements hold:*

- (i) A is injective over $\mathcal{K}_{m,n}^g[V]$ for some kinetic order V with $Z(V) = Z$.
- (ii) For all sets $I, J \subseteq \{1, \dots, n\}$ of cardinality s , if $A_{I,J}$ is nonsingular, then $\det(V_{J,I})$ has the same fixed sign for all V in $\Sigma(Z)$.

Item (ii) can be replaced by the following: (ii) Z has a signed A -determinant. In particular the proposition is true by choosing the kinetic order $V = V(Z)$. The first condition guarantees that all coefficients in the polynomial expression of the determinant $\det(J_c(\tilde{f}_{\kappa,V}))$ have the same sign or are zero, and that at least one coefficient is nonzero. The second condition ensures that this property is preserved for all kinetic orders V in $\Sigma(Z)$.

Remark 9.21. Using Theorem 8.1, we have the following. If $\mathcal{K}_0 = \bigcup_{V \in \mathbf{V}} \mathcal{K}_{m,n}^g[V]$ for some set \mathbf{V} and the determinant $\det(J_c(\tilde{f}_{\kappa,V}))$ does not vanish for all $(\kappa, V) \in \mathcal{K}_0$, then A is injective over \mathcal{K}_0 , irrespective of whether Z has a signed A -determinant or not. For example, if $\det(J_c(\tilde{f}_{\kappa,V}))$ is not zero provided that $v_{j,1} > v_{j,2}$ for some j , then A is injective over $\mathcal{K}_0 = \{\mathcal{K}_{m,n}^g[V] \mid v_{j,1} > v_{j,2}, Z(V) = Z\}$.

The next proposition provides a characterization of the injectivity of a matrix A over $\bigcup_{Z|Z_1 \preceq Z \preceq Z_2} \mathcal{K}_{m,n}^g(Z)$.

Proposition 9.22. *Let A be an $n \times m$ matrix of rank s , and $Z_1 \preceq Z_2$ two $m \times n$ influence specifications. The following statements are equivalent:*

- (i) A is injective over $\bigcup_{Z|Z_1 \preceq Z \preceq Z_2} \mathcal{K}_{m,n}^g(Z)$.
- (ii) Z_2 has a signed A -determinant, and A is injective over $\mathcal{K}_{m,n}^g[V_1]$ for some V_1 in $\Sigma(Z_1)$.
- (iii) A is injective over $\mathcal{K}_{m,n}^g(Z_1)$ and $\mathcal{K}_{m,n}^g(Z_2)$.

In particular the proposition is true for the kinetic order $V_1 = V(Z_1)$. The first part of (ii) guarantees that all coefficients in the polynomial expression of the determinant $\det(J_c(\tilde{f}_{\kappa,V_2}))$ have the same sign or are zero for all V_2 such that $Z(V_2) = Z_2$. Hence, by Lemma 9.17(ii), this property is preserved for all kinetic orders W with $Z(W) \preceq Z_2$. The second part of (ii) ensures that at least one term is nonzero for all W with $Z_1 \preceq Z(W)$.

A natural choice for the smaller influence specification Z_1 is in many contexts the complex

dependent influence specification Z_C given by the kinetic order Y . Corollary 9.20 and the discussion above also imply the following corollary.

Corollary 9.23. *Let A be the $n \times m$ stoichiometric matrix. Assume that A is not injective over the set of mass-action kinetics $\mathcal{K}_{m,n}^g(Y)$ and that the determinant $\det(J_c(\tilde{f}_{\kappa,Y}))$ is not identically zero. Then A is not injective over $\mathcal{K}_{m,n}^g[V]$ for any kinetic order V such that $Z_C \preceq Z(V)$.*

Example 9.24. Consider the network in Example 3.2 with the kinetic order V introduced in Example 7.2. The kinetic orders in $\Sigma(Z(V))$ are positively parameterized by the matrix

$$Z_X = \begin{pmatrix} x_1 & x_2 & 0 & 0 \\ 0 & 0 & 0 & x_3 \\ 0 & 0 & 0 & x_4 \\ \text{sign}(v)x_7 & 0 & x_5 & 0 \end{pmatrix}.$$

The kinetic orders W with $Z_C \preceq Z(W) \preceq Z(V)$ also include the possibility $x_7 = 0$. The polynomial p_Z corresponding to the determinant of \widetilde{AZ}_X is

$$(x_1 + x_2 + x_3 + x_4)x_5 + x_2x_4 + \text{sign}(v)x_7x_2.$$

If $v \geq 0$, then all coefficients are positive. In that case it follows from Proposition 9.19 and Lemma 9.17(i) that the network is injective over $\mathcal{K}_{m,n}^g(Z(V))$ and in particular over $\mathcal{K}_{m,n}^g(Z_C)$ (corresponding to $v = 0$). If $v < 0$, then the term $\text{sign}(v)x_7x_2$ is negative while the rest are positive, and the network is not injective over $\mathcal{K}_{m,n}^g(Z(V))$. If $v < 0$ and the kinetic order W fulfills $x_4 > x_7$, then all terms are positive. It follows that the network is injective over $\mathcal{K}_{m,n}^g[W]$ (Proposition 8.4; see also Remark 9.21) even though it is not injective over $\mathcal{K}_{m,n}^g(Z(V))$.

Example 9.25. Consider the network in Example 3.2 with the reaction dependent influence specification $Z_{\mathcal{R}}$. The kinetic orders V with $Z(V) = Z_{\mathcal{R}}$ are positively parameterized by

$$Z_X = \begin{pmatrix} x_1 & x_2 & 0 & -x_3 \\ -x_4 & -x_5 & 0 & x_6 \\ -x_7 & 0 & -x_8 & x_9 \\ 0 & -x_{10} & x_{11} & 0 \end{pmatrix}$$

and $x_i > 0$. The monomials in the determinant of \widetilde{AZ}_X have positive coefficients. It follows that Proposition 9.19 holds and that the network is injective over $\mathcal{K}_{4,4}^g(Z_{\mathcal{R}})$. Example 9.24 showed that the network is injective over $\mathcal{K}_{4,4}^g(Z_C)$. Hence, it follows from Proposition 9.22 that the network is injective over $\bigcup_{Z|Z_C \preceq Z \preceq Z_{\mathcal{R}}} \mathcal{K}_{4,4}^g(Z)$.

The Mathematica code implementing the algorithm to decide whether Example 3.2 is injective over $\mathcal{K}_{4,4}^g(Z_{\mathcal{R}})$ is shown in Figure 2.

Remark 9.26. In general a network will not be injective over the set of all power-law kinetics. In the case of Example 8.5, the term $t = vk_1k_4c_1^v c_3$ is the only term depending on v , that is, the kinetic order. It changes sign with v , whereas none of the other nonzero terms do. Hence, the network cannot be injective over all power-law kinetics.

Remark 9.27. The decomposition (9.3) of $\det(\widetilde{AZ}_X)$ is precisely the *core determinant* of A , as defined in [21, Lemma 3.7] for the complex dependent influence specification.

```

Define the stoichiometric matrix A:
A = Transpose[{{-1,-1,0,1},{1,1,0,-1},{1,0,1,-1},{0,1,-1,0}}];
Define the matrix ZX:
ZX = {{x[1],x[2],0,-x[3]},{-x[4],-x[5],0,x[6]},{-x[7],0,-x[8],x[9]},
      {0,-x[10],x[11],0}};
{s,n,lengthx,Mtilde} = {MatrixRank[R],Length[R[[1]]],11,A.ZX};
Find a reduced basis of Im(A)⊥:
If[s<n,
  F = RowReduce[NullSpace[A]];
  For[i=1,i<=Length[F],i++,
    Mtilde[[Flatten[Position[F[[i]],x_/;x!=0]][[1]]]]]=F[[i]];
  ];
Compute the determinant of  $\widetilde{AZ}_X$ :
det = Expand[Determinant[Mtilde]];
Check the signs of the coefficients:
Rules = {};
monomials = Flatten[MonomialList[det]];
For[i=1,i<=lengthx,i++,AppendTo[Rules,x[i]->1]];
sign = DeleteCases[DeleteDuplicates[Sign[monomials/.Rules]],0];
If[Length[sign] == 1, Print["The network IS injective"],
  Print["The network is NOT injective"]; ];

```

Figure 2. The algorithm, implemented in Mathematica, to decide whether Example 3.2 is injective over $\mathcal{K}_{4,4}^g(Z_{\mathcal{R}})$.

9.6. Injectivity of systems defined by submatrices of A . The conditions presented in the propositions in the previous sections relate to submatrices of A . For $J \subseteq \{1, \dots, n\}$, let $A_{*,J}$ ($V_{J,*}$) be the restriction of A (V) to the columns (rows) with indices in J .

Theorem 9.28. *Let A be an $n \times m$ matrix of rank s , V an $m \times n$ kinetic order, and J an index set of size s such that $A_{*,J}$ has rank s . Assume that A is injective over $\mathcal{K}_{m,n}^g[V]$. Then either*

- (i) $A_{*,J}$ is injective over $\mathcal{K}_{s,n}^g[V_{J,*}]$ and all steady states are nondegenerate, or
- (ii) $A_{*,J}$ has only degenerate steady states.

The theorem relates to [17, Cor. 8.1 and 8.2], where injectivity of a network is studied relative to injectivity of the network augmented with the “missing” outflow reactions. Also, the theorem relates to Joshi and Shiu [25]. They consider a network obtained by restricting a larger network such that the stoichiometric dimension is maintained. If the smaller network has multiple steady states, then so does the larger. Theorem 9.28 cannot be used to draw the same conclusion, since noninjectivity does not imply that there are multiple steady states.

Example 9.29. Consider Example 9.6. The system has stoichiometric matrix $A = (1, -1)$, rank one, and kinetic order $V = (1, 2)$. There are two possible choices of index set, $J = \{1\}$ and $J = \{2\}$. The matrices $A_{*,i}$ are injective over $\mathcal{K}_{1,1}^g[V_{i,*}]$, $i = 1, 2$, but A is not injective over $\mathcal{K}_{1,1}^g[V]$.

10. Injectivity for strictly monotonic kinetics. In this section we extend the results on injectivity for power-law kinetics in sections 8 and 9 to cover Z -injectivity of a matrix A over the set of strictly monotonic kinetics $\mathcal{K}_{m,n}(Z)$. The following theorem is the main theorem of

this article.

Theorem 10.1. *Let A be an $n \times m$ matrix and Z an $m \times n$ influence specification. The following four statements are equivalent:*

- (i) A is Z -injective over $\mathcal{K}_{m,n}(Z)$.
- (ii) A is Z -injective over $\mathcal{K}_{m,n}^d(Z)$.
- (iii) A is injective over $\mathcal{K}_{m,n}^g(Z)$.
- (iv) Z is A -SNS.

The theorem implies that for a matrix to be Z -injective over $\mathcal{K}_{m,n}(Z)$ it is sufficient for it to be injective over \mathcal{K}_0 with $\mathcal{K}_{m,n}^g(Z) \subseteq \mathcal{K}_0 \subseteq \mathcal{K}_{m,n}(Z)$. In [17, Prop. 5.2] it is shown that injectivity and Z -injectivity are equivalent notions for mass-action kinetics. Theorem 10.1 also implies that [17, Prop. 5.2] holds generally, namely that A is Z -injective over $\mathcal{K}_{m,n}(Z)$ if and only if A is injective over $\mathcal{K}_{m,n}(Z)$.

Theorem 10.2. *Let A be an $n \times m$ matrix. Then the following are equivalent:*

- (i) $\ker(J_c(f_K)) \cap \text{Im}(A) = \{0\}$ for all $c \in \mathbb{R}_+^n$ and $K \in \mathcal{K}_{m,n}^d(Z)$.
- (ii) $\ker(J_c(f_{\kappa,V})) \cap \text{Im}(A) = \{0\}$ for all $c \in \mathbb{R}_+^n$ and $(\kappa, V) \in \mathcal{K}_{m,n}^g(Z)$.

If either of the two statements holds, then A is Z -injective over $\mathcal{K}_{m,n}(Z)$.

Recall from (6.1) that $\ker(J_c(f_K)) \cap \text{Im}(A) = \{0\}$ if and only if $\det(J_c(\tilde{f}_K)) \neq 0$.

Corollary 10.3. *If A is injective over $\mathcal{K}_{m,n}^d(Z)$, then A cannot have positive degenerate steady states.*

The corollary follows immediately from (6.1). The same result holds for weakly monotonic kinetics ([38]; see Definition 12.1) and for mass-action kinetics [17].

Example 10.4. According to Example 9.25, the network in Example 3.2 is injective over $\bigcup_{Z|Z_C \preceq Z \preceq Z_{\mathcal{R}}} \mathcal{K}_{m,n}^g(Z)$. It follows from Theorem 10.1 that the network is Z -injective over $\mathcal{K}_{m,n}(Z)$ for any Z such that $Z_C \preceq Z \preceq Z_{\mathcal{R}}$.

Remark 10.5. The criterion that Z be A -SNS is computationally efficient and can easily be implemented using symbolic software (see also Figure 2). It requires calculation of the matrix \widetilde{AZ}_X , its determinant, and the expansion of the determinant. The complexity of expanding the determinant depends on the number of species influencing a reaction as well as the size of the matrix, while the complexity of computing the determinant depends on the size of the matrix only. The criterion provided in Corollary 9.18 is computationally more demanding, as it requires investigating all minors of a certain size.

11. Graphical representation of the criterion. We have shown that a matrix A is injective over the set of kinetics strictly monotonic with respect to an influence specification Z if and only if Z is A -SNS. The property of being A -SNS relies on computing the symbolic determinant of \widetilde{AZ}_X . Since visual inspection is often more appealing than computation, injectivity-based criteria to preclude multistationarity have been interpreted in graph-theoretical terms [11, 3, 2, 39]. Generally, the outcome does not provide a full characterization of injectivity but only a sufficient graphical condition that guarantees injectivity of A . In this section we show that the decomposition (9.3) can be interpreted directly in terms of circuits in the DSR-graph.

The procedure basically relies on a variant of the DSR-graph (directed-species-reaction-graph) introduced in [2], using the matrices A and Z_X . To fix the notation, consider two sets $\mathcal{S} = \{S_1, \dots, S_n\}$ (“species”) and $\mathcal{R} = \{r_1, \dots, r_m\}$ (“reactions”). The DSR-graph, $G_{A,Z}$, associated with (A, Z_X) is defined in the following way. The set of nodes of the graph is $\mathcal{S} \cup \mathcal{R}$,

and hence there are $n + m$ nodes. There is a directed edge from a species S_i to a reaction r_j if and only if $z_{j,i} \neq 0$. This edge is assigned a symbolic label $e_{j,i} := z_{j,i} \cdot x_{j,i}$. There is a directed edge from a reaction r_j to a species S_i with label $a_{i,j}$ if and only if $a_{i,j} \neq 0$.

A circuit in a graph G is a sequence of distinct nodes i_1, \dots, i_l such that there is a directed edge from i_k to i_{k+1} for all $k \leq l - 1$ and one from i_l to i_1 . A circuit must involve at least one edge. In this specific setting, any circuit involves an even number of edges. The label of a circuit is the product of the labels of the edges in the circuit. Two circuits are disjoint if they do not have any common nodes. A circuit has sign (-1) if the number of species nodes in the circuit is even.

A k -nucleus is a collection of disjoint circuits which involves k nodes. The label $l(D)$ of a k -nucleus D is the product of the labels of the edges in the nucleus. The sign of a k -nucleus is $(-1)^q$, where q is the number of circuits with even number of species nodes. That is, if $D = C_1 \cup \dots \cup C_a$ is a disjoint union of circuits, then

$$\text{sign}(D)l(D) = \prod_{i=1}^a \text{sign}(C_i)l(C_i).$$

Proposition 11.1. *Fix two sets $I, J \subseteq \{1, \dots, n\}$ of cardinality s , and consider the submatrices $A_{I,J}$ and $(Z_X)_{J,I}$. Let $D_s(I, J)$ be the set of $2s$ -nuclei of $G_{A,Z}$ with nodes S_i for $i \in I$ and r_j for $j \in J$. Then*

$$\det(A_{I,J}) \det((Z_X)_{J,I}) = \sum_{D \in D_s(I,J)} \text{sign}(D)l(D).$$

It follows from this proposition that injectivity of A with respect to Z can be decided from the DSR-graph as follows:

- (1) Classify all circuits C of the graph $G_{A,Z}$ according to the number of species nodes that are involved (up to s). Assign $\text{sign}(C)l(C)$ to each of them.
- (2) Consider all products of circuit labels with sign for which the number of species nodes adds up to s .
- (3) Each label has the form $\lambda x_{j_1, i_1} \dots x_{j_s, i_s}$ for some scalar λ . Keep only the monomials for which there is no repetition among i_1, \dots, i_s and among j_1, \dots, j_s .
- (4) Add the terms with the same variables.

According to Proposition 11.1, the terms obtained after step (4) are exactly the terms in the decomposition of the determinant (9.3). Using this representation, sufficient (that is, not necessary) conditions for injectivity might be developed by relaxing the information initially encoded in the DSR-graph, in the spirit of [3, 2, 11, 39].

Example 11.2. Consider the network defined by the reactions $r_1: S_1 + S_2 + S_3 \rightarrow 2S_1 + S_2 + 2S_3$, $r_2: S_1 + S_3 \rightarrow S_1 + S_2 + S_3$, $r_3: S_3 \rightarrow S_1 + S_2 + 2S_3$ and the complex dependent influence specification $Z = Z_C$. In this case $s = 2$. The DSR-graph of this network is shown in Figure 3. We enumerate all circuits of the graph and classify them according to the number of species nodes:

# Species nodes	1	2
Label	$x_{1,1}, x_{3,1}, x_{3,3}$	$-x_{2,1}x_{3,2}, -x_{2,1}x_{3,3}, -x_{1,1}x_{3,3}, -x_{1,2}x_{2,1}$

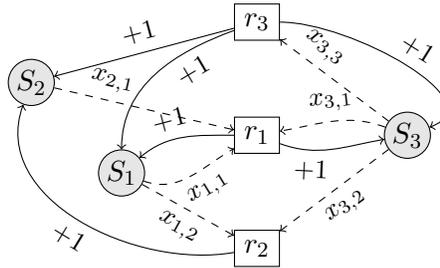


Figure 3. DSR-graph of Example 11.2.

We take the products of circuit labels for which the number of species nodes adds to $s = 2$ and avoid index repetition:

$$-x_{2,1}x_{3,2}, \quad -x_{2,1}x_{3,3}, \quad -x_{1,1}x_{3,3}, \quad -x_{1,2}x_{2,1}, \quad \text{and} \quad x_{1,1}x_{3,3}.$$

(The last is obtained by combining two circuits with one species node.) Note that the circuit with label $x_{3,1}$ cannot be combined with any other circuit because there would be index repetitions. We group the monomials together, whereby the coefficient of $x_{1,1}x_{3,3}$ becomes zero. The remaining three monomials are the terms of the polynomial $p_Z(X)$. Since the terms have the same sign, the network is injective.

12. Extensions to other types of influence specifications. Shinar and Feinberg [38] introduce the term “weakly monotonic kinetics,” which in some sense imposes a weaker requirement on the kinetics than the term “strictly monotonic kinetics” introduced here (Definition 9.3 and Lemma 9.5). In this section we assume that we have a network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ and an influence specification Z such that $\text{supp}(y_j) \subseteq z_j^+ \cup z_j^-$. That is, the enhancers and inhibitors of a reaction include all species involved in the reactant complex y_j . In chemical reaction theory it is typically required that the species in the reactant complex have positive influence on the reaction [20, 38] and not negative or neutral, as in Definition 9.1. However, relaxation of this assumption can be found, for example, in S-systems theory.

Definition 12.1 (see [38]). *A kinetics K for a network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is weakly monotonic with respect to an influence specification Z if, for each pair of nonoverlapping concentration vectors $a, b \in \Omega_K$, the following implications hold for all j :*

- (i) *if $K_j(a) > K_j(b)$, then $\text{sign}(a_i - b_i) = z_{j,i} \neq 0$ for some i ;*
- (ii) *if $K_j(a) = K_j(b)$, then $a_i = b_i$ for all $i \in \text{supp}(y_j)$, or $\text{sign}(a_i - b_i) = z_{j,i} \neq 0$ and $\text{sign}(a_\ell - b_\ell) = -z_{j,\ell} \neq 0$ for some distinct i, ℓ .*

Let $\mathcal{K}_{m,n}^w(Z)$ denote the set of kinetics that are weakly monotonic with respect to Z .

Using the characterization of strictly monotonic kinetics provided in Lemma 9.5, we find that the two definitions differ in (ii), where it is required that $a_i = b_i$ for all $i \in z_j^+ \cup z_j^-$ and not just for $i \in \text{supp}(y_j)$. In this sense, Definition 12.1 imposes a weaker requirement on the kinetics than Definition 9.3 and

$$\mathcal{K}_{m,n}(Z) \subset \mathcal{K}_{m,n}^w(Z).$$

In [38], an influence specification Z must fulfill $z_{j,i} = +$ for $i \in \text{supp}(y_j)$. Definition 9.3 stipulates that all species play an equal role in the definition, whereas Definition 12.1 singles

out the species in the reactant complex to have special importance. Below we show that our determinant criterion also applies to the broader definition of influence specification.

The determinant criterion in Theorem 10.1(iv) can be adapted to derive a determinant criterion for a network \mathcal{N} to be Z -injective over $\mathcal{K}_{m,n}^w(Z)$. We first note that the influence specification \tilde{Z} given by $\tilde{z}_{j,i} = z_{j,i}$ for $i \in \text{supp}(y_j)$ and zero otherwise is a minimal element among all influence specifications Z' for \mathcal{N} fulfilling $\text{supp}(y_j) \subseteq z_j^+ \cup z_j^-$ and $Z' \preceq Z$. Also note that if a, b are Z -nonoverlapping, then they are Z' -nonoverlapping for all influence specifications Z' such that $Z' \preceq Z$. Hence, we have that

$$(12.1) \quad Z' \preceq Z \quad \text{implies} \quad \mathcal{K}_{m,n}^w(Z') \subseteq \mathcal{K}_{m,n}^w(Z).$$

Lemma 12.2. *If $K \in \mathcal{K}_{m,n}^w(Z)$ is a power-law kinetics, then there is $\tilde{Z} \preceq Z' \preceq Z$ such that $K \in \mathcal{K}_{m,n}^g(Z')$. That is,*

$$\mathcal{K}_{m,n}^w(Z) \cap \mathcal{K}_{m,n}^g = \bigcup_{Z' | \tilde{Z} \preceq Z' \preceq Z} \mathcal{K}_{m,n}^g(Z').$$

Theorem 12.3. *Let $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a network with influence specification Z . The following statements are equivalent:*

- (i) \mathcal{N} is Z -injective over $\mathcal{K}_{m,n}^w(Z)$.
- (ii) \mathcal{N} is Z -injective over $\bigcup_{Z' | \tilde{Z} \preceq Z' \preceq Z} \mathcal{K}_{m,n}^g(Z')$.
- (iii) \mathcal{N} is injective over $\bigcup_{Z' | \tilde{Z} \preceq Z' \preceq Z} \mathcal{K}_{m,n}^g(Z')$.

Taking this together with Proposition 9.22, we can derive a determinant criterion for a network \mathcal{N} to be Z -injective over $\mathcal{K}_{m,n}^w(Z)$. Further, it is straightforward to derive statements similar to those in section 10 for $\mathcal{K}_{m,n}^w(Z)$.

Remark 12.4. Shinar and Feinberg [38] introduce the concepts of a *concordant network* and of a network being *concordant with respect to an influence specification Z* . To be concordant depends on the kinetics associated with the network only through the influence specification Z . They show that to be concordant with respect to Z is equivalent to being injective over $\mathcal{K}_{m,n}^w(Z)$. Theorems 12.3 and 10.1 provide an equivalent characterization in terms of the influence specification through properties of the matrices Z and A and bring out an explicit relationship to the set of power-law kinetics.

Remark 12.5. For Windows-based platforms, the CRN Toolbox [13] provides a test for injectivity over $\mathcal{K}_{m,n}^w(Z)$ for the influences introduced in [38].

13. The P -matrix property. In [4, 2], an injectivity-related criterion is given to preclude the existence of multiple steady states in \mathcal{C}^1 dynamical systems admitting a decomposition of the form $f(c) = AK(c)$. The kinetics K is required to be *nonautocatalytic* (NAC), which is a condition that also involves the form of A . We introduce it in terms of a corresponding network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$. In our terminology, NAC implies that (a) no species appear both in the reactant and the product complex of a reaction, and (b) the influence specification fulfills $Z \preceq Z_{\mathcal{R}}$. This class of dynamical systems includes the differentiable kinetics $\mathcal{K}_{m,n}^d(Z)$ (assuming further that the rate functions are \mathcal{C}^1 in the domain of differentiability). In particular, multistationarity in networks with power-law kinetics can be precluded using the criterion.

The focus is on conditions for injectivity of the “open network,” which is the network obtained by adding the outflow reactions $S \rightarrow 0$, $S \in \mathcal{S}$, to the network, unless they are already present. The species S is required to be the only species with nonzero (positive) influence on the reaction. If the reaction is already in the network, it must fulfill this requirement too.

If the open network can be constructed and is injective, then the initial network cannot have multiple nondegenerate steady states [2]. Therefore, multistationarity can be precluded in an arbitrary network, provided that it can be precluded in the corresponding open network. However, networks exist that are injective but for which the corresponding open network is not injective (see Example 13.2).

Injectivity of the open network follows from the results of Gale and Nikaidô [18] after determining that the Jacobian of the system associated with the open network is a P -matrix, or, equivalently, that the Jacobian of the system associated with the initial network is a P_0 -matrix [2]. A square matrix is said to be a P -matrix if all principal minors of the matrix are positive. If the principal minors are nonnegative, then the matrix is said to be a P_0 -matrix. We proceed to discuss the relationship between the P_0 -matrix property and our criteria.

The next proposition is established in [2] (stated using our terminology).

Proposition 13.1 (see [2], Lemma 3.5). *Let A be a stoichiometric matrix, Z an influence specification, and V a kinetic order such that $Z(V) \preceq Z$. If*

$$(*) \quad (-1)^\ell \det(A_{I,J}) \det(V_{J,I}) \geq 0 \text{ for all sets } I, J \subseteq \{1, \dots, n\} \text{ of cardinality } n - \ell, \text{ for all } \ell,$$

then $-J_c(f_{\kappa,V})$ (minus the Jacobian) is a P_0 -matrix.

If we require the kinetics to be NAC, then $Z(V) \preceq Z_{\mathcal{R}}$, and the corresponding entries in $-V$ and A have the same sign. The determinant criterion in Proposition 8.4(ii) (without the requirement that one product be nonzero) is implied by criterion (*). Also if (*) holds for all kinetic orders V such that $Z(V) = Z$, then the criterion in Corollary 9.20(ii) is implied by criterion (*). However, as Example 13.2 below shows, the opposite is not true. Hence, our criterion is weaker than criterion (*). The additional requirement in Proposition 8.4 and Corollary 9.20(ii) that one term be nonzero is necessary (and sufficient) to guarantee that A is injective. In fact, if all terms are zero, then all steady states are degenerate (see [17] for a discussion that relates injectivity of the open network to that of the initial network for mass-action kinetics).

In [2], the authors further provide a graphical condition on the DSR-graph that implies that the Jacobian is a P -matrix and consequently that the network is injective.

Example 13.2. Consider the network \mathcal{N} defined by the set of reactions $\mathcal{R} = \{S_1 + S_2 + S_3 \rightarrow 2S_1 + S_2 + 2S_3, S_1 + S_3 \rightarrow S_1 + S_2 + S_3, C \rightarrow S_1 + S_2 + 3S_3\}$ and complex dependent influence specification $Z = Z_C$. For a kinetic order V with $Z(V) = Z$, let

$$V = \begin{pmatrix} v_{1,1} & v_{2,1} & v_{3,1} \\ v_{1,2} & 0 & v_{3,2} \\ 0 & 0 & v_{3,3} \end{pmatrix}, \quad A = \begin{pmatrix} 1 & 0 & 1 \\ 0 & 1 & 1 \\ 1 & 0 & 2 \end{pmatrix}.$$

The stoichiometric space has maximal dimension, and

$$\det(AV) = -v_{1,2}v_{2,1}v_{3,3}.$$

Consequently, \mathcal{N} (or A) is injective over $\mathcal{K}_{m,n}^g(Z)$ (Proposition 9.19), and hence also over $\mathcal{K}_{m,n}(Z)$ (Theorem 10.1). However, the product of the minors obtained by removing the second row and column is positive, while that obtained by removing the third row and column is negative. Hence, $-J_c(f_{\kappa,V})$ is not a P_0 -matrix. In fact, the open network associated with \mathcal{N} with influence specification Z is not injective.

Example 13.3. Consider Example 11.2, which is similar to Example 13.2 but with the coefficient of S_3 changed in the last reaction. The stoichiometric space has dimension two. All nonzero products involving 2×2 matrices in criterion (*) have negative sign, and hence (*) is not fulfilled. However, since all products have the same sign (as we saw in Example 11.2), then the network is injective over $\mathcal{K}_{m,n}(Z)$.

14. The interaction graph. Conditions for the preclusion of multistationarity have also been given for generic dynamical systems described by ODEs, and we will here review one condition due to Kaufman, Soulé, and Thomas [27, 40] that closely relates to our work. This condition is also based on the Jacobian of the system and takes the form of a graphical condition. Specifically, we will interpret a result of [27] in terms of our framework and show, by example, that our criterion might decide on injectivity when the criterion in [27] fails. For this we need some preliminaries.

Let a dynamical system $\dot{c} = F(c) = (F_1(c), \dots, F_n(c))$ be given such that $c = (c_1, \dots, c_n) \in \Omega \subseteq \mathbb{R}^n$, where Ω is a product of open intervals of \mathbb{R} and F_j is differentiable in the interior of Ω . The interaction graph $G(c)$ at c is the labeled directed graph with node set $\{1, \dots, n\}$ and labels in the set $\{-, +\}$ such that there is an edge from node i to node j if $\partial F_j(c)/\partial c_i \neq 0$. The edge has label given by $\text{sign}(\partial F_j(c)/\partial c_i)$. Denote by $\widehat{G}(c)$ the $n \times n$ sign matrix with (j, i) th entry $\text{sign}(\partial F_j(c)/\partial c_i)$. It encodes the same information as $\widehat{G}(c)$. We use the definition of a circuit and a k -nucleus given in section 11. However, in this section, the sign of a circuit is the product of the labels of the edges in the circuit. The sign of a k -nucleus is $(-1)^{p+1}$, where p is the number of circuits in the k -nucleus with sign equal to $+$, i.e., positive [40]. A k -nucleus is variable if one edge in one of the circuits does not have constant sign in c .

In [27, Thm. 2] (see below), a mild regularity condition is imposed on the function F . To keep the presentation clear, the reader is referred to the original paper for its description. We refer to it as condition (C).

Theorem 14.1 (see [27]). *Assume that the system $\dot{c} = F(c)$ has two nondegenerate steady states and that F fulfills condition (C). Then one of the following statements is true:*

- (i) *There exists $c \in \Omega$ such that $G(c)$ has two n -nuclei of different sign.*
- (ii) *There is a variable n -nucleus.*

The existence of nondegenerate steady states implies that the Jacobian of F is nonsingular for all c and that a n -nucleus exists for some c . If neither (i) nor (ii) above are fulfilled, then the system cannot have multiple nondegenerate steady states. There is no a priori restriction to pairs of *positive* steady states (unless $\Omega \subseteq \mathbb{R}_+^n$). If (ii) is not fulfilled, then preclusion of multiple steady states must follow from the failure of (i). Therefore, in relating our work to [27], we assume that $G(c)$ does not depend on c ; that is, $G(c) = G$ for all c (and (ii) is not fulfilled by hypothesis).

Theorem 14.1 can be rephrased in our terminology as a statement about the preclusion of multiple nondegenerate steady states in any dynamical system with interaction graph G .

In particular, we show that failure of condition (i) is equivalent to noninjectivity of certain matrices A over the class of differentiable kinetics.

In what follows we assume that the first s rows of \widehat{G} are nonzero and that the last $n - s$ rows are identically zero. This can always be obtained by permuting the order of the variables c_1, \dots, c_n . If G is the (constant) interaction graph associated with a dynamical system as above, then a zero row of \widehat{G} corresponds to a constant F_j . If a zero row exists, then the Jacobian of F is necessarily singular and Theorem 14.1 cannot be applied to preclude multistationarity. In general, there might be many decompositions A, Z of the system such that the sign-pattern of AZ is \widehat{G} . Theorem 14.1 does not distinguish between these. In order to relate the theorem to our setting, we introduce a family of decompositions A and Z .

Definition 14.2. Let $\widehat{G} = (g_{i,j})_{i,j}$ be an $n \times n$ sign matrix with nonzero rows $1, \dots, s$. For each $j = 1, \dots, s$, choose a set $H_j \subseteq \{1, \dots, s\}$. We associate with these sets an $n \times (2s)$ stoichiometric matrix $A = (a_{i,j})_{i,j}$ and an $(2s) \times n$ influence specification $Z = (z_{j,i})_{j,i}$ by

$$\begin{aligned} a_{j,j} &= 1, & z_{j,i} &= g_{j,i}, & i &\in H_j, \\ a_{j,j+s} &= -1, & z_{j+s,i} &= -g_{j,i}, & i &\in \{1, \dots, s\} \setminus H_j, \end{aligned}$$

for $i = 1, \dots, n$, $j = 1, \dots, s$, and zero otherwise.

In other words, the top $s \times (2s)$ block of A is composed of two diagonal matrices adjacent to each other, and the bottom $n - s$ rows are zero. Z consists of the first s rows of \widehat{G} duplicated, but with a change of sign in some entries. The definition can be cast in terms of a reaction network with species $\{S_1, \dots, S_n\}$ and set of reactions $\mathcal{R} = \{0 \rightarrow S_j, S_j \rightarrow 0 \mid j = 1, \dots, s\}$. This network has stoichiometric matrix A with rank s . Clearly, the sign pattern of AZ is \widehat{G} by construction. Furthermore, for any $K \in \mathcal{K}_{2s,n}^d(Z)$, the system $f_K(c) = AK(c)$ has interaction graph G .

Theorem 14.3. Let G be an interaction graph, and define A , Z , and s as in Definition 14.2. The following two statements are equivalent:

- (i) A is Z -injective over $\mathcal{K}_{2s,n}^d(Z)$.
- (ii) G has at least one s -nucleus, and all s -nuclei of G have the same sign.

Note that (ii) is independent of the choice of H_j in Definition 14.2, and hence statement (i) is also independent of the choice.

Assume that $s = n$ and that A is Z -injective with A, Z chosen as in Definition 14.2. Then any dynamical system $\dot{c} = F(c)$ with associated interaction graph G cannot have multiple nondegenerate positive steady states. If F fulfills condition (C), then by Theorems 14.3 and 14.1(i), multiple nondegenerate steady states are precluded (not only positive steady states). This is, in particular, true if we choose $H_j = \{1, \dots, s\}$ for all j . In this case, we might choose $A = I_n$ (the $n \times n$ identity matrix) and $Z = \widehat{G}$, as the bottom half of Z in Definition 14.2 is identically zero. These results lead to the following corollary (using Proposition 9.19), which was proven in [19], following a more direct route.

Corollary 14.4. Let \widehat{G} be an $n \times n$ I_n -SNS matrix. Then, any dynamical system $\dot{c} = F(c)$ in \mathbb{R}^n that fulfills condition (C) and has constant sign matrix \widehat{G} cannot have multiple nondegenerate steady states.

We finish the section with two examples that illustrate the relationship between the criteria.

Example 14.5. Consider Example 9.11. Karlebach and Shamir [26] model the gene network depicted in Figure 1(b) as

$$\dot{c}_1 = \frac{\alpha_1}{1 + \beta_1 c_3} - \delta_1 c_1, \quad \dot{c}_2 = \frac{\alpha_2 c_1}{1 + \beta_2 c_1} - \delta_2 c_2, \quad \dot{c}_3 = \frac{\alpha_3 c_1 c_2}{(1 + \beta_3 c_1)(1 + \beta_4 c_2)} - \delta_3 c_3$$

for positive parameters $\alpha_i, \beta_i, \delta_i$. Here degradation of each gene G_1, G_2, G_3 is incorporated. The interaction graph G associated with the system is constant and

$$\widehat{G} = \begin{pmatrix} - & + & + \\ 0 & - & + \\ - & 0 & - \end{pmatrix}.$$

This matrix is I_n -SNS ($n = 3$) and, therefore, the system cannot have multiple nondegenerate steady states.

Using the stoichiometric matrix $A = I_n$ effectively corresponds to analyzing injectivity of a network with only inflow reactions ($0 \rightarrow G_i$) and influence specification given by \widehat{G} . Since, in our terminology, a kinetics must be positive, the entry $-$ in position $(1, 1)$ of \widehat{G} corresponds to a decreasing kinetics in c_1 for the inflow reaction $0 \rightarrow G_1$. This is different from the system we started from, which had a negative summand $(-\delta_1 c_1)$. Alternatively, each \dot{c}_j might be separated into two components, one representing the reaction $0 \rightarrow G_i$, the other $G_i \rightarrow 0$.

As we can deduce from the results above, preclusion of multistationarity by the methods of [27] is essentially preclusion of multistationarity in networks in which only inflow reactions are considered. Knowledge about the underlying network structure allows us to preclude multistationarity for a bigger class of dynamical systems. We “see” not only the signs of the entries of the Jacobian, but also the terms that contribute to the signs. This is illustrated in the following simple example.

Example 14.6. Consider the sign matrix \widehat{G} with entries $g_{1,2} = g_{2,1} = +$ and $g_{1,1} = g_{2,2} = -$. This matrix is not I_n -SNS, and hence multistationarity cannot be excluded from Theorem 14.1. Consider now a network with reactions $r_1: S_1 \rightarrow S_2$ and $r_2: S_2 \rightarrow 0$, and stoichiometric matrix A given by the reactions r_1, r_2 . The dimension of the stoichiometric subspace is $n = 2$. For any kinetics $K \in \mathcal{K}_{2,2}$ the ODE system associated with the network is of the form

$$\dot{c}_1 = -K_1(c), \quad \dot{c}_2 = K_1(c) - K_2(c).$$

Consider the influence specification Z with nonzero terms: $z_{1,1} = z_{2,2} = +$ and $z_{1,2} = -$. If $K \in \mathcal{K}_{2,2}^d(Z)$, then the Jacobian of the species formation rate function has interaction graph G . Further, the only set of reactions of cardinality $s = n = 2$ is $\{r_1, r_2\}$. By calculation, Z is A -SNS, and it follows from Proposition 9.19 and Theorem 10.1 that the network is Z -injective over $\mathcal{K}_{2,2}^d(Z)$ and multistationarity cannot occur.

15. Hill-type kinetics and injectivity. Let A be an $n \times m$ stoichiometric matrix, and Z an $m \times n$ influence specification. The key to the statements in section 10 is that whenever there are two nonoverlapping stoichiometrically compatible concentration vectors a, b and $f_K(a) = f_K(b)$ for some kinetics $K \in \mathcal{K}_{m,n}$, then we can find two positive stoichiometrically compatible concentration vectors \tilde{a}, \tilde{b} and $f_{\kappa,V}(\tilde{a}) = f_{\kappa,V}(\tilde{b})$ for some power-law kinetics

$(\kappa, V) \in \mathcal{K}_{m,n}^g(Z)$. However, the latter property could be fulfilled by many classes of kinetics other than the class of power-law kinetics.

One such class of kinetics is *Hill-type kinetics*, which is often employed in modeling of biochemical reaction networks. In this section we will show that being Z -injective over $\mathcal{K}_{m,n}^g(Z)$ is equivalent to being injective over a similar class of Hill-type kinetics. In particular, this implies that injectivity over $\mathcal{K}_{m,n}(Z)$ can be settled by applying Hill-type kinetics rather than power-law kinetics.

We say that a kinetics is of Hill type with respect to an $m \times n$ influence specification Z if $K = (K_1, \dots, K_m)$ takes the form

$$K_j(c) = k_j \prod_{i=1}^n \frac{c_i^{v_{j,i}}}{\delta_{j,i} + c_i^{v_{j,i}}},$$

with $c \in \overline{\mathbb{R}}_+^n$ (defined by continuity at the boundary), $k_j \in \mathbb{R}_+$, $\delta_j \in \overline{\mathbb{R}}_+^n$, and $v_j \in \mathbb{R}^n$ for $j = 1, \dots, m$ such that

$$\text{supp}^+(v_j) = z_j^+, \quad \text{supp}^-(v_j) = z_j^-, \quad \text{and} \quad \text{supp}(\delta_j) = \text{supp}(v_j).$$

The definition is very similar to that of power-law kinetics, with the only difference being the factor $\delta_{j,i}$ in the denominators. A term with $v_{j,i} > 0$ defines a positive influence, while a term with $v_{j,i} < 0$ defines a negative influence. Compared to power-law kinetics, the constant $\delta_{j,i}$ moderates a negative influence for low concentrations.

Let $\kappa = (k_1, \dots, k_m)$, $\mathbf{d} = (\delta_1, \dots, \delta_m)$, and V be an $m \times n$ matrix. We denote a Hill-type kinetics by $K = (\kappa, \mathbf{d}, V)$, and the set of Hill-type kinetics with respect to Z by $\mathcal{K}_{m,n}^H(Z)$. Hill-type kinetics include Michaelis–Menten kinetics as a special case when $v_{j,i}$ is one [8]. In contrast, power-law kinetics are not of Hill type. However, power-law kinetics can be obtained as a limiting case of Hill-type kinetics by letting k_j and the nonzero entries of v_j tend to infinity such that $k_j / \prod_i v_{j,i}$ converges to a positive constant.

Hill-type kinetics might be considered biochemically more reasonable than power-law kinetics as they are defined for all $\overline{\mathbb{R}}_+^n$ in contrast to power-law kinetics that might not be defined for points on the boundary of $\overline{\mathbb{R}}_+^n$. In addition, Hill-type kinetics or Michaelis–Menten kinetics are often obtained when variables (species) are eliminated from the modelling equations [8].

Theorem 15.1. *Let A be an $n \times m$ stoichiometric matrix, Z an $m \times n$ influence specification, and $a, b \in \overline{\mathbb{R}}_+^n$. Then the following hold:*

- (i) *For every Hill-type kinetics $K = (\kappa, \mathbf{d}, V) \in \mathcal{K}_{m,n}^H(Z)$ there exists a power-law kinetics $(\lambda, W) \in \mathcal{K}_{m,n}^g(Z)$ such that $Z(W) = Z$, $f_K(a) = f_{\lambda,W}(a)$, and $f_K(b) = f_{\lambda,W}(b)$.*
- (ii) *For every power-law kinetics $(\lambda, W) \in \mathcal{K}_{m,n}^g(Z)$ there exists a Hill-type kinetics $K = (\kappa, \mathbf{d}, V) \in \mathcal{K}_{m,n}^H(Z)$ such that $Z(V) = Z$, $f_K(a) = f_{\lambda,W}(a)$, and $f_K(b) = f_{\lambda,W}(b)$.*

In particular, $f_{\lambda,W}(a) = f_{\lambda,W}(b)$ for some power-law kinetics $(\lambda, W) \in \mathcal{K}_{m,n}^g(Z)$ if and only if $f_K(a) = f_K(b)$ for some Hill-type kinetics $K = (\kappa, \mathbf{d}, V) \in \mathcal{K}_{m,n}^H(Z)$ such that $Z(V) = Z(W)$.

As a consequence, injectivity of a stoichiometric matrix A over $\mathcal{K}_{m,n}(Z)$ is guaranteed by the injectivity of A over $\mathcal{K}_{m,n}^H(Z)$. It also follows that A is injective over $\mathcal{K}_{m,n}^g(Z)$ if and only if A is injective over $\mathcal{K}_{m,n}^H(Z)$. Furthermore, we have that A has multiple positive steady states in some stoichiometric class with respect to a Hill-type kinetics if and only if A has

multiple positive steady states in the same stoichiometric class with respect to a power-law kinetics.

Appendix. Proofs.

Proof of Proposition 5.2. We have that $v \in \ker(M)$ if and only if $Mv = 0$. By assumption the top d rows of M are expressed as linear combinations of the bottom $s = n - d$ rows of M :

$$(0, \dots, 0) = \omega^j M = M_j + \sum_{i=d+1}^n \omega_i^j M_i,$$

where M_i is the i th row in M . Hence, $v \in \ker(M)$ is equivalent to requiring that the scalar product of the bottom s rows of M and v be zero. On the other hand, we have that $v \in F$ if and only if $\omega^i \cdot v = 0$ for all i . It follows that $\ker(M) \cap F = \ker(\widetilde{M})$ and hence $\ker(M) \cap F = \ker(\widetilde{M}) = \{0\}$ if and only if \widetilde{M} has maximal rank, that is, if and only if $\det(\widetilde{M}) \neq 0$. ■

Proof of Proposition 5.3. Consider the characteristic polynomial of M given as the determinant of $M - \lambda I_{n \times n}$. The right-hand side of the equality in the proposition is $(-1)^d$ times the coefficient of λ^d . Let P be the matrix whose top d rows are $\omega^1, \dots, \omega^d$ and that agrees with the identity matrix in the bottom s rows. By assumption, $\omega^1, \dots, \omega^d$ is a reduced basis; hence the determinant of P is 1. Therefore

$$\det(M - \lambda I_{n \times n}) = \det(PM - \lambda P I_{n \times n}) = \det(PM - \lambda P).$$

Since the vectors $\omega^1, \dots, \omega^d$ are orthogonal to the columns of M , the matrix PM has zero rows in the top d rows and agrees with M in the bottom s rows. It follows that

$$PM - \lambda P = \begin{pmatrix} & -\lambda \omega^1 & & \\ & \vdots & & \\ & -\lambda \omega^d & & \\ M_{\{d+1, \dots, n\}, \{1, \dots, n\}} - \lambda I_{s \times s} & & & \end{pmatrix}.$$

The coefficient of $(-1)^d \lambda^d$ of the characteristic polynomial of M is thus precisely given as the determinant of \widetilde{M} . ■

Proof of Proposition 8.2. Using (5.1), we have that

$$\det(J_c(\widetilde{f}_{\kappa, V})) = \sum_{I, J \subseteq \{1, \dots, n\}, \#I = \#J = s} \det(A_{I, J}) \det((\partial K)_{J, I}).$$

We have $(\partial K)_{j, i} = (k_j c^{v_j}) c_i^{-1} v_{j, i}$. That is, each term in the j th row of ∂K is multiplied by $k_j c^{v_j}$, and each term in the i th column of ∂K is multiplied by c_i^{-1} . It follows that

$$\partial K = \text{diag}(u_1, \dots, u_m) V \text{diag}(g_1, \dots, g_n)$$

with $u_j = k_j c^{v_j}$ and $g_i = c_i^{-1}$. Hence,

$$\det((\partial K)_{J, I}) = \prod_{j \in J} u_j \prod_{i \in I} g_i \det(V_{J, I}).$$

The coefficient of $\prod_{j \in J} k_j$ is given by summing these terms over all possible sets $I \subseteq \{1, \dots, n\}$ of cardinality s , and we obtain the expression in the statement. ■

Proof of Proposition 8.4. If (ii) holds, then (i) is a consequence of Theorem 8.1 and Proposition 8.2. To show that (i) implies (ii) consider the proof of Proposition 5.3 and the notation introduced there. We have that

$$\det(J_c(\tilde{f}_{\kappa, V})) = \sum_{I, J \subseteq \{1, \dots, n\}, \#I = \#J = s} \det(A_{I, J}) \det(V_{J, I}) \prod_{j \in J} u_j \prod_{i \in I} g_i.$$

This is a linear polynomial in u_* and g_* , and the coefficient of each monomial is given by the product of the two determinants. If two coefficients have opposite signs, then we can find values for u_* and g_* that make the polynomial vanish (section 2). ■

Proof of Lemma 9.5. We first prove the forward implication, that is, that a strictly monotonic kinetics fulfills (i) and (ii). Assume that $K_j(a) > K_j(b)$. We show that

$$(\#) \quad \exists i : a_i > b_i \text{ and } z_{j,i} = +, \text{ or } a_i < b_i \text{ and } z_{j,i} = -.$$

To prove this, we assume that the contrary holds; that is, for all i ,

$$(A.1) \quad a_i \leq b_i \text{ if } z_{j,i} = + \quad \text{and} \quad a_i \geq b_i \text{ if } z_{j,i} = -.$$

Let $\tilde{a} = a \wedge b$ be the minimum of a and b , $\tilde{a}_i = \min(a_i, b_i)$. By definition, $\tilde{a} \in \Omega_K$. Recall that $K_j(c)$ does not depend on c_i for which $z_{j,i} = 0$ and $K_j(c) = 0$ whenever $c \notin \Omega_K(z_j^+)$. Since K respects the influence specification we have, by monotonicity and (A.1),

$$(A.2) \quad K_j(a) \leq K_j(\tilde{a}) \leq K_j(b).$$

However, this contradicts that $K_j(a) > K_j(b)$, implying that (#) is true, and hence also (i).

Assume now $K_j(a) = K_j(b)$. If $K_j(a) = 0$, then there are $i, j \in z_j^+$ such that $a_i = b_j = 0$. Since a and b are nonoverlapping, this cannot be the case, and consequently $K_j(a) \neq 0$. It follows that either $a_i = b_i$ for all i such that $z_{j,i} \neq 0$, or $a_i \neq b_i$ for some i such that $z_{j,i} \neq 0$. If for all such indices $\text{sign}(a_i - b_i)z_{j,i}$ takes the same value $\epsilon = +$ or $-$, then by monotonicity $\text{sign}(K_j(a) - K_j(b)) = \epsilon \neq 0$, which is a contradiction. Therefore, there exist two indices i, ℓ fulfilling (ii). This completes the first part of the proof.

To prove the reverse implication, assume that (i) and (ii) are fulfilled. Let $c, d \in \Omega_K(z_j^+)$ be two vectors that differ only in the i th coordinate. If $K_j(c) > K_j(d)$, then by (i) we have $\text{sign}(c_i - d_i) = z_{j,i} \neq 0$. It follows that if $z_{j,i} = 0$, then $K_j(\cdot)$ is constant in the i th coordinate. If $i \in z_j^+ \cup z_j^-$ and $K_j(c) = K_j(d)$, then according to (ii) we have $c_i = d_i$ contradicting $c_i \neq d_i$. (The second option cannot occur since c and d differ in exactly one coordinate.) Therefore $K_j(c) \neq K_j(d)$. Using (i), we conclude that $K_j(\cdot)$ is increasing/decreasing in the i th coordinate depending on the sign of $z_{j,i}$. This completes the proof. ■

Proof of Lemma 9.17. (i) Z has a signed A -determinant if and only if the polynomial $p_Z(X)$ has constant sign when evaluated in positive values of the nonzero entries of X . The equivalence follows from the fact that each variable has degree zero or one in $p_Z(X)$. (ii) The polynomial $p_{Z'}(X)$ can be obtained from $p_Z(X)$ by setting some variables to zero. Statements (a)–(c) follow from this observation and statement (i). ■

Proof of Proposition 9.19. By Lemma 9.14, A is injective over $\mathcal{K}_{m,n}^g(Z)$ if and only if A is injective over $\mathcal{K}_{m,n}^g[V]$ for all V such that $Z(V) = Z$. If Z is A-SNS, then each of the nonzero terms $p_{Z,I,J}$ is sign-nonzero and has the same sign for all I, J , and at least one of them is nonzero. By Proposition 8.4, this implies that A is injective over $\mathcal{K}_{m,n}^g[V]$ for all V .

Reciprocally, let us assume that A is injective over $\mathcal{K}_{m,n}^g[V]$ for all V . Then by Proposition 8.4, for each fixed V , there is at least one nonzero term $p_{Z,I,J}(|V|)$, and all nonzero terms have the same sign. It follows that $p_Z(|V|) \neq 0$ for all V . If there exist V_1, V_2 in $\Sigma(Z)$ such that the signs of $p_Z(|V_1|)$ and $p_Z(|V_2|)$ are different, then by continuity we could find V_0 such that $p_{Z,I,J}(|V_0|) = 0$. (The set of kinetic orders with associated influence Z inherits a Euclidean topology from the Euclidean space it is embedded in.) This contradicts that A is injective over $\mathcal{K}_{m,n}^g[V_0]$. Therefore, the sign of $p_Z(|V|)$ is independent of V , and thus by definition Z is A-SNS. ■

Proof of Proposition 9.22. If A is injective over $\bigcup_{Z|Z_1 \preceq Z \preceq Z_2} \mathcal{K}_{m,n}^g(Z)$, then (iii) is trivially fulfilled, and (ii) follows from Proposition 9.19. Proposition 9.19 and Lemma 9.17(ii) give that (iii) implies (i). Finally, if (ii) holds, then by Lemma 9.17(ii) we have that Z_1 has a signed A-determinant. It follows from Corollary 9.20 that (iii) holds. ■

Proof of Corollary 9.23. Since the determinant $\det(J_c(f_{\kappa,Y}))$ is not identically zero, there is a term in its expansion in κ with positive coefficient and a term with negative coefficient. Since $Z_c \preceq Z(V)$, the terms in the polynomial expansion of $\det(J_c(\tilde{f}_{\kappa,V}))$ in κ cannot all have the same sign. Thus Proposition 8.4 implies that $\mathcal{K}_{m,n}^g[V]$ is not injective. ■

Proof of Theorem 9.28. Assume that A is injective over $\mathcal{K}_{m,n}^g[V]$. Proposition 8.4(ii) implies that the nonzero products $\det(A_{I,J}) \det(V_{J,I})$ have the same sign δ for all sets $I, J \subseteq \{1, \dots, n\}$ of cardinality s and that at least one of the products is nonzero. For the matrix $A_{*,J}$ there is only one choice of column indices, namely the set $J = \{1, \dots, s\}$ (s is the rank of $A_{*,J}$). Observe that $\det(V_{J,I}) = \det(V_{\{1, \dots, s\}, I})$. If $\det(A_{I,J}) \det(V_{J,I}) = 0$ for all I , then all steady states (if there are any) are degenerate (see (6.1)). If for some I we have $\det(A_{I,J}) \det(V_{J,I}) \neq 0$, then it follows from Proposition 8.4 that $A_{*,J}$ is injective over $\mathcal{K}_{m,s}^g[V_{J,*}]$, and hence all steady states are nondegenerate. ■

Proof of Theorem 10.1. The proof is inspired by arguments presented in [38]. By Lemma 9.8, (i) implies (ii), and since power-law kinetics are differentiable with respect to the influence specification, (ii) implies (iii). (iii) and (iv) are equivalent according to Proposition 9.19. Let us prove that (iii) implies (i). Assume that A is injective over $\mathcal{K}_{m,n}^g(Z)$ but not Z -injective over $\mathcal{K}_{m,n}(Z)$. Then there exist $K \in \mathcal{K}_{m,n}(Z)$ and distinct nonoverlapping vectors $a, b \in \overline{\mathbb{R}}_+^n$ such that $\gamma := a - b \in \text{Im}(A)$ and $f_K(a) = f_K(b)$. We seek a contradiction to the fact that A is injective over $\mathcal{K}_{m,n}^g(Z)$; that is, we seek a power-law kinetics (κ, V) such that $f_{\kappa,V}(\tilde{a}) = f_{\kappa,V}(\tilde{b})$ for two vectors $\tilde{a}, \tilde{b} \in \mathbb{R}_+^n$ with $\tilde{a} - \tilde{b} \in \text{Im}(A)$.

For a positive constant $\delta > 0$ and a positive constant vector $\zeta \in \mathbb{R}_+^n$, define

$$\tilde{K}_j(c) = K_j(c) + \delta, \quad \tilde{a} = a + \zeta, \quad \text{and} \quad \tilde{b} = b + \zeta$$

such that $\tilde{K}_j(a) - \tilde{K}_j(b) = K_j(a) - K_j(b)$, $\tilde{a} - \tilde{b} = a - b$, and \tilde{a}, \tilde{b} are positive vectors in \mathbb{R}_+^n . Therefore $\tilde{K}_j(a) > \tilde{K}_j(b)$ if and only if $K_j(a) > K_j(b)$, $a - b \in \text{Im}(A)$ if and only if $\tilde{a} - \tilde{b} \in \text{Im}(A)$, and $a_i > b_i$ if and only if $\tilde{a}_i > \tilde{b}_i$ (and similarly for equality). Since a, b are nonoverlapping, $K_j(a)$ and $K_j(b)$ cannot both be zero for the same reaction. Assume that we

can find a kinetic order V such that $Z(V) = Z$ and such that for all reactions

$$(A.3) \quad \frac{\tilde{K}_j(a)}{\tilde{K}_j(b)} = \frac{\tilde{a}^{v_j}}{\tilde{b}^{v_j}} = \prod_{i=1}^n \left(\frac{\tilde{a}_i}{\tilde{b}_i}\right)^{v_{j,i}}.$$

Then, if we define κ by $k_j = \tilde{K}_j(b)/\tilde{b}^{v_j}$, we have

$$\tilde{K}_j(b) = k_j \tilde{b}^{v_j} \quad \text{and} \quad \tilde{K}_j(a) = \tilde{K}_j(b) \frac{\tilde{a}^{v_j}}{\tilde{b}^{v_j}} = k_j \tilde{a}^{v_j},$$

and thus $f_K(a) = f_K(b)$ implies $f_{\kappa,V}(\tilde{a}) = f_{\kappa,V}(\tilde{b})$.

Let us prove (A.3). Assume that $K_j(a) > K_j(b)$. Then, by Lemma 9.5, there exists i for which $\text{sign}(a_i - b_i) = z_{j,i} \neq 0$. Suppose that $a_i > b_i$ (that is, $\tilde{a}_i > \tilde{b}_i$) and $z_{j,i} = +$. Let $v_{j,\ell} = z_{j,\ell} \cdot \varepsilon$ for all $\ell \neq i$ and some positive $\varepsilon \in \mathbb{R}_+$. With this choice, (A.3) holds if we can find ε and $v_{j,i} > 0$ (because $z_{j,i} = +$) such that

$$(A.4) \quad 1 < \frac{\tilde{K}_j(a)}{\tilde{K}_j(b)} = \left(\frac{\tilde{a}_i}{\tilde{b}_i}\right)^{v_{j,i}} \prod_{\ell \neq i} \left(\frac{\tilde{a}_\ell}{\tilde{b}_\ell}\right)^{z_{j,\ell} \cdot \varepsilon}.$$

Since the function $v \mapsto (\tilde{a}_i/\tilde{b}_i)^v$ is increasing ($\tilde{a}_i/\tilde{b}_i > 1$), starts at 1, and tends to infinity as v increases, we can indeed find $v_{j,i} > 0$, potentially by choosing ε small, such that (A.4) holds. The case $b_i < a_i$ is treated similarly.

If $K_j(b) > K_j(a)$, we proceed in the same way, by interchanging the role of a and b . Finally, assume that $K_j(a) = K_j(b)$. Then, by Lemma 9.5, either $a_i = b_i$ for all $i \in z_j^+ \cup z_j^-$ or $\text{sign}(a_i - b_i) = z_{j,i} \neq 0$ and $\text{sign}(a_\ell - b_\ell) = -z_{j,\ell} \neq 0$ for some distinct i, ℓ . In the first case the kinetic vector v_j with $v_{j,i} = z_{j,i} \cdot 1$ fulfills (A.3), and further v_j satisfies $Z(V) = Z$. In the second case, we have four scenarios depending on $z_{j,i} = +, -$ and $z_{j,\ell} = +, -$. If $z_{j,i} = z_{j,\ell} = +$, then we can find, as above, $v_{j,i}, v_{j,\ell} > 0$ such that

$$1 = \frac{\tilde{K}_j(a)}{\tilde{K}_j(b)} = \left(\frac{\tilde{a}_i}{\tilde{b}_i}\right)^{v_{j,i}} \left(\frac{\tilde{a}_\ell}{\tilde{b}_\ell}\right)^{v_{j,\ell}} \prod_{u \neq i,j} \left(\frac{\tilde{a}_u}{\tilde{b}_u}\right)^{z_{j,u} \cdot \varepsilon},$$

because $\tilde{a}_i > \tilde{b}_i$ and $\tilde{a}_\ell < \tilde{b}_\ell$. Hence, $v_j = (v_{j,1}, \dots, v_{j,n})$ with $v_{j,u} = z_{j,u} \cdot \varepsilon$, $u \neq i, \ell$, fulfills (A.3). The other three scenarios are treated in the same way. In conclusion, we can find a power-law kinetics such that $f_{\kappa,V}$ is not injective. ■

Proof of Theorem 10.2. Clearly (i) implies (ii). Assume now that (ii) holds. It is equivalent to A being injective over $\mathcal{K}_{m,n}^g(Z)$, which again is equivalent to Z being A -SNS (Proposition 9.19). Now consider condition (i). It is equivalent to $\det(J_c(\tilde{f}_K)) \neq 0$ for all $c \in \mathbb{R}_+^n$ and $K \in \mathcal{K}_{m,n}^d(Z)$ (see (6.1)). The Jacobian of \tilde{f}_K is $J_c(\tilde{f}_K) = A(\partial K)$, where $\partial K = \partial K(c)$ is the $m \times n$ matrix with $\partial K_{j,i} = \partial K_j(c)/\partial c_i$. By definition of $K \in \mathcal{K}_{m,n}^d(Z)$, we have $z_{j,i} = \text{sign}((\partial K)_{j,i})$. Since Z is A -SNS, $\det(\widetilde{AZ(V)}) \neq 0$ for all kinetic orders V with $Z(V) = Z$. In particular this is true for the kinetic order given by $V = \partial K$. Hence condition (i) is true. ■

Proof of Proposition 11.1. Let \mathfrak{S}_s denote the set of permutations of s elements. By reordering the species and reaction sets, we can assume that $I = J = \{1, \dots, s\}$. Then, by the definition of the determinant,

$$\det(A_{I,J}) \det((Z_X)_{J,I}) = \sum_{\sigma, \tau \in \mathfrak{S}_s} \text{sign}(\sigma) \text{sign}(\tau) \prod_{i=1}^s a_{i, \sigma(i)} e_{\tau(i), i}.$$

Fix a nonzero summand for some pair of permutations σ, τ . Then $a_{i, \sigma(i)} \neq 0$ and $e_{i, \tau(i)} \neq 0$ for all i . It follows that in $G_{A,Z}$ there is an edge from $r_{\sigma(i)}$ to S_i and an edge from S_i to reaction $r_{\tau(i)}$ for all i . Further, the set of these edges forms a $2s$ -nucleus $D_{\sigma, \tau}$ with label $\prod_{i=1}^s a_{i, \sigma(i)} e_{\tau(i), i}$. Indeed, each species node S_i has precisely one ingoing edge with label $a_{i, \sigma(i)}$ and one outgoing edge with label $e_{\tau(i), i}$, and similarly for each reaction node r_j . Reciprocally, each $2s$ -nucleus of $G_{A,Z}$ with vertices $S_1, \dots, S_s, r_1, \dots, r_s$ gives rise to a determinant term: for each species node S_i consider the ingoing and an outgoing edge $r_j \rightarrow S_i \rightarrow r_{j'}$, and define $\sigma(i) = j$ and $\tau(i) = j'$.

It remains to check that $\text{sign}(\tau) \text{sign}(\sigma) = \text{sign}(D_{\sigma, \tau})$. The sign of $\tau\sigma$ agrees with the sign of $\tau\sigma^{-1}$, which in turn agrees with $(-1)^p$ to the number p of cycles in the permutation with even number of elements. Consider the graph in the reaction nodes r_1, \dots, r_s obtained from $D_{\sigma, \tau}$ by removing the species nodes and joining two reaction nodes if they are connected through a species node. There is a correspondence between cycles of $\tau\sigma^{-1}$ and circuits in this collapsed graph. Therefore, the sign of $\tau\sigma^{-1}$ is precisely $(-1)^p$. ■

Proof of Lemma 12.2. Assume that $K \in \mathcal{K}_{m,n}^w(Z)$ is a power-law kinetics with kinetic order V . Then $K \in \mathcal{K}_{m,n}^g(Z')$ with $Z' = Z(V)$. Let us prove that $Z' \preceq Z$. Let i be such that $z'_{j,i} = +$, that is, $v_{j,i} > 0$. Consider $a, b \in \mathbb{R}_+^n$ such that $a_u = b_u, i \neq u$, and $a_i > b_i$. Then $K_j(a) > K_j(b)$ because K is a power-law kinetics. By Definition 12.1(i) and using that a, b differ only in the index i , we have $z_{j,i} = \text{sign}(a_i - b_i) = +$. Therefore, $z'_{j,i} = z_{j,i}$. We proceed similarly if $z'_{j,i} = -$ to conclude that $Z' \preceq Z$. ■

Proof of Theorem 12.3. By Lemma 12.2, (i) implies (iii). (ii) and (iii) are equivalent due to Theorem 10.1. That (iii) implies (i) is proved similarly to the proof of Theorem 10.1: the vector $v_j \in \mathbb{R}^n$ is likewise chosen such that (A.4) is fulfilled for the given influence specification Z . ■

Proof of Theorem 14.3. The matrix A is injective over $\mathcal{K}_{2s,n}^d(Z)$ if and only if Z is A -SNS, that is, the nonzero coefficients of $p_Z(X)$ have constant sign and at least one is nonzero. The polynomial $p_Z(X)$ is the determinant of the symbolic matrix \widetilde{AZ}_X . Since the $n - s$ rows of A are zero, a basis of $\text{Im}(A)^\perp$ is $\{e^{s+1}, \dots, e^n\}$, where e^j is the j th unit vector (of length n). Then, an easy computation shows that $p_Z(X)$ is the upper-left $s \times s$ minor of AZ_X . By construction, the sign pattern of the upper-left $s \times s$ minor of AZ_X is the upper-left $s \times s$ submatrix of $\widehat{G}, \widehat{G}_L$.

On the other hand, consider the interaction graph G . Only nodes $1, \dots, s$ have incoming edges; hence a node $j > s$ cannot be part of any circuit of G . Consequently, any s -nucleus of G contains precisely the nodes $1, \dots, s$ and is a nucleus in the subgraph G_L of G given by these nodes. The matrix associated with this subgraph is \widehat{G}_L .

Let t be a nonzero term in the expansion of the upper-left $s \times s$ minor of AZ_X , and $N(t)$ the corresponding nucleus of G_L . From [40, Lemma 1] we have

$$\text{sign}(N(t)) = \text{sign}(t)(-1)^{s+1}.$$

Consequently, all terms t have the same sign if and only if all s -nuclei have the same sign, and there is a nonzero term if and only if there is an s -nucleus. Using Corollary 9.18, this proves the equivalence between (i) and (ii). ■

Proof of Theorem 15.1. Let $a, b \in \mathbb{R}_+^n$, $(\lambda, W) \in \mathcal{K}_{m,n}^g(Z)$, and $Z = Z(W)$, with $\lambda = (l_1, \dots, l_m)$. For each $j = 1, \dots, m$, define $\delta_{j,i} = 0$ and $v_{j,i} = 0$ for all $i \in z_j^0$ (that is, for all i such that $w_{j,i} = 0$). Let $M_j \in \mathbb{R}_+$ be such that $M_j a_i^{w_{j,i}} < 1$ and $M_j b_i^{w_{j,i}} < 1$ for all $i \in z_j^+ \cup z_j^-$. Then we can find $\delta_{j,i} \in \overline{\mathbb{R}}_+$ and $v_{j,i} \in \mathbb{R}$ such that

$$(A.5) \quad \frac{a_i^{v_{j,i}}}{\delta_{j,i} + a_i^{v_{j,i}}} = M_j a_i^{w_{j,i}} \quad \text{and} \quad \frac{b_i^{v_{j,i}}}{\delta_{j,i} + b_i^{v_{j,i}}} = M_j b_i^{w_{j,i}}.$$

Let $\mathbf{d} = (\delta_1, \dots, \delta_m)$, $V = (v_{j,i})_{j=1, \dots, m, i=1, \dots, n}$, and define $\kappa = (k_1, \dots, k_m)$ by $k_j = l_j / M_j^J$, where J is the cardinality of $z_j^+ \cup z_j^-$. Then $Z(V) = Z(W)$ and $K = (\kappa, \mathbf{d}, V) \in \mathcal{K}_{m,n}^H(Z)$. Further,

$$l_j a^{w_j} = k_j \prod_{i=1}^n \frac{a_i^{v_{j,i}}}{\delta_{j,i} + a_i^{v_{j,i}}},$$

where $w_j = (w_{j,1}, \dots, w_{j,n})$, and similarly for b . It follows that $f_K(a) = f_{\kappa, W}(a)$ and $f_K(b) = f_{\kappa, W}(b)$. This proves (ii). To prove (i) we follow the reverse procedure by choosing M_j and $w_{j,i}$ to fulfill (A.5). ■

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