Classification of multistationarity for reaction networks with one-dimensional stoichiometric subspaces

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These notes *are coming from a rough first version of our paper "Multistationarity and nondegenerate multistationarity of networks with one-dimensional stoichiometric subspace", available on arXiv. That version of that paper contains a simpler and shorter proof of part 3 of our main theorem (Theorem 4.1 here). However, the proof here is a hands-on case-by-case algebraic approach, which may be valuable in other ways.*

Contents

1 Introduction

Multistationarity (i.e. the existence or two or more compatible positive equilibrium points) underlies switching behavior in biochemical systems, and is a key mathematical feature of systems that generate multiple outputs in response to different external signals or stimuli [2, 15, 16]. This phenomenon is crucial in important cell behaviors, including generating sustained oscillatory responses, remembering transitory stimuli, differentiation, or apoptosis [24, 36, 26, 6, 27].

While the question of determining which reaction networks admit multistationarity is very much open, many of powerful techniques relating the structure of a reaction network with its capacity for multistationarity are known. These include tools based on the injectivity of the vector field [10, 11, 12, 22, 35, 25, 3], degree theory[8, 7], and inheritance, where the multistationarity of a reaction network is inherited from multistationarity of its substructures [3, 5]. This creates the possibility of "lifting" multistationarity from idealized network motifs [1] to larger and more realistic networks. There is already a significant amount of work on cataloguing classes of motifs by their presence or absence of multistationarity. These include all bimolecular open networks with two reactions (both reactions reversible or irreversible) [**?**], fully open as well as isolated sequestration networks in arbitrary number of species and reactions [**?**], fully open networks with cyclic DSR graph (CST networks, [14]), and networks with two reactions [21].

Our work adds to the catalog the class of reaction networks with one-dimensional stoichiometric answering in the affirmative a conjecture posed by Joshi and Shiu:

Conjecture 1.1 (Question 6.1 [21])**.** *A reaction network with one-dimensional stoichiometric subspace and more than one source complex has the capacity for multistationarity if and only if it has a one-species embedded subnetwork with the pattern* $(\rightarrow, \leftarrow)$*, and another (possibly the same) with pattern* $(\leftarrow, \rightarrow)$*.*

Additionally, we characterize which networks with one-dimensional stoichiometric subspace can have *nondegenerate* equilibria. The classification of these networks with nondegenerate equilibria was needed in our proof of Conjecture 1.1, but it is also important on its own, for example inheritance results only apply for nondegenerate equilibria. Our classification of nondegeneracy extends and generalizes results from the literature [21, 31, 23]. In particular we prove a conjecture by Shiu and de Wolff regarding characterization of nondegenerate multistationarity for networks with one irreversible and one reversible reaction.

Conjecture 1.1 is known to hold for special cases. In particular, the conjecture is true for networks with two reactions (Joshi and Shiu [21]) and under some technical additional assumptions (Lin, Tang and Zhang [23]). These are discussed in detail in Section 4.2.

Our results are developed for mass action kinetics, although our proof extends without difficulty to the more general *power law* kinetics, an important, used to model a variety of biological phenomena including genetic circuits and developmental systems [28, 29]. [30].

The paper is structured as follows: general reaction networks terminology is introduced in section [**?**]; section 3 sets notation for networks with one-dimensional stoichiometric subspace and defines classes of networks that our main theorem (Theorem 4.1) depend on. The main result, examples, and connection with literature are presented in section 4, and section **??** contains the proof.

2 Preliminaries

2.1 Reaction networks and kinetics

Throughout the paper $\{e_1, \ldots, e_n\}$ denotes the standard basis of $\mathbb{R}^n$ and $\mathbb{R}^n_{>0}$, $\mathbb{R}^n_{\geq 0}$ denote the subsets of $\mathbb{R}^n$ containing vectors with positive and non-negative entries respectively. The set of n-dimensional vectors with nonnegative integer entries is denoted by $\mathbb{Z}^n_{\geq 0}$.

We review some standard terminology on reaction networks.

A *reaction* on a list of *species* $X = (X_1, \ldots X_n)$ has the general form

$$a_1X_1 + a_2X_2 + \ldots + a_nX_n \rightarrow b_1X_1 + b_2X_2 + \ldots + b_nX_n, \tag{1}$$

where and $a = (a_1, \ldots, a_n)$ and $b = (b_1, \ldots, b_n)$ are vectors in $\mathbb{Z}^n_{\geq 0}$. Entries a_i and b_i are called *stoichiometric coefficients* of species X_i in a and b. The *source complex* of (1) is $a \cdot X := a_1X_1 + a_2X_2 + \ldots + a_nX_n$, and $b \cdot X$ is called the *product complex* of $\mathcal{N}$. The vector $b - a$ is called the *reaction vector* of (1).

A *reaction network* $\mathcal{N}$ on a list of species $X = (X_1, \ldots, X_n)$ is a finite list of reactions on X. We require that source and product complexes differ for each reaction, and that no reaction is listed multiple times.

Once an order has been chosen for reactions in $\mathcal{N}$, their reaction vectors form the columns of the *stoichiometric matrix* $\Gamma \in \mathbb{Z}^{n\times m}$. The image of Γ is called the *stoichiometric subspace* of the network.

The vector of *concentrations* of $X_1, \ldots, X_n$ is denoted by $x \in \mathbb{R}^n_{\geq 0}$. In deterministic spatially homogeneous models the time evolution of concentration is commonly modelled with *mass action kinetics*, where the *reaction rate* of $a \to b$ is given by $\kappa x^a := \kappa x_1^{a_1} \ldots x_n^{a_n}$. Here κ is a positive constant that depends on the reaction, called the *rate constant* of the reaction.

A reaction network $\mathcal{N}$ with an assignment of rate constants $\kappa = [\kappa_1, \ldots, \kappa_m]$ is called a *mass action system* and is denoted by $(\mathcal{N}, \kappa)$. The set of ODEs

The time evolution of the concentration vector x is governed by the ODE system of $(\mathcal{N}, \kappa)$:

$$\frac{\mathrm{d}x}{\mathrm{d}\tau} = \Gamma r(x(\tau)). \tag{2}$$

τ denotes the time variable, and $r(x) = [r_1(x), \ldots r_m(x)]^t$ is the vector of reaction rates (i.e. the *rate vector*). Note that $x(\tau)$ stays nonnegative for any $\tau \geq 0$ (see for example [34] volpert? it has section "Positiveness of the solution"

2.2 Compatibility classes and multistationarity

Integrating (2) with respect to time we have

$$x(\tau) = x(0) + \Gamma \int_0^T r(x(s))\mathrm{d}s,$$

in other words the solutions of (2) are constrained to affine sets of the form

$$(\eta + \text{im } \Gamma) \cap \mathbb{R}_{\geq 0},$$

where $\eta \in \mathbb{R}^n_{\geq 0}$. These are called *compatibility classes*.

A *positive equilibrium*, or *positive steady state* of a mass action system $(\mathcal{N}, \kappa)$ is a point $x^* \in \mathbb{R}^n_{>0}$ such that

$$\Gamma r(x^*) = 0.$$

Roughly speaking, *multistationarity* refers to the existence of two or more positive equilibria. Note however that when the dimension of the stoichiometric space is smaller than the number of species we typically obtain a continuum of equilibria. With dynamics being constrained to compatibility classes, the relevant multistationarity question is at the level of each compatibility class.

Definition 2.1. *(Capacity for MPE). We say that a reaction network* $\mathcal{N}$ has the capacity for multiple positive equilibria (MPE) *if there exist an assignment of rate constants* κ *such that the reaction system* $(\mathcal{N}, \kappa)$ *has two or more positive equilibria belonging to the same compatibility class of* $\mathcal{N}$.

Example 2.2. Consider the reaction network [1]

$$\mathcal{N}_1 = \{X_1 + X_2 \to 2X_1 + 2X_2, \quad X_1 + X_2 \to 0, \quad 0 \to X_1 + X_2.\} \tag{3}$$

[1] $0 = 0X_1 + 0X_2$ denotes the *zero complex*, which may be interpreted as a placeholder for the exterior of the environment where the reactions take place, or for species that we do not include in our model. For example (3) may represent the biochemically realistic network $X_1 + X_1 \to 2X_3$, $2X_3 \to X_1 + X_2$, where X_3 is so abundant that it is considered constant for all practical purposes, and not included in the model.

Letting κ_1 and κ_2 denote the rate constants of the two reactions, under mass action equilibrium points satisfy the equation

$$\Gamma r(x) = \begin{bmatrix} 1 & -1 & 1 \\ 1 & -1 & 1 \end{bmatrix} \begin{bmatrix} \kappa_1 x_1 x_2 \\ \kappa_2 x_1 x_2 \\ \kappa_3 \end{bmatrix} = 0,$$

or $(\kappa_1 - \kappa_2)x_1x_2 + \kappa_3 = 0$; this curve is called *the steady state manifold* of mass action system $(\mathcal{N}_1, \kappa)$. The stoichiometric subspace of $\mathcal{N}_1$ is one-dimensional and compatibility classes are cosets of $\text{im}\Gamma = \text{span}([1,1]^t)$ intersected with the positive quadrant, i.e. line segments of the form $x_2 - x_1 = T$ (Figure 1(a)). Positive equilibria in the compatibility class $x_2 - x_1 = T$ are obtained by solving the system

$$(\kappa_1 - \kappa_2)x_1x_2 + \kappa_3 = 0, \quad x_2 - x_1 = T.$$

This has no positive solutions for $\kappa_1 > \kappa_2$ and exactly one solution when $\kappa_1 < \kappa_2$. The stoichiometric class $x_2 - x_1 = T$ contains no equilibrium points or exactly one equilibrium point $(\frac{-T+\sqrt{T^2-\frac{4\kappa_3}{\kappa_1-\kappa_2}}}{2}, \frac{T+\sqrt{T^2-\frac{4\kappa_3}{\kappa_1-\kappa_2}}}{2})$. Reaction $\mathcal{N}_1$ does not have the capacity for MPE.

Example 2.3. The reaction network

$$\mathcal{N}_2 = \{2X_1 + X_2 \to 3X_1, \quad X_1 \to X_2\} \tag{4}$$

is a subnetwork of a bistable network for modeling apoptosis [18] and is one of the simplest networks with bistability [19, 4].

Assigning rate constants $\kappa_1 = \kappa_2 = 1$ to reactions above, equilibria are computed by solving the equation

$$\Gamma r(x) = \begin{bmatrix} 1 & -1 \\ -1 & 1 \end{bmatrix} \begin{bmatrix} x_1^2 x_2 \\ x_1 \end{bmatrix} = 0,$$

and the steady state manifold of $(\mathcal{N}_2, \kappa)$ in the positive orthant is $x_1x_2 = 1$. The stoichiometric subspace is one-dimensional, spanned by $[1,-1]^t$ and compatibility have the form $x_1 + x_2 = T$. Positive equilibria in the compatibility class $x_1 + x_2 = T$ are obtained by solving the system

$$x_1x_2 = 1, \quad x_1 + x_2 = T.$$

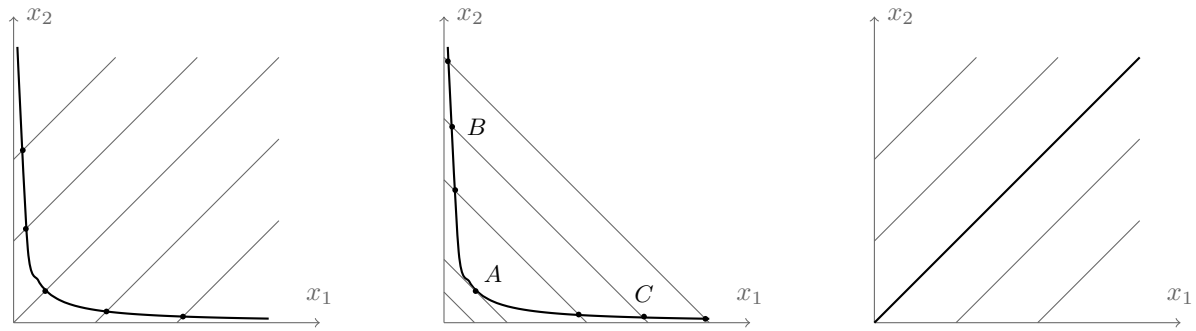
This gives $x_1^2 - Tx_1 + 1 = 0$; there are no positive equilibria if $T < 2$, one positive equilibrium $(x_1, x_2) = (1, 1)$ if $T = 2$ and two positive equilibria $(\frac{T+\sqrt{T^2-4}}{2}, \frac{T-\sqrt{T^2-4}}{2})$ and $(\frac{T-\sqrt{T^2-4}}{2}, \frac{T+\sqrt{T^2-4}}{2})$ if $T > 2$ (Figure 1(b)). $\mathcal{N}_2$ has the capacity for MPE.

Nondegenerate equilibria. At equilibrium point A in Figure 1(b) the steady state manifold and the compatibility class intersect tangentially, while at equilibrium points B and C the intersection is transversal. This distinction is an important one: A is called a *degenerate equilibrium*, while B and C are called *nondegenerate equilibria*. To be precise, a positive equilibrium point x^* is called nondegenerate if the kernel of the Jacobian matrix of (2) computed at x^* intersects the stoichiometric subspace at 0 only [11, Definition 4]:

$$\ker(\Gamma Dr(x)|_{x=x^*}) \cap \text{im } \Gamma = \{0\}. \tag{5}$$

Equivalently, a positive equilibrium x^* is nondegenerate if the Jacobian of the vector field projected on compatibility classes (*reduced Jacobian* [3, Appendix A.] or *core determinant* [17]) is nonzero. Conveniently for calculations, the reduced Jacobian is the sum of all $k \times k$ principal minors of the Jacobian matrix $\Gamma Dr(x)_{x=x^*}$, where $k = \text{rank } \Gamma$ is the dimension of the stoichiometric subspace [3].

Definition 2.4. *(Capacity for MPNE). We say that a reaction network $\mathcal{N}$* has the capacity for multiple positive nondegenerate equilibria (MPNE) *if there exist an assignment of rate constants κ such that the mass action system $(\mathcal{N}, \kappa)$ has two or more positive nondegenerate equilibria belonging to the same compatibility class of $\mathcal{N}$.*



(a) (b) (c)

Figure 1: Various scenarios for multistationarity. Steady state manifolds are drawn in bold, and compatibility classes with thin lines. (a) Reaction network (3) does not have the capacity for MPE. Each compatibility class contains exactly one nondegenerate equilibrium. (b) Reaction network (4) has the capacity for MPNE. Compatibility classes may contain no equilibria, one degenerate equilibrium (point A), or two nondegenerate equilibria. (c) Reaction network (6) has the capacity for MPE, but not the capacity for MPNE. When equilibria exist, a whole compatibility class is made out of equilibria.

The Jacobian matrix of network $\mathcal{N}_1$ in example 2.3 taken with rate constants $\kappa_1 = \kappa_2 = 1$ is

$$\Gamma Dr(x) = \begin{bmatrix} 2x_1x_2 - 1 & x_1^2 \\ -2x_1x_2 + 1 & -x_1^2 \end{bmatrix}$$

and its reduced Jacobian is equal to $-x_1^2 + 2x_1x_2 - 1$. At equilibrium points x^* this expression is equal to $-(x_1^*)^2 + 1$, and it follows that $(1, 1)$ is a degenerate equilibrium, whereas all other equilibrium points are nondegenerate. Reaction network (4) has the capacity for MPNE.

Some reaction networks exhibit pathological multistationarity behaviour, in that equilibria, if they exists, are all degenerate.

Example 2.5. Consider the reaction network

$$\mathcal{N}_3 = \{X_1 + 2X_2 \to 2X_1 + 3X_2, \quad 2X_1 + X_2 \to X_1\} \tag{6}$$

The steady state manifold in the positive quadrant is found from

$$\Gamma r(x) = \begin{bmatrix} 1 & -1 \\ 1 & -1 \end{bmatrix} \begin{bmatrix} \kappa_1 x_1 x_2^2 \\ \kappa_2 x_1^2 x_2 \end{bmatrix} = 0,$$

i.e. $\kappa_1 x_2 - \kappa_2 x_1 = 0$. The stoichiometric subspace of $\mathcal{N}_3$ is one-dimensional, spanned by $[1, 1]^t$ and compatibility classes are of the form $x_2 - x_1 = T$. Positive equilibria in the compatibility class $x_2 - x_1 = T$ obey the equation $(\kappa_1 - \kappa_2)x_1 + \kappa_1 T = 0$, which has positive solutions if and only if $\kappa_1 = \kappa_2$ and $T = x_2 - x_1 = 0$. In other words, all positive points in the compatibility class $x_2 - x_1 = 0$ are equilibria of $\mathcal{N}_3$, and no other equilibria exist (Figure 1(c)). It is easy to check that all equilibria are degenerate. The reduced Jacobian $\kappa_1 x_2^2 - \kappa_2 x_1^2$ is zero at equilibrium points. Therefore $\mathcal{N}_3$ has the capacity for MPE, but does not have the capacity for MPNE.

We conclude this section with a useful observation that allows us to remove species with corresponding zero coordinates in each reaction vector; their concentrations are constant functions of time. Let $\mathcal{N}$ be a reaction network with stoichiometric matrix Γ and suppose row i_0 of Γ is zero. If a is a complex of $\mathcal{N}$ we let $\bar{a}$ denote the complex obtained by removing species i_0 from a, and let

$$\bar{\mathcal{N}} = \{\bar{a} \to \bar{b} | a \to b \in \mathcal{N}\}.$$

($\bar{\mathcal{N}}$ is obtained from $\mathcal{N}$ by removing species i_0 from all reactions). If κ_k denotes the rate constant of $a \cdot X \to b \cdot X$ we define $\bar{\kappa}_k = \kappa_k C^{a_{i_0}}$ to be the rate constant of $\bar{a} \to \bar{b}$. We have $\kappa_k x^a = \bar{\kappa}_k \bar{a}^{\bar{x}}$, so that $r(x) = \bar{r}(\bar{x})$ where $\bar{r}$ denotes the rate vector of $(\bar{\mathcal{N}}, \bar{\kappa})$.

Proposition 2.6. *With notations above, $y = (y_1, \ldots, y_n) \in \mathbb{R}^n_{>0}$ is a (degenerate/nondegenerate) equilibrium point of $(\mathcal{N}, \kappa)$ if and only if $\bar{y} = (y_1, \ldots, y_{i_0-1}, y_{i_0+1}, \ldots, y_n)$ is a (degenerate/nondegenerate) equilibrium point of $(\bar{\mathcal{N}}, \bar{\kappa})$.*

Proof. We may assume that $i_0 = 1$. By separating the first row in Γ we write in block matrix form

$$\Gamma r(y) = \Gamma \bar{r}(\bar{y}) = \begin{bmatrix} 0 \\ \bar{\Gamma} \end{bmatrix} \bar{r}(\bar{y}) = [0 \quad \bar{\Gamma}\bar{r}(\bar{y})],$$

so $\Gamma r(y) = 0$ if and only if $\bar{\Gamma}\bar{r}(\bar{y}) = 0$.

For the nondegeneracy part we use (5). A straightforward calculation shows that $Dr(x) = D_{r(x)} R D_{1/x}$, where R denotes the matrix having the source complexes of $\mathcal{N}$ as rows, and D_η denotes the diagonal matrix with entries of vector η on the diagonal. Let $v \in \operatorname{im} \Gamma$ be a nonzero vector. We have $v_1 = 0$ and $\bar{v} = [v_2, \ldots, v_n] \in \operatorname{im} \bar{\Gamma}$, $\bar{v} \neq 0$. Using block matrix forms we have

$$\Gamma Dr(x)|_{x=y} v = \begin{bmatrix} 0 \\ \bar{\Gamma} \end{bmatrix} D_{\bar{r}(\bar{x})} \begin{bmatrix} R_1 & \bar{R} \end{bmatrix} \begin{bmatrix} 1/x_1 & 0 \\ 0 & D_{1/\bar{x}} \end{bmatrix} \begin{bmatrix} 0 \\ \bar{v} \end{bmatrix} = \begin{bmatrix} 0 \\ \bar{\Gamma} D_{\bar{r}(\bar{x})} \bar{R} \bar{v} \end{bmatrix} = \begin{bmatrix} 0 \\ \bar{\Gamma} D\bar{r}(\bar{x})_{\bar{x}=\bar{y}} \bar{v} \end{bmatrix}$$

so $\Gamma Dr(x)|_{x=y} v = 0$ if and only if $\bar{\Gamma} D\bar{r}(\bar{x})_{\bar{x}=\bar{y}} \bar{v} = 0$, therefore y is nondegenerate if and only if $\bar{y}$ is. □

Throughout the rest of the paper we assume that Γ does not contain zero rows.

Inheritance of multistationarity. The following result is an essential tool in our proofs.

Theorem 2.7 (Theorem 3.1 [20], Theorem 1 [4])**.** *Let $\mathcal{N}$ be a reaction network on species $X_1, \ldots, X_n$ and $\mathcal{N}'$ a reaction network obtained from $\mathcal{N}$ by adding a reaction on species $X_1, \ldots, X_n$ whose reaction vector is in the stoichiometric subspace of $\mathcal{N}$. If $\mathcal{N}$ has the capacity for MPNE, so does $\mathcal{N}'$.*

We note that the result in Theorem 2.7 is one of the simplest examples of network modification that preserve nondegenerate multistationarity

2.3 Reaction networks, embedded graphs, and arrow diagrams

A reaction network can be specified (uniquely) by its source complexes and corresponding reaction vectors. For the purpose of this paper, it is useful to introduce the following, even though it comes at the price of a slight abuse of terminology.

Definition 2.8. *(Reaction network).* A *reaction network $\mathcal{N}$ on n species is a finite set of* reactions

$$a_k \to a_k + w_k^l, \quad l \in \{1, \ldots m'_k\}$$

where for each $k \in \{1, \ldots, m\}$ $(w_k^l \in \mathbb{Z}^n)_{1 \leq l \leq m'_k}$ are nonzero pairwise distinct vectors.

Note that $a_1, \ldots, a_k$ are pairwise distinct and there are $m'_k \geq 1$ reactions associated with source complex a_k. The terminology introduced so far applies naturally to our extended notion of reaction network. In particular, $a_1, \ldots, a_k$ are called *source complexes* of $\mathcal{N}$; letting $m' = \sum_{k=1}^m m'_k$, the $n \times m'$ matrix with columns $w_1^1, \ldots, w_1^{m'_1}, \ldots, w_m^1, \ldots, w_m^{m'_m}$ is called the *stoichiometric matrix* of the network; im Γ is called its *stoichiometric subspace*; and if $\eta \in \mathbb{R}^n_{>0}$ then $(\eta + \operatorname{im} \Gamma) \cap \mathbb{R}^n_{\geq 0}$, is called the *compatibility class of η*.

Each reaction $a_k \to a_k + w_k^l$ is associated a *rate constant* κ_k^l. Letting

$$r(x) = [\kappa_1^1 x^{a_1}, \ldots, \kappa_1^{m'_1} x^{a_1}, \ldots, \kappa_k^1 x^{a_k} \kappa_m^1 x^{a_m}, \ldots, \kappa_m^{m'_m} x^{a_m}]^t$$

the ODE system (2) is called the *polynomial dynamical system* associated to $(\mathcal{N}, \kappa)$. Positive equilibrium points, degeneracy/nondegeneracy, and the capacity for MPE or MPNE are defined as in section 2.2.

Definition 2.9. (Subnetwork) A subnetwork of a reaction network $\mathcal{N}$ is a reaction network given by a subset of the reactions of $\mathcal{N}$.

Remark 2.10. Mass action systems introduced in section 2.1 fall within the setup of this section. We note however that not every reaction network in the sense of Definition 2.8 is a reaction network in the classical sense: in definition 2.8 complexes $a_k + w_k^l$ are in $\mathbb{Z}^n$, but not necessarily in $\mathbb{Z}^n_{\geq 0}$. Some dynamical properties of polynomial dynamical systems are different from those of classical reaction networks, for instance the positive orthant may not be forward invariant: the reaction $0 \to -1$ on one species is such an example.

Remark 2.11. A particularly useful feature of our extended notion of reaction network in Definition 2.8 is that replacing all reaction vectors by their negatives (i.e. changing directions of arrows in the embedded graph) yields a new reaction network with the same positive equilibria as the original one. This allows us to reduce the number of cases in some of the proofs.

Remark 2.12. The results in this paper apply with almost verbatim proofs if we even further extend Definition 2.8 to allow source complexes and reaction vectors to have *real* entries, i.e. the vector field is a *signomial* vector function; reaction rates in this case are called *power law* [30]. A number of results on various dynamical aspects of mass-action kinetics (like multistationarity [3], persistence and global stability [13, 9]) apply more generally for power-law kinetics.

A reaction network $\mathcal{N}$ can be depicted naturally as a set of arrows from $a \in \mathbb{Z}^n_{\geq 0}$ to $b \in \mathbb{Z}^n_{\geq 0}$ for each reaction $a \to b \in \mathcal{N}$; see Figure 2(a) for an example. Following [9] we call this the *embedded graph of* $\mathcal{N}$. Note that the embedded graph of a reaction network $\mathcal{N}$ identifies $\mathcal{N}$ uniquely up to permutation of species.[2]

The *arrow diagram* of $\mathcal{N}$ is obtained by replacing all arrows from a_k to $a_k + w_k^l$ in the embedded graph by arrows starting at a_k in the direction of $sign(w_k^l) \in \{-1, 0, 1\}^n$. Vectors from the same source complex going in the same direction are drawn as one. The length of arrows in the arrow diagram is not important; see Figure 2(b). b can be negative?

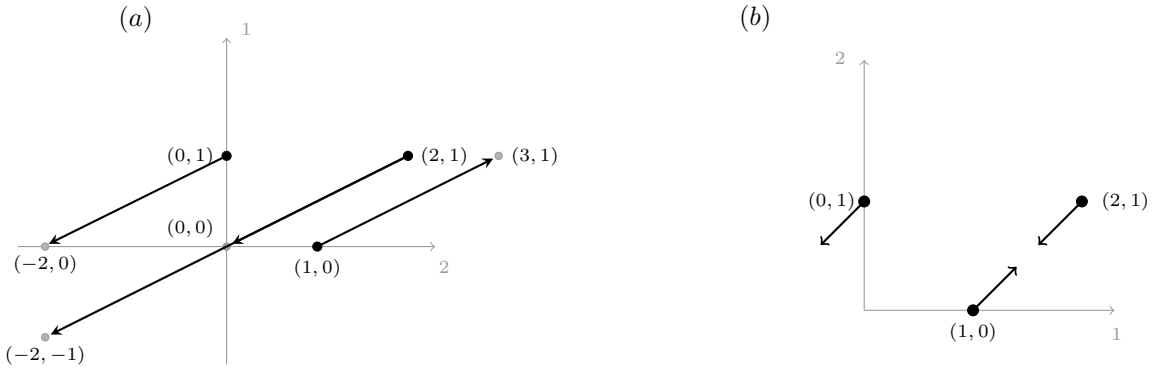


Figure 2: (a) Embedded graph and (b) arrow diagram of reaction network $\{(0,1) \to (2,2),\ (2,1) \to (0,0),\ (2,1) \to (-2,-1),\ (1,0) \to (3,1))\}$.

2.4 Network projections

Definition 2.13. Let $\mathcal{N}$ be a reaction network as in Definition 2.8 and let I be a nonempty ordered subset of $\{1, \ldots, n\}$. The *projection of* $\mathcal{N}$ *on* I, denoted by $\mathcal{N}_I$ is the reaction network on $|I|$ species with reactions $p_I(a_k) \to p_I(a_k + w_k^l)$ where p_I denotes the orthogonal projection on coordinates $\mathbb{Z}^I$. If $p_I(a_k) = p_I(a_k + w_k^l)$ then that reaction is discarded from $\mathcal{N}_I$. Duplicate reactions are also discarded from $\mathcal{N}_I$.

[2]This is not true in the original definition of an euclidean embedded graph [9]; in that work the embedded graph is defined starting from an ODE system rather than a network, like we do here.

In other words, $\mathcal{N}_I$ is obtained by removing species X_i, $i \notin I$ from all reactions in $\mathcal{N}$ and then discarding any trivial reactions where the source complex and the product complex is the same. We note that for reaction networks with one-dimensional stoichiometric subspace no projection of a reaction can be trivial under our assumption that Γ contains only nonzero rows. Moreover, while two diferent reactions in $\mathcal{N}$ may have the same projection in $\mathcal{N}_I$, we list each reaction in $\mathcal{N}_I$ only once.

Projections of networks are called *embedded subnetworks* by other authors [21].

The embedded graph of $\mathcal{N}_I$ is the orthogonal projection on coordinates I of the embedded graph of $\mathcal{N}$, discarding trivial reactions.

If $|I| = 1$ or $|I| = 2$ we call $\mathcal{N}_I$ a *1D projection*, respectively a *2D projection* of $\mathcal{N}$. Note that if I_1 and I_2 are permutations of each other, then $\mathcal{N}_{I_1}$ and $\mathcal{N}_{I_1}$ are identical up to a permutation of species. In particular the 2D projections on (i, j) and (j, i) are reflections of each other with respect to the main diagonal of the coordinate system, Figure 3.

Example 2.14. Let

$$\mathcal{N} = \{2X_1 + X_3 \to X_1 + X_2 + 3X_3,\ X_1 + X_2 \to 2X_2 + 2X_3,\ X_2 + 2X_3 \to X_1\}.$$

Dropping X from notation the 2D projections of $\mathcal{N}$ on $(1, 2)$ and $(2, 1)$ are

$$\begin{aligned} \mathcal{N}_{(1,2)} &= \{(2,0) \to (1,1),\ (1,1) \to (0,2),\ (0,1) \to (1,0)\} \\ \mathcal{N}_{(2,1)} &= \{(0,2) \to (1,1),\ (1,1) \to (2,0),\ (1,0) \to (0,1)\} \end{aligned}$$

and the 1D projection on (3) is

$$\mathcal{N}_{(3)} = \{1 \to 3,\ 0 \to 2,\ 2 \to 0\}$$

Figure 3 illustrates arrow diagrams of some 2D and 1D projections of $\mathcal{N}$.

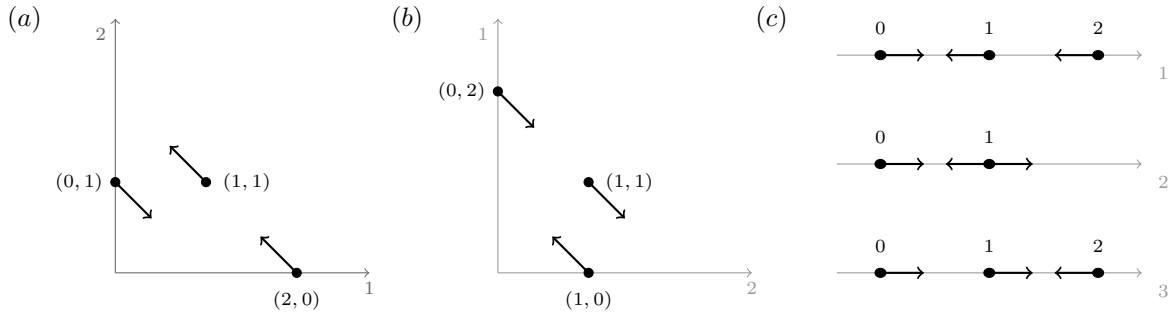


Figure 3: Arrow diagrams of projections of reaction network $\mathcal{N}$ in example 2.14. $(a), (b)$: 2D projections $\mathcal{N}_{(1,2)}$ and $\mathcal{N}_{(2,1)}$; the two pictures are reflections of each other about the diagonal. (c): 1D projections $\mathcal{N}_{(1)}$, $\mathcal{N}_{(2)}$, $\mathcal{N}_{(3)}$.

3 Reaction networks with one-dimensional stoichiometric subspace

3.1 A simplification: at most two reaction for each source.

Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace, and consider the subnetwork $\mathcal{N}'$ of $\mathcal{N}$ given by the reactions associated with a fixed source complex a_k. All reaction vectors w_k^l are scalar multiples of $w = w_k^1$. Suppose $w_k^l = \lambda_l w$ where $\lambda_l > 0$ for $l \in I^+ \subset \{1, \ldots, m_k'\}$ and $\lambda_l < 0$ for $l \in I^- \subset \{1, \ldots, m_k'\}$. The polynomial dynamical system (2) of $\mathcal{N}'$ is given by

$$\dot{x} = x^{a_k} \sum_{l=1}^{m_k'} \kappa_k^l w_k^l = x^{a_k} \sum_{l \in I^+} (\kappa_k^l \lambda_l) w + x^{a_k} \sum_{l \in I^-} \kappa_k^l (-\lambda_l)(-w),$$

which is the same ODE system as that of reaction network $\{a_k \to a_k + w,\ a_k \to a_k - w\}$ with rate constants $\sum_{l\in I^+} \kappa_k^l \lambda_l$ and $-\sum_{l\in I^-} \kappa_k^l \lambda_l$. Applying this trick for each source complex we may replace $\mathcal{N}$ by a network that has one or two reactions per source complex, in the latter case the two reactions having opposite directions, i.e. reaction vectors that are negative multiples of each other. We adopt this simplification throughout the remainder of the paper.

Next we introduce notation which will be used consistently throughout the paper without further mention. Occasionally we override some of this common notation to simplify presentation (for example when $m = 3$ in Section **??**). It will be clear from the context when that is the case.

3.2 Notations

1 $\mathcal{N}$ denotes a reaction network on $n \geq 1$ species with $m \geq 1$ source complexes and one-dimensional stoichiometric subspace.

2 The index sets for species and source complexes are denoted by S and R respectively:

$$S = \{1, \ldots, n\} \text{ and } R = \{1, \ldots, m\}.$$

3 $v \in \mathbb{R}^n$ spans the stoichiometric subspace of $\mathcal{N}$. The sign pattern of v is encoded in the sets

$$S^+ = \{i \in S | v_i > 0\}, \quad S^- = \{i \in S | v_i < 0\}.$$

Recall that Proposition 2.6 allows us to assume that v does not have zero coordinates.

4.1 If a_k is involved in only one reaction, that reaction is denoted by

$$a_k \to a_k',$$

and we let

$$a_k' - a_k = \lambda_k v.$$

The rate constant of $a_k \to a_k'$ is denoted by κ_k.

4.2 If a_k is involved in two reactions, these are denoted by

$$a_k \to a_k'^+,\ a_k \to a_k'^-$$

and we let

$$a_k'^+ - a_k = \lambda_k^+ v,\ a_k'^- - a_k = \lambda_k^- v$$

where $\lambda_k^+ > 0$ and $\lambda_k^+ < 0$.

The rate constant of $a_k \to a_k'^+$ is denoted by κ_k^+ and that of reaction $a_k \to a_k'^-$ by κ_k^-.

We say that two reactions *have the same direction* if their corresponding λ values have the same sign, and that they *have opposite directions* otherwise.

4.3 The following sets indicate the source complexes that have reactions in each of the two directions:

$$\begin{aligned} R^+ &= \{k \in R | a_k \text{ is associated with two reactions or } \lambda_k > 0\} \\ R^- &= \{k \in R | a_k \text{ is associated with two reactions or } \lambda_k < 0\} \\ R^0 &= \{k \in R | a_k \text{ is associated with two reactions}\} = R^+ \cap R^-. \end{aligned}$$

5 The mass-action ODE system for the $(\mathcal{N}, \kappa)$ is given by

$$\frac{dx}{d\tau} = F(x), \text{ where } F(x) = \left(\sum_{k\in R\setminus R^0} \lambda_k \kappa_k + \sum_{k\in R^0} (\lambda_k^+ - \lambda_k^-) \right) x(\tau)^{a_k} v.$$

Note that we use τ to denote the time variable. Variable t is used as follows:

6 The positive stoichiometric class of $\eta \in \mathbb{R}^n_{>0}$ is parameterized by $\eta + tv$. The bounds for t are computed from $\eta_i + tv_i > 0$ for all $i \in S$, i.e. $t \in (\alpha^\eta, \beta^\eta)$ where

$$\alpha^\eta = -\min_{i \in S^+} \frac{\eta_i}{v_i} \text{ and } \beta^\eta = -\max_{i \in S^-} \frac{\eta_i}{v_i}. \tag{7}$$

7 We let

$$f(\eta, \kappa; t) = \sum_{k \in R \setminus R^0} \lambda_k \kappa_k (\eta + tv)^{a_k} + \sum_{k \in R^0} (\lambda_k^+ - \lambda_k^-)(\eta + tv)^{a_k}.$$

We view f as a function of t that depends on the parameters η, κ. The domain of $f(\eta, \kappa; t)$ is $(\alpha^\eta, \beta^\eta)$, see (7).

3.3 Alt-complete and zigzag reaction networks

Definition 3.1. 1. We say that a reaction network $\mathcal{N}$ on one species *contains the* $(\rightarrow, \leftarrow)$ *pattern* if it contains reactions $a \to a'$, $b \to b'$ with $a < a'$, $b' < b$ and $a < b$. $\mathcal{N}$ *has the* $(\leftarrow, \rightarrow)$ *pattern* if it contains reactions $a \to a'$, $b \to b'$ with $a' < a$, $b' > b$ and $a < b$.

2. We say that a reaction network $\mathcal{N}$ with with one-dimensional stoichiometric subspace contains the $(\rightarrow, \leftarrow)$ (or $(\leftarrow, \rightarrow)$ pattern if there exists a 1D projection of $\mathcal{N}$) that has this pattern.

In other words a reaction network $\mathcal{N}$ on one species contains one of the patterns above if its arrow diagram does; note that for each pattern the two source complexes must be different.

Definition 3.2. *(Class $\mathcal{A}_c$: alt-complete networks).* A reaction network $\mathcal{N}$ with one-dimensional stoichiometric subspace is called *alt-complete* if it both $(\rightarrow, \leftarrow)$ and $(\leftarrow, \rightarrow)$ patterns. The two 1D projections may be on the same coordinate. The class of alt-complete networks is denoted by $\mathcal{A}_c$. We write $\mathcal{N} \in \mathcal{A}_c$.

We make a few remarks on the case when R^0 is empty; this situation is an important part in our analysis. First note that the direction (positive or negative) of the projection of $a_k \to a'_k$ on i is given by the sign of $\lambda_k v_i$. The 1D projection $\mathcal{N}_{(i)}$ of $\mathcal{N}$ contains the $(\rightarrow, \leftarrow)$ pattern if and only if there exist $k, l \in R$ such that

$$a_{ki} < a_{li}, \quad \lambda_k v_i > 0, \text{ and } \lambda_l v_i < 0. \tag{8}$$

Likewise, $\mathcal{N}_{(i)}$ contains the $(\leftarrow, \rightarrow)$ pattern if and only if there exists $k, l \in K$ such that

$$a_{ki} < a_{li}, \quad \lambda_k v_i < 0, \text{ and } \lambda_l v_i > 0. \tag{9}$$

If the $(\rightarrow, \leftarrow)$ pattern is missing from all 1D projections of $\mathcal{N}$ then for any $k \in R^+, l \in R^-$ and for all $i \in S$ we have

$$(a_{ki} - a_{li}) v_i \geq 0 \tag{10}$$

Indeed, if not, since $\lambda_k > 0$ and $\lambda_l < 0$ then we either have

$$a_{ki} < a_{li}, \ \lambda_k v_i > 0 \text{ and } \lambda_l v_i < 0$$

or

$$a_{li} < a_{ki}, \ \lambda_l v_i > 0 \text{ and } \lambda_k v_i < 0,$$

both of which define a $(\rightarrow, \leftarrow)$ pattern in $\mathcal{N}_{(i)}$, contradiction.

Similarly, if the $(\leftarrow, \rightarrow)$ pattern is missing from all 1D projections of $\mathcal{N}$ then for any $k \in R^+, l \in R^-$ and for all $i \in S$ we have

$$(a_{ki} - a_{li}) v_i \leq 0. \tag{11}$$

Following [21] we introduce a class of networks that is central to this paper.

Definition 3.3. Let $\mathcal{N} = \{a \to a', b \to b'\}$ be a reaction network on two species with one-dimensional stoichiometric subspace spanned by $v \in \mathbb{R}^2$. We say that $\mathcal{N}$ is a *zigzag* and if

1. $a \to a'$ and $b \to b'$ have opposite directions and
2. $v_1 v_2 (b_1 - a_1)(b_2 - a_2) < 0$.

   The *slope* of zigzag $\mathcal{N}$ is defined as the slope of $b - a$, i.e. $\frac{b_2 - a_2}{b_1 - a_1}$.

Part 2 of Definition 3.3 simply says that the slopes of v and $b - a$ are nonzero and of different signs, in other words the arrow diagram of $\mathcal{N}$ is one of those in Figure 4. The slope of the zigzag is not zero or $\pm\infty$, in other words the rectangles in the figure ("boxes" in terminology from [21]) are not degenerate, i.e. are not line segments.

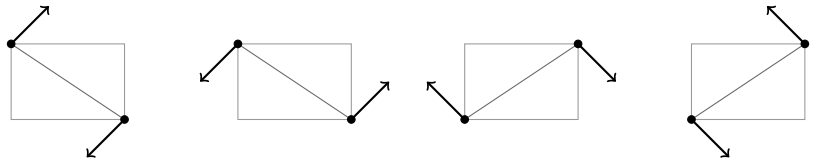


Figure 4: Arrow diagrams of zigzags.

Definition 3.4. Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace. A subnetwork of a 2D projection of $\mathcal{N}$ which is a zigzag is called a *zigzag projection of* $\mathcal{N}$.

Definition 3.5. *(class $\mathcal{Z}$).* Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace. $\mathcal{N}$ is called a *zigzag network* if it has a zigzag projection.

Note that zigzag network are alt-complete.

Definition 3.6. *(class $\mathcal{Z}_{-1}$).* A network $\mathcal{N}$ is said to be of class $\mathcal{Z}_{-1}$ if $\mathcal{N}$ is a zigzag network and all zigzag projections of $\mathcal{N}$ have slope -1. We write $\mathcal{N} \in \mathcal{Z}_{-1}$.

Examples 3.7.

1. The reaction network in Figure 2 contains the $(\to, \leftarrow)$ pattern in both its 1D projection, and contains the $(\leftarrow, \to)$ pattern in its (1) projection. This network is alt-complete, but not a zigzag network.

2. The reaction network $\mathcal{N}$ in Example 2.14 contains the $(\to, \leftarrow)$ pattern on all of its 1D projections, but it does not contain the $(\to, \leftarrow)$ pattern. This network is not alt-complete.

3. Let $\mathcal{N} = \{(0,1,0) \to (1,2,-1),\ (1,0,1) \to (0,-1,2)\}$. This network contains the $(\to, \leftarrow)$ pattern on its (1) projection, and the $(\leftarrow, \to)$ on its (2) and (3) projection. $\mathcal{N}$ is alt-complete. Moreover, $\mathcal{N}$ is a zigzag network (for example $\mathcal{N}_{(1,2)}$ is a zigzag), but it is not in $\mathcal{Z}_{-1}$ since $\mathcal{N}_{(1,3)}$ is a zigzag of slope 1.

It is clear that zigzag networks are "minimally" alt-complete, in that only two reactions are required to produce both $(\to, \leftarrow)$ and $(\leftarrow, \to)$ patterns. Other networks, like the one in Figure 2, require three reactions to produce these patterns. Yet other networks require four reactions for this purpose, see Figure 5 (c) for a typical example. The latter case requires a fairly restrictive arrow diagram; network like these are said to belong to class $\mathcal{S}_2^{nz}$ as we discuss in the next section.

3.4 Special classes of networks

The following classes of reaction networks with structural defining properties play a crucial role in the classification of multistationarity for networks with one-dimensional stoichiometric subspace: our main result shows that these classes encompass all alt-complete networks without capacity for MPNE.

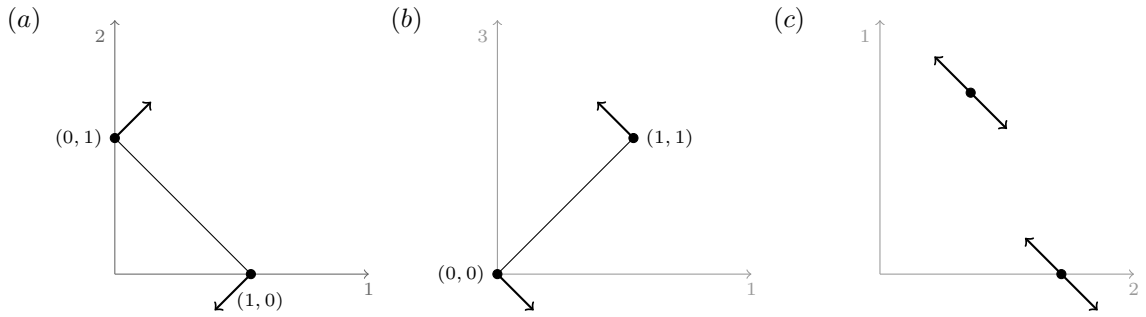


Figure 5: Arrow diagrams of $(a), (b)$: 2D projections of reaction network $\mathcal{N}$ in Example 3.7 *3.* $\mathcal{N}_{(1,2)} \in \mathcal{Z}_{-1}$, $\mathcal{N}_{(1,3)} \in \mathcal{Z} \setminus \mathcal{Z}_{-1}$. $\mathcal{N}$ is a zigzag network, but not a $\mathcal{Z}_{-1}$ network. (c): a reaction network that requires four reactions to form the $(\rightarrow, \leftarrow)$ and $(\leftarrow, \rightarrow)$ patterns.

Definition 3.8. *(Class $\mathcal{S}_1$)* A reaction network $\mathcal{N}$ with one-dimensional stoichiometric subspace is said to be *of class $\mathcal{S}_1$ (single-source network)* if $\mathcal{N}$ contains exactly one source complex and two reactions of opposite directions. We write $\mathcal{N} \in \mathcal{S}_1$.

Definition 3.9. *(Class $\mathcal{S}_2^z$)* A reaction network $\mathcal{N}$ with one-dimensional stoichiometric subspace is said to be *of class $\mathcal{S}_2^z$* if it contains exactly two source complexes a, b and has reactions in both directions starting at each of a, b; and there exist $i, j \in S$, $i \neq j$ such that

1. $\mathcal{N}_{(i,j)} \in \mathcal{Z}_{-1}$, i..e $\mathrm{v}_i v_j > 0$ and $b_i - a_i = -(b_j - a_j) \neq 0$
2. $a_s = b_s$ for all $s \in S \setminus \{i, j\}$.

We write $\mathcal{N} \in \mathcal{S}_2^z$.

Definition 3.10. *(Class $\mathcal{S}_2^{nz}$)* A reaction network $\mathcal{N}$ with one-dimensional stoichiometric subspace is said to be *of class $\mathcal{S}_2^{nz}$* if it contains exactly two source complexes and $\mathcal{N} \in \mathcal{A}_c \setminus \mathcal{Z}$. We write $\mathcal{N} \in \mathcal{S}_2^{nz}$.

Definition 3.11. *(Class $\mathcal{L}$)* A reaction network $\mathcal{N}$ with one-dimensional stoichiometric subspace is said to be *of class $\mathcal{L}$* if there exist $i, j \in S$, $i \neq j$ such that

1. there exists $\delta \in \mathbb{R}^2_{>0}$ such that

$$[a_{ki}, a_{kj}]^t = \delta + p_k[1, -1]^t \text{ for all } k \in R$$

   where p_k are pairwise distinct, $p_k < 0$ for all $k \in R^+ \setminus R^0$, $p_k = 0$ for $k \in R^0$, and $p_l > 0$ for all $l \in R^- \setminus R^0$;

2. $a_{ks} = a_{ls}$ for all $k, l \in R$ and for all $s \in S \setminus \{i, j\}$.

We write $\mathcal{N} \in \mathcal{L}$.

Definition 3.12. *(Class $\mathcal{C}$)* A reaction network $\mathcal{N}$ with one-dimensional stoichiometric subspace is said to be *of class $\mathcal{C}$* if it is alt-complete, it contains at least three source complexes, and there exists $\gamma \in \mathbb{Z}^n$ such that

$$a_k - \gamma \in \{0, e_1, \ldots, e_n\} \text{ for all } k \in R.$$

γ is called the *corner of $\mathcal{N}$*. We write $\mathcal{N} \in \mathcal{C}$.

The classes of networks defined above are easily characterized with pictures. Networks of class $\mathcal{S}_2^z$ have a 2D projection (i, j) with arrow diagram in Figure 6, left. The line connecting the two projected source complexes has slope -1. The 1D projections on the remaining species have a single source complex.

Networks of class $\mathcal{C}$ are alt-complete with location of source complexes illustrated in Figure 6, right; γ may or may not be a source complex. One may check if a given network $\mathcal{N}$ is in class $\mathcal{C}$ by computing the vector

$$\gamma = (\min_{k\in R} a_{k2}, \min_{k\in R} a_{km}, \ldots, \min_{k\in R} a_{km}), \tag{12}$$

for if $\mathcal{N} \in \mathcal{C}$ then necessarily γ is the corner of $\mathcal{N}$. We then simply check that $a_k - \gamma \in \{e_1, \ldots, e_n\}$.

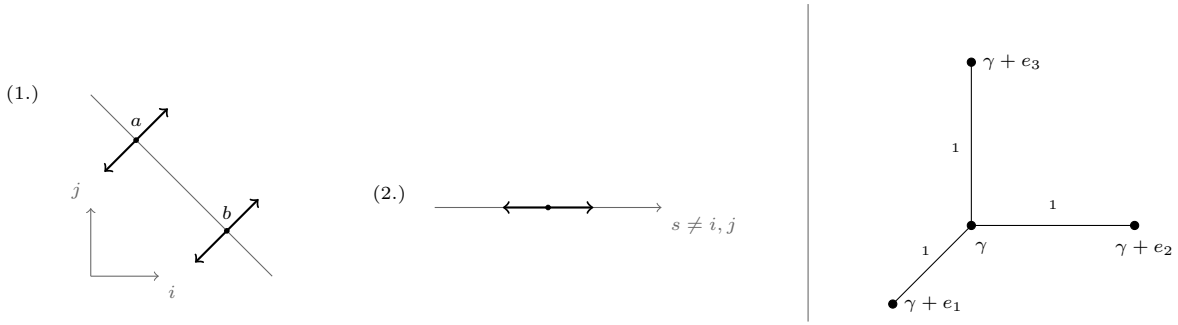


Figure 6: Classes $\mathcal{S}_2^z$ and $\mathcal{C}$. Left: $\mathcal{S}_2^z$ networks have two source complexes with reactions of all directions (for a total of four reactions), an (i, j) projection containing a zigzag of slope -1, and projections on all other species have a single source complex. Right: The possible locations of source complexes for networks of class $\mathcal{C}$ when $n = 3$ are of the form $\gamma, \gamma + e_1, \gamma + e_2, \gamma + e_3$.

Networks of class $\mathcal{L}$ have a 2D (i, j) projection having one of the arrow patterns in Figure 7, whereas the 1D projections on the remaining species contain a single source complex. Note that the line containing all projections of source complexes has slope -1, and δ separates the reactions according to their direction. For networks of class $\mathcal{L}$ R^0 contains zero or one elements; if there exists a source complex a_k with reactions in both directions, then $a_k = \delta$. Note that we have

$$\max_{k\in K^+} a_{ki} \leq \min_{l\in K^-} a_{li} \textit{Is this about the provided picture?} \tag{13}$$

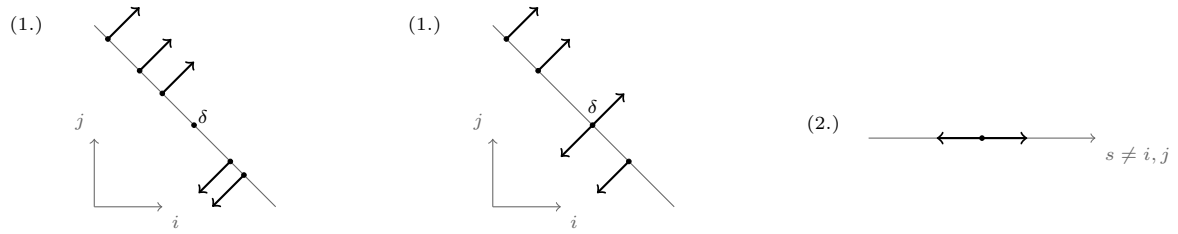


Figure 7: Class $\mathcal{L}$. Arrow diagrams of *Left (1.)*: the (i, j) projection, corresponding to $|R^0| = 0$ and $|R^0| = 1$ respectively. *Right (2.)*: projections on all other species have a single source complex.

Finally, networks $\mathcal{N}$ of class $\mathcal{S}_2^{nz}$ are precisely those with two distinct source complexes a and b, both having reactions in both directions; and such that $(b - a)$ is in the closure of the sign class of v or $-v$:

$$b - a \in \mathcal{Q}_0(v) \text{ or } b - a \in \mathcal{Q}_0(v) \textit{thesame}$$

where $Q_0(v) = \{u \in \mathbb{R}^n | u_i v_i \geq 0\}$ (under our assumption that v has only nonzero coordinates). This follows as $\mathcal{N} \notin \mathcal{Z}$ is equivalent to saying that for any $i, j \in S$ we have $v_i v_j (b_i - a_j)(b_j - a_j) \geq 0$. $\mathcal{S}_2^{nz}$ are also completely characterized by their 2D projections. At least one of these projections must have one of the arrow diagrams in Figure 8, and all 2D projections either have a single source complex or one of the arrow diagrams in Figure 8, up to permuting i and j.

Do we need remark about the number of species? Only networks of class S_2^{nz} or S_1 can be on one species. Corollary 3.8??: $r + s \geq 4$ for every MPNE.

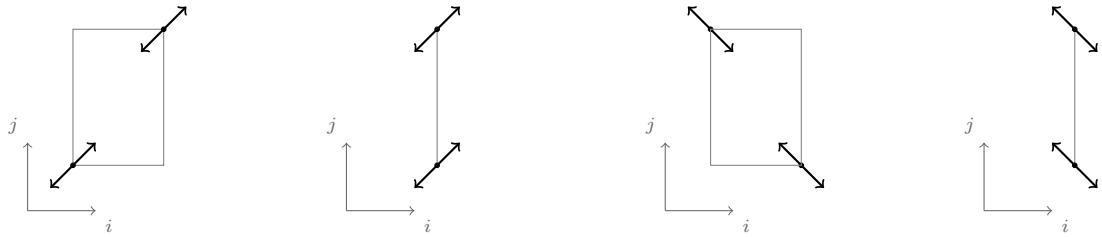


Figure 8: Class $\mathcal{S}_2^{nz}$. There are two source complexes with reactions of all directions (for a total of four reactions). All 2D projections have either one source complex or have one of the arrow diagrams in the figure, up to interchanging i and j. Not all 2D projections can have one source complex.

Remark 3.13. *(Relations between classes of networks)* It is easily seen that networks of classes $\mathcal{L}$, $\mathcal{S}_2^z$ and $\mathcal{S}_2^{nz}$ are alt-complete. Figure 9 shows the set-theoretical relations between the various classes of networks defined in the paper. These are easily checked straight from the definitions.

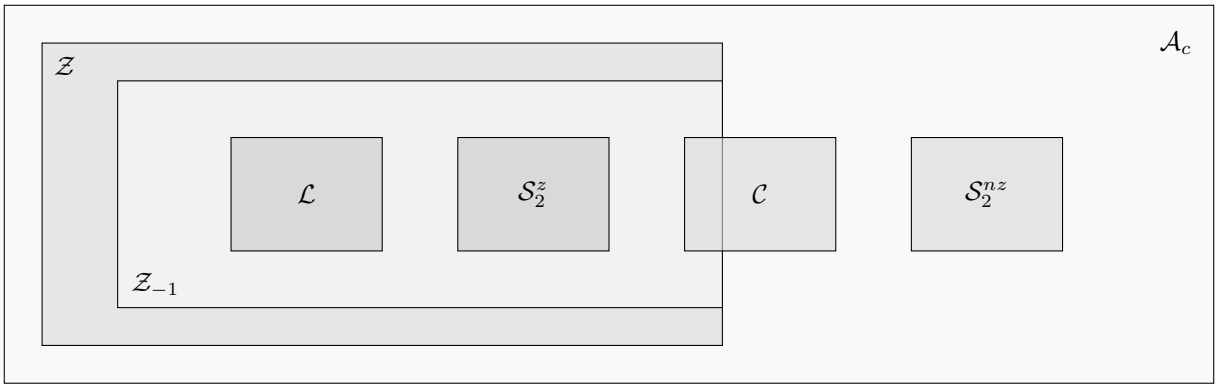


Figure 9: Inclusion relations between classes of networks $\mathcal{A}_c$, $\mathcal{Z}$, $\mathcal{Z}_{-1}$, $\mathcal{L}$ and $\mathcal{C}$.

4 Main result, examples, and discussion

4.1 Characterization of capacicity for MPE/MPNE for reaction networks with one-dimensional stoichiometric subspace

Following our discussion in section 3.2 we first remove species with corresponding v coordinates equal to zero, and therefore we assume $v \neq 0$.

Theorem 4.1. *Let $\mathcal{N}$ be a reaction network one-dimensional stoichiometric subspace. Then*

1. *If $\mathcal{N}$ has capacity for multiple equilibria then either $\mathcal{N}$ is alt-complete or is a single-source network.*

2(i). If $\mathcal{N}$ is alt-complete and $\mathcal{N} \notin \mathcal{S}_2^z \cup \mathcal{S}_2^{nz} \cup \mathcal{L} \cup \mathcal{C}$ then $\mathcal{N}$ has the capacity for nondegenerate multiple equilibria.

2(ii). If $\mathcal{N} \in \mathcal{S}_1 \cup \mathcal{S}_2^z \cup \mathcal{S}_2^{nz} \cup \mathcal{L} \cup \mathcal{C}$ then $\mathcal{N}$ has the capacity for multiple equilibria, but it does not have the capacity for multiple nondegenerate equilibria.

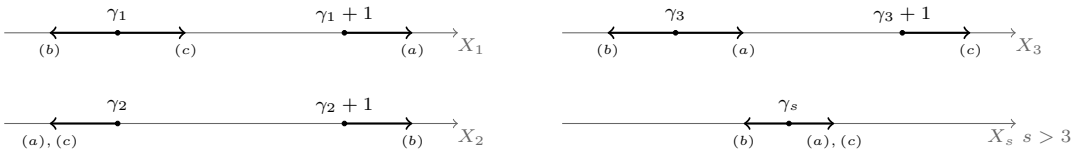


Figure 10: If $\mathcal{N}' \in \mathcal{C}$ and γ is not a source complex and $sign(v) = (+, -, +)$ then N' is not alt-complete.

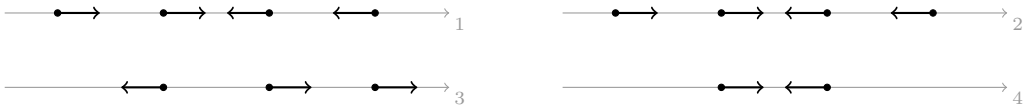


Figure 11: 1D projections of network $\mathcal{N}$ in example 2.14.

All hypotheses of Theorem 4.1 may be checked by inspecting arrow diagrams of 1D and 2D projections. Often times checking 1D projection is enough; let $\mathcal{A}_c^1$ denote the class of reaction network with one-dimensional stoichiometric subspace that have a 1D projection containing both $(\rightarrow, \leftarrow)$ and $(\leftarrow, \rightarrow)$ patterns. We have the following Define $\mathcal{A}_c^1$ as $(\rightarrow, \leftarrow, \rightarrow)$ or $(\leftarrow, \rightarrow, \leftarrow)$

Corollary 4.2. *If $\mathcal{N} \in \mathcal{A}_c^1$ then $\mathcal{N}$ has the capacity for MPNE.*

Proof. Since $\mathcal{N} \in \mathcal{A}_c$ it is enough to show that 1D projections of networks in $\mathcal{S}_2^z \cup \mathcal{S}_2^{nz} \cup \mathcal{L} \cup \mathcal{C}$ do not have both $(\rightarrow, \leftarrow)$ and $(\leftarrow, \rightarrow)$ patters. This is easily checked from the definitions of these classes. □

The tree in Figure 12 is one example of an efficient algorithm for deciding the capacity for MPE and MPNE for any network $\mathcal{N}$ with two or more source complexes and one-dimensional stoichiometric subspace. v is assumed to have nonzero coordinates. The conditions at each node are checked with very short calculations and by inspecting 1D arrrow diagrams and at most one 2D arrow diagram.

Example 4.3. Consider the network $\mathcal{N}$ on 5 species:

$$(0,1,2,0,2) \rightarrow (1,2,3,0,1), \quad (1,0,3,1,2) \rightarrow (2,1,4,1,1),$$
$$(2,2,1,2,1) \rightarrow (1,1,0,2,2), \quad (3,3,1,0,1) \rightarrow (2,2,0,0,2)$$

The stoichiometric space of $\mathcal{N}$ is spanned by $v = (1,1,1,0,-1)$. We note that $v_4 = 0$ and remove the fourth species. We follow the roadmap in Figure 12. The four 1D projections are depicted in Figure 11 using arrow diagrams. We see that $\mathcal{N} \in \mathcal{A}_c \setminus \mathcal{A}_c^1$, and all four projections have two or more source complexes. It remains to check if $\mathcal{N} \in \mathcal{C}$, see (12). We have $\gamma = (0,0,1,1)$ and note that, for example $(0,1,2,2) - (0,0,1,1) \notin \{e_1, e_2, e_3, e_4\}$. Therefore $\mathcal{N} \notin \mathcal{C}$ and $\mathcal{N}$ has the capacity for MPNE.

Left branch in Decision tree: if $b - a$ has only one nonzero coordinate?

More examples of arrow diagrams and their capacity for MPE/MPNE are given in Figure 13. These include at least one network from each of the sets forming the partition of $\mathcal{A}_c$ in Figure 9.

4.2 Discussion and past results

The question of multistationarity for networks with one-dimensional stoichiometric subspace has been the focus of a number of recent papers [21, 31, 32, 23, 33]. These works are motivated by the question of structural conditions for multistationarity for reaction networks with one-dimensional subspace, and are all connected to Conjecture 1.1, which was the motivation for this work. Our result shows that the conjecture is true up to the trivial case of a network with only one source complex. Joshi and Shiu solved the case of networks with one or two species,two (possibly reversible) reactions and also characterized their capacity for MPNE using arrow diagrams. Theorem 4.1 extends this characterization of MPNE to the general case,

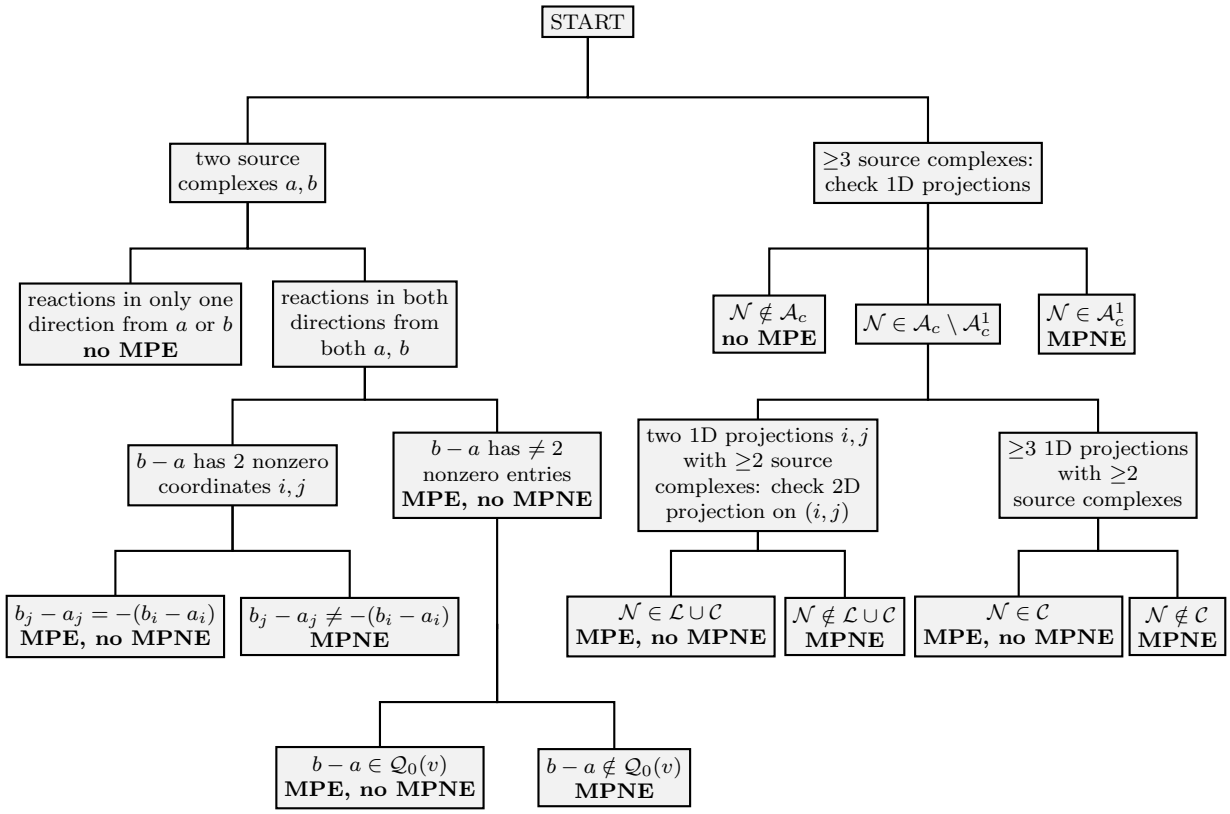


Figure 12: Decision tree for deciding the capacity for MPE and MPNE for reaction networks $\mathcal{N}$ with two or more source complexes and one-dimensional stoichiometric subspace.

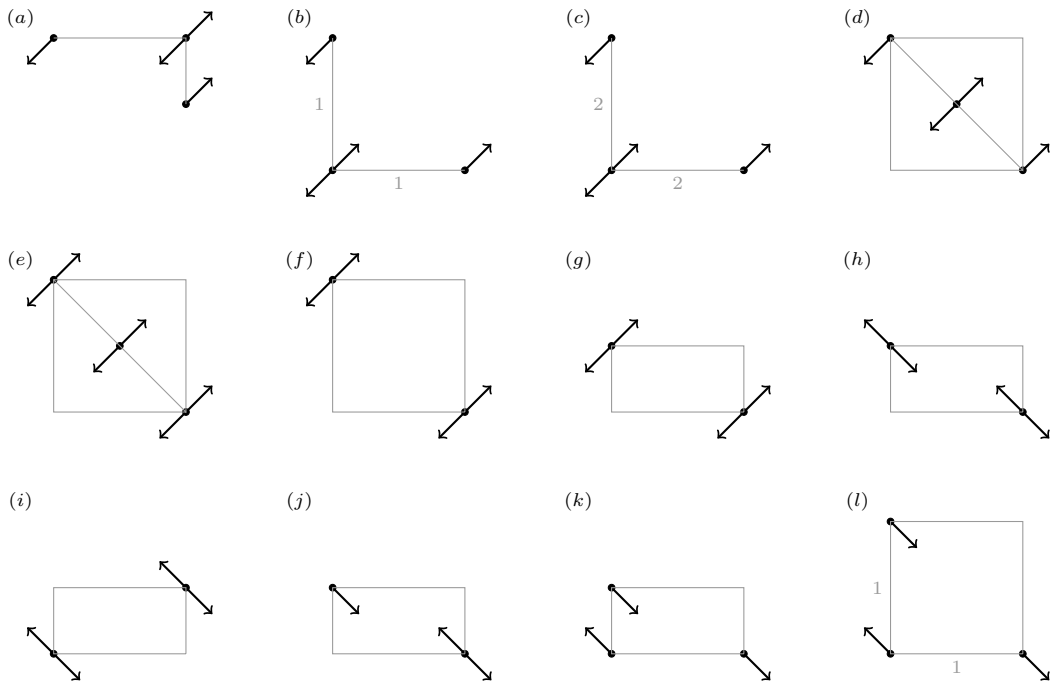


Figure 13: Examples of arrow diagrams and their capacity for MPE/MPNE. (a) $\mathcal{A}_c \setminus (\mathcal{Z} \cup \mathcal{C} \cup \mathcal{S}_2^{nz})$: MPNE. $\mathcal{Z} \setminus \mathcal{Z}_{-1}$ need to change slope for this description (b) $\mathcal{C} \cap \mathcal{Z}$: MPE, no MPNE. (c) $\mathcal{Z}_{-1} \setminus (\mathcal{L} \cup \mathcal{C} \cup \mathcal{S}_2^{z})$: MPNE. (d) $\mathcal{L}$: MPE, no MPNE. (e): $\mathcal{Z}_{-1} \setminus (\mathcal{L} \cup \mathcal{C} \cup \mathcal{S}_2^{z})$: MPNE. (f) $\mathcal{S}_2^{z}$: MPE, no MPNE. (g) $\mathcal{Z} \setminus \mathcal{Z}_{-1}$: MPNE. (h) $\mathcal{S}_2^{nz}$: MPE, no MPNE. (i) $\mathcal{Z} \setminus \mathcal{Z}_{-1}$: MPNE. (j) not $\mathcal{A}_c$: no MPE. (k) $\mathcal{A}_c \setminus (\mathcal{Z} \cup \mathcal{C} \cup \mathcal{S}_2^{nz})$: no MPE.MPNE (l) $\mathcal{C} \setminus \mathcal{Z}$: MPE, no MPNE.

revealing new structural sources of degeneracy for three or more species. We review the relevant results in [21] further down this section. Some of these results are used as a starting point in our proof of sufficiency in Conjecture 1.1, where $n = 3$ is the first case treated.

Other partial results towards Conjecture 1.1 are known. Lin et al.[23, Theorem 4.3] proved that alt-complete is necessary for multistationarity under the assumption that the network cannot have an infinite number of positive equilibria for any choice of rate constants. This excludes all networks that have the capacity for MPE but not MPNE, but also some networks that have the capacity for MPNE (see Figure 13)(e). We give a short proof of the general statement for this implication (section 5.3). Lin et al. also show that alt-complete in sufficient for multistationarity if there exist two reactions in the network such that the subnetwork consisting of the two reactions admits at least one and finitely many positive steady states[23, Theorem 4.7]. We believe that it is possible to find a structural characterization of latter condition, and use that path to prove Conjecture 1. However, our proof is self-contained and independent of these results.

Other work on multistationarity addressed conditions for the existence of three or more positive equilibria [23], conditions for multistability and the number of stable equilibria [32, 33], and conditions for the existence of nondegenerate multiple equilibria. Joshi and Shiu showed that (1) networks with one irreversible and one reversible reactions for and (2) networks with two reversible reactions must necessarily have one-dimensional stoichiometric subspace to be multistationary, and they characterized the capacity for MPE for these networks [21, Theorems 2.8, 5.12]. In subsequent work Shiu and de Wolff characterized the capacity for MPNE for networks of type (1) and (2) above for the special case of two species [31]. These results can be viewed as corollaries of our Theorem 4.1, and so does the general case of any number of species, posed as an open question in [31]:

Proposition 4.4 ([31] Conjecture 5.1)**.** *A network $\mathcal{N}$ consisting of one pair of reversible reactions and one*

irreversible reaction has the capacity for MPNE if and only if $\mathcal{N}$ has one-dimensional stoichiometric subspace and $\mathcal{N} \in \mathcal{A}_c^1$.

Proof. First we remove species corresponding to zero coordinates in v. One implication follows from Corollary 4.2. For the other implication, suppose $\mathcal{N}$ has the capacity for MPNE. Then $\mathcal{N}$ must have one-dimensional stoichiometric subspace as discussed above. By Theorem 4.1 part 1, $\mathcal{N}$ must be alt-complete. Let $\mathcal{N} = \{a \rightleftharpoons b, c \to c'\}$. In all 1D projections $a \rightleftharpoons b$ gives a $(\to, \leftarrow)$ pattern. Since $\mathcal{N}$ is alt-complete, there must exist a 1D projection $\mathcal{N}_{(i)}$ that also contains the $(\leftarrow, \to)$ pattern, so $\mathcal{N} \in \mathcal{A}_c^1$. □

The same short argument can be applied to characterize the capacity for MPNE for networks composed of two reversible reactions and any number of species, generalizing Theorem 3.6 in [31]:

Proposition 4.5. *A network $\mathcal{N}$ consisting two pairs of reversible reactions has the capacity for MPNE if and only if $\mathcal{N}$ has one-dimensional stoichiometric subspace and $\mathcal{N} \in \mathcal{A}_c^1$ (equivalently, a 1D projection of $\mathcal{N}$ contains the $(\to, \leftarrow, \to, \leftarrow)$ pattern.*

A review of results for one and two species. The next theorems collects some of the implications of Theorems 3,6 5.1 and 5.2 in [21].

Theorem 4.6. *[21, Theorem 3.6] Let $\mathcal{N}$ be a reaction network on one species. Then*

1. *$\mathcal{N}$ has the capacity for MPE if and only if $\mathcal{N} \in \mathcal{A}_c^1$ or $\mathcal{N}$ has exactly one or two source complexes, both with reactions in both directions (i.e. its arrow diagram is $(\leftarrow\bullet\rightarrow)$ or $(\leftarrow\bullet\rightarrow, \leftarrow\bullet\rightarrow)$*
2. *$\mathcal{N}$ has the capacity for MPNE if and only if $\mathcal{N} \in \mathcal{A}_c^1$.*

Theorem 4.7. *[21, Theorems 5.1, 5.2] Let $\mathcal{N} = \{a \to a', b \to b'\}$ be a reaction network with one-dimensional stoichiometric subspace spanned by $v \in \mathbb{R}^n$ and composed of two reactions with opposite directions. Assume that all coordinates of v are nonzero and let $\beta = [(a_1' - a_1)(b_1 - a_1), \ldots, (a_n' - a_n)(b_n - a_n)]$. Then*

1. *$\mathcal{N}$ has the capacity for multiple nondegenerate equilibria if (i) $\beta_i < 0$ and $\beta_j > 0$ for some $i, j \in \{1, \ldots, n\}$ and (ii) if $\beta_s = 0$ for all $s \notin \{i, j\}$ then the projection of $\mathcal{N}$ on (i, j) is not a zigzag of slope -1.*
2. *$\mathcal{N}$ has the capacity for multiple equilibria, but not the capacity for multiple nondegenerate equilibria if $\beta_i < 0$ and $\beta_j > 0$ are the only nonzero coordinates of β, and the projection of $\mathcal{N}$ on (i, j) is a zigzag of slope -1.*

Note that condition (i) (i.e. $\beta_i < 0$ and $\beta_j > 0$) in part 1 of Theorem 4.7 can be rewritten as $v_i(b_i - a_i) < 0$ and $v_j(b_j - a_j) > 0$. Since the two reactions have opposite directions, this is equivalent to saying $\mathcal{N}_{(i,j)}$ is a zigzag. Moreover, condition (ii) in part 1 of Theorem 4.7 is equivalent to saying that $\mathcal{N} \notin \mathcal{L}$ (and condition (ii) in part 2 is equivalent to $\mathcal{N} \in \mathcal{L}$).

We have the following

Lemma 4.8. *Let $\mathcal{N}$ be a reaction network with stoichiometric subspace of dimension 1 and composed of two reactions. Then $\mathcal{N}$ is alt-complete if and only if $\mathcal{N}$ is a zigzag network.*

Proof. (8) and (9) imply that $\mathcal{N} \in \mathcal{A}_c$ if and only if $\lambda_1\lambda_2 < 0$ and $v_i v_j (a_{1i} - a_{2i})(a_{1j} - a_{2j}) < 0$ for some $i, j \in S$ which is equivalent to $\mathcal{N} \in \mathcal{Z}$ according to Definitions 3.4 and 3.5. □

With the observation above and Lemma 4.8, Theorem 4.7 can be restated equivalently as follows

Theorem 4.9. *Let $\mathcal{N}$ be an alt-complete reaction network with one-dimensional stoichiometric subspace.*

1. *If $\mathcal{N} \notin \mathcal{L}$ then $\mathcal{N}$ has the capacity for nondegenerate multiple equilibria;*
2. *If $\mathcal{N} \in \mathcal{L}$ then $\mathcal{N}$ has the capacity for multiple equilibria, but does not have the capacity for multiple nondegenerate equilibria.*

In view of Proposition 2.6, this implies our Theorem 5.6 2(i) and 2(ii) for the case when $\mathcal{N}$ is composed of two reactions.

We conclude with a few consequences of Theorems 4.6 and 4.9 that will be used later in our proofs.

Lemma 4.10. *Let $\mathcal{N} = \{a \cdot X \to a' \cdot X, b \cdot X \to b' \cdot X\}$ and suppose $\mathcal{N}_{(i,j)} \in \mathcal{Z}$ is the only 2D projection of $\mathcal{N}$ with a zigzag subnetwork. Then $a_s = b_s$ for all $s \in \{1, \ldots, n\} \setminus \{i, j\}$.*

Proof. We have $v_i v_j (a_i - b_i)(a_j - b_j) < 0$. Assume that there exists $s \notin \{i, j\}$ such that $a_s \neq b_s$. Then $v_i v_s (a_i - b_i)(a_s - b_s) < 0$ or $v_j v_s (a_j - b_j)(a_s - b_s) < 0$ and therefore $\mathcal{N}_{(i,s)} \in \mathcal{Z}$ or $\mathcal{N}_{(j,s)} \in \mathcal{Z}$, which is a contradiction. □

We conclude this section with a couple of useful consequences of Theorem 4.9. These corollaries are about networks with *any* number of reactions.

Corollary 4.11. *Let $\mathcal{N}$ be a network with any number of reactions. If $\mathcal{N} \in \mathcal{Z} \setminus \mathcal{Z}_{-1}$ then $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.*

Proof. By hypothesis, there exists a subnetwork $\mathcal{N}'$ of $\mathcal{N}$ with two reactions such that $\mathcal{N}' \in \mathcal{Z} \setminus \mathcal{Z}_{-1}$. Since $\mathcal{Z} \subset \mathcal{A}_c$ and $\mathcal{L} \subset \mathcal{Z}_{-1}$ we have $\mathcal{N}' \in \mathcal{A}_c \setminus \mathcal{L}$. By Theorem 4.9 part 1 we conclude that $\mathcal{N}'$ has the capacity for multiple nondegenerate equilibria, and it follows by Theorem 2.7 that $\mathcal{N}$ does as well. □

Corollary 4.12. *Let $\mathcal{N}$ be a network with one-dimensional stoichiometric subspace and any number of reactions. If $\mathcal{N}$ has a subnetwork $\mathcal{N}'$ composed of two reactions such that $\mathcal{N}' \in \mathcal{Z}_{-1} \setminus \mathcal{L}$ then $\mathcal{N}$ admits nondegenerate multiple equilibria.*

Proof. We have $\mathcal{N}' \in \mathcal{A}_c \setminus \mathcal{L}$ and the proof is identical to that of Corollary 4.11. □

5 Proofs

This section proceed as follows. We begin with some remarks on the interpretation of nonegeneracy in terms of $f(\eta, \kappa; t)$ in section 5.1, and we discuss some simplifications and assumptions that can be made without loss of generality in section 5.2. Parts 1 and 2(ii) of Theorem 4.1 are proved in sections 5.3 and 5.4. The bulk of the proof is that of part 2(i), given in section **??**.

5.1 Steady states and $f(\eta, \kappa; t)$

Clearly, $\eta + t_0 v \in \mathbb{R}^n_{>0}$ is a steady state of $(\mathcal{N}, \kappa)$ if and only if

$$f(\eta, \kappa; t_0) = 0 \tag{14}$$

and therefore studying whether the equation $f(t) = 0$ has multiple positive roots is the object of this paper. Even more, the condition for nondegeneracy of an equilibrium is very natural when written in terms of f:

Proposition 5.1. *A steady state $\eta + t_0 v$ of the polynomial dynamical system $(\mathcal{N}, \kappa)$ is degenerate if and only if $f'(\eta, \kappa; t_0) = 0$.*

Proof. We have $f(t)v = F(\eta + tv)$ and $f'(t)v = DF|_{\eta+tv} v$. Then $f'(t_0) = 0$ if and only if v is an eigenvector of $DF|_{\eta+t_0 v}$ corresponding to the zero eigenvalue, i.e. if and only if $\eta + t_0 v$ is degenerate. □

In some of our proofs it is convenient to write f as a product. The following proposition is useful in that case.

Proposition 5.2. *Suppose $\eta + t_0 v$ is a steady state of the reaction system $(\mathcal{N}, \kappa)$ and that $f(t) = p(t)q(t)$ where $p(t_0) \neq 0$. Then $\eta + t_0 v$ is degenerate if and only if $q'(t_0) = 0$.*

Proof. $f'(t_0) = p'(t_0)q(t_0) + p(t_0)q'(t_0) = p(t_0)q'(t_0)$, so $f'(t_0) = 0$ if and only if $q'(t_0) = 0$. □

5.2 Simplifying remarks and assumptions

Recall that we are assuming that v does not have zero coordinates. The next easy result allows us to assume that the entries of v are 1 or -1. We will assume this throughout the paper to simplify some of the calculations in the proofs. However, our results are stated in generality, independently of this assumption.

Proposition 5.3. *Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace. Denote $|v| = (|v_1|, \dots, |v_n|)$ and let $\tilde{v}_i = \frac{v_i}{|v_i|}$, $\tilde{\eta}_i = \frac{\eta_i}{|v_i|}$ for all $i \in S$. If $k \in R \setminus R^0$ we let $\tilde{\kappa}_k = \kappa_k |v|^{a_k}$, and if $k \in R^0$ we let $\tilde{\kappa}_k^+ = \kappa_k^+ |v|^{a_k}$ and $\tilde{\kappa}_k^- = \kappa_k^- |v|^{a_k}$. Let $\tilde{\mathcal{N}}$ denote the reaction network with reactions $a_k \to a_k + \lambda_k \tilde{v}$ for $k \in R \setminus R^0$ and $a_k \to a_k + \lambda_k^+ \tilde{v}$, $a_k \to a_k + \lambda_k^- \tilde{v}$ for $k \in R^0$. Then $\eta + t_0 v$ is a (nondegenerate/degenerate) steady state of $(\mathcal{N}, \kappa)$ if and only if $\tilde{\eta} + t_0 \tilde{v}$ is a (nondegenerate/degenerate) steady state of $(\tilde{\mathcal{N}}, \tilde{\kappa})$.*

Proof.

$$\begin{aligned} f(\eta, \kappa; t) &= \sum_{k \in R \setminus R^0} \lambda_k \kappa_k (\eta + tv)^{a_k} + \sum_{k \in R^0} (\lambda_k^+ - \lambda_k^-)(\eta + tv)^{a_k} \\ &= \sum_{k \in R \setminus R^0} \kappa_k \lambda_k \prod_{i \in S} |v_i|^{a_{ki}} \prod_{i \in S} (\tilde{\eta}_i + t\tilde{v}_i)^{a_{ki}} + \sum_{k \in R^0} (\lambda_k^+ - \lambda_k^-) \prod_{i \in S} |v_i|^{a_{ki}} \prod_{i \in S} (\tilde{\eta}_i + t\tilde{v}_i)^{a_{ki}} \\ &= \sum_{k \in R \setminus R^0} \tilde{\kappa}_k \lambda_k (\tilde{\eta} + t\tilde{v})^{a_k} + \sum_{k \in R^0} (\tilde{\lambda}_k^+ - \tilde{\lambda}_k^-)(\tilde{\eta} + t\tilde{v})^{a_k} \\ &= f(\tilde{\eta}, \tilde{\kappa}; t) \end{aligned}$$

and the conclusion follows from (14) and Proposition 5.1. □

It is useful to note that under the assumption $v = sign(v)$ the embedded graph and the arrow diagram of $\mathcal{N}$ are identical up to the length of arrows.

Remark 5.4. The following assumptions can be made without loss of generality and independently of each other. These will be used in proofs to reduce the number of cases without further explanation.

1 permuting species labels;

2 permuting labels of source complexes in R^+ and permuting labels of source complexes in R^-;

3 setting a certain coordinate of v to 1. This can be done by replacing v with $-v$ as a basis of the stoichiometric subspace, if necessary. The network does not change.

4 setting a certain λ_k, $k \notin R^0$ to 1. This is done by replacing all reaction vectors with their negatives, i.e. reversing the direction of all reactions. This changes the reaction network, but $f(\eta, \kappa; t)$ simply changes sign. Equilibria and their degeneracy properties stay the same.

5.3 Proof of part *1*: necessary conditions for multistationarity

We prove part 1 of Theorem 4.1. Assume that $\mathcal{N}$ is not a single-source network and that it does not have 1D projections containing the arrow pattern $(\to, \leftarrow)$ (the case when $\mathcal{N}$ does not have 1D projections containing the arrow pattern $(\leftarrow, \to)$ is proved similarly.) We write

$$f(\eta, \kappa; t) = \sum_{k \in R^+} \kappa_k (\eta + tv)^{a_k} - \sum_{l \in R^-} \kappa_l (\eta + tv)^{a_l}. \tag{15}$$

and differentiate two cases. First, if $R^+ = \emptyset$ or $R^- = \emptyset$ then $f(\eta, \kappa; t)$ is either strictly positive or strictly negative on $(\alpha^\eta, \beta^\eta)$ and therefore $f(\eta, \kappa; t) = 0$ does not have solutions.

On the other hand, if $R^+ \neq \emptyset$ and $R^- \neq \emptyset$, then (see (10)) for any $k \in R^+, l \in R^-$ and $i \in S$ we have $(a_{ki} - a_{li})v_i \geq 0$. In other words for $i \in S^+$ we have $\max\limits_{l \in R^-} a_{li} \leq \min\limits_{k \in R^+} a_{ki}$ and for $i \in S^-$ we have $\max\limits_{k \in R^+} a_{ki} \leq \min\limits_{l \in R^-} a_{li}$.

Let $\delta \in \mathbb{R}^n$ be such that that

$$\begin{aligned} \max_{l\in R^-} a_{li} \leq \delta_i \leq \min_{k\in R^+} a_{ki} \quad \text{if } i \in S^+ \\ \max_{k\in R^+} a_{ki} \leq \delta_i \leq \min_{l\in R^-} a_{li} \quad \text{if } i \in S^-. \end{aligned} \tag{16}$$

Since R^+ and R^- are both nonempty and since $\mathcal{N}$ has at least two different source complexes there must exist $(k_0, l_0) \in R^+ \times R^-$ such that $a_{k_0} \neq a_{l_0}$. Let $i_0 \in S$ be such that $a_{k_0 i_0} \neq a_{l_0 i_0}$. We refine our choice of δ (16) to ensure that $\delta_{i_0} - a_{k_0 i_0} \neq 0$ and $\delta_{i_0} - a_{l_0 i_0} \neq 0$. Setting (15) equal to zero yields

$$\sum_{k\in R^+} \kappa_k (\eta + tv)^{a_k - \delta} = \sum_{l\in R^-} \kappa_l (\eta + tv)^{a_l - \delta}. \tag{17}$$

Note that exponents $a_k - \delta$ on the left hand side of (17) have coordinates of the same sign or zero, with at least one (i.e. $a_{k_0 i} - \delta_i$) being nonzero. The same holds for the right hand side of (17), and the sign there is the opposite of the sign in the left hand side. It follows that the two sums in equality (17) are strictly monotonic functions of t on $(\alpha^\eta, \beta^\eta)$ with different monotonicities. Therefore (17) has at most one solution in t, and $\mathcal{N}$ does not have the capacity for multiple positive equilibria.

5.4 Proof of part *2(ii)*: capacity for MPE, but not MPNE

Case $\mathcal{N} \in \mathcal{S}_1$ If $\mathcal{N}$ is a single source network with rate constants κ^+ and κ^- then equilibria exist if and only if $\kappa^+ = \kappa^-$. In that case $f(\eta, \kappa; t)$ is identically zero for any η and all equilibria are degenerate.

Case $\mathcal{N} \in \mathcal{S}_2^z$ Denote $\mathcal{N} = \{a \to a', a \to a'', b \to b', b \to b''\}$ and the corresponding rate constants by $\kappa_a^+, \kappa_a^-, \kappa_b^+, \kappa_b^-$ respectively. Suppose that the $(1,2)$ projection of $\mathcal{N}$ has the arrow diagram in Figure ?? class L, and let $d = a_2 - b_2 = b_1 - a_1 \neq 0$. The equation $f(\eta, \kappa; t) = (\kappa_a^+ - \kappa_a^-)(\eta + tv)^a + (\kappa_b^- - \kappa_b^-)(\eta + tv)^b = 0$ is equivalent to

$$\begin{aligned} h(\eta, \kappa; t) &= (\kappa_a^+ - \kappa_a^-) + (\kappa_b^- - \kappa_b^-)(\eta + tv)^{b-a} \\ &= (\kappa_a^+ - \kappa_a^-) + (\kappa_b^- - \kappa_b^-)\left(\frac{\eta_1 + t}{\eta_2 + t}\right)^d = 0. \end{aligned} \tag{18}$$

If $\eta_1 \neq \eta_2$ then $h(\eta, \kappa; t)$ is strictly monotonic and $f(\eta, \kappa; t)$ has at most one zero. On the other hand, if $\eta_1 = \eta_2$ then equation (18) has solutions if and only if $(\kappa_a^+ - \kappa_a^-) + (\kappa_b^- - \kappa_b^-) = 0$, in which case $f(\eta, \kappa; t)$ is identically zero, and $\mathcal{N}$ has multiple equilibria, all degenerate.

Case $\mathcal{N} \in \mathcal{S}_2^{nz}$ Denote $\mathcal{N} = \{a \to a', a \to a'', b \to b', b \to b''\}$ and the corresponding rate constants by $\kappa_a^+, \kappa_a^-, \kappa_b^+, \kappa_b^-$ respectively. Suppose that the $(1,2)$ projection of $\mathcal{N}$ has one of the arrow diagrams in Figure **??**. The equation $f(\eta, \kappa; t) = (\kappa_a^+ - \kappa_a^-)(\eta + tv)^a + (\kappa_b^- - \kappa_b^-)(\eta + tv)^b = 0$ is equivalent to

$$\begin{aligned} h(\eta, \kappa; t) &= (\kappa_a^+ - \kappa_a^-) + (\kappa_b^- - \kappa_b^-)(\eta + tv)^{b-a} \\ &= (\kappa_a^+ - \kappa_a^-) + (\kappa_b^- - \kappa_b^-) \prod_{k\in K^+} (\eta_k + t)^{b_k - a_k} \prod_{l\in K^-} (\eta_l - t)^{b_l - a_l} = 0. \end{aligned}$$

Since $\mathcal{N} \notin \mathcal{Z}$ we have $v_i v_j (b_i - a_i)(b_j - a_j) \geq 0$ for all $i, j \in S$, which implies that $sign(b_k - a_k)$ is the same for all $k \in K^+$, $sign(b_l - a_l)$ have the same sign for all $l \in K^-$ and the two signs are opposite. Then $h(\eta, \kappa; t)$ is a monotonic function which has zeros if and only if it is identically zero. This happens when $\kappa_a^+ = \kappa_a^-$ and $\kappa_b^+ = \kappa_b^-$, and all equilibria are degenerate.

Case $\mathcal{N} \in \mathcal{L}$ Let $\mathcal{N} \in \mathcal{L}$ and suppose $\mathcal{N}_{(1,2)} \in \mathcal{Z}_{-1}$. The slope of the projection of v on $(1,2)$ is positive and we set $v_1 = v_2 = 1$. Let $\delta \in \mathbb{R}^2$ such that

$$\begin{bmatrix} a_{k1} \\ a_{k2} \end{bmatrix} = \delta + p_k \begin{bmatrix} 1 \\ -1 \end{bmatrix} \text{ for all } k \in R$$

where $p_k < 0$ for $R \in R^+ \setminus R_0$, $p_k = 0$ for $k \in R^0$, and $p_k > 0$ for $k \in R^- \setminus R_0$.

Then

$$h(\eta, \kappa; t) := \frac{f(\eta, \kappa; t)}{(\eta + tv)^\delta} = \sum_{k \in R^+ \setminus R^0} \kappa_k \left(\frac{\eta_1 + t}{\eta_2 + t} \right)^{p_k} + \sum_{k \in R^0} (\kappa_k^+ - \kappa_k^-) - \sum_{l \in R^- \setminus R^0} \kappa_l \left(\frac{\eta_1 + t}{\eta_2 + t} \right)^{p_l} \tag{19}$$

Since $R^+ \setminus R_0$ and $R^- \setminus R_0$ are not both empty and since the exponents in the corresponding sums have opposite signs, $h(\eta, \kappa; t)$ is a strictly monotonic function if $\eta_1 \neq \eta_2$, and $f(\eta, \kappa; t)$ has at most one zero. If $\eta_1 = \eta_2$ then $h(\kappa, \eta; t) = \sum_{k \in R^+ \setminus R^0} \kappa_k + \sum_{k \in R^0} (\kappa_k^+ - \kappa_k^-) - \sum_{l \in R^- \setminus R^0} \kappa_l$. Equilibria exist if and only if and $h(\eta, \kappa; t)$ is identically zero. All equilibria are degenerate in this case.

Case $\mathcal{N} \in \mathcal{C}$ Let γ denote the corner of $\mathcal{N}$ (see Definition 3.12). The source complexes of $\mathcal{N}$ different from γ are given by

$$a_j = \gamma + e_{i_j},\ j \in \{1, \ldots, m\}$$

where e_{i_j} is the standard i_j Euclidean unit vector; i_j are pairwise distinct for $j \in \{1, \ldots, m\}$. As γ may or may not be a source complex, the list of source complexes of $\mathcal{N}$ is either $a_1, \ldots, a_m$ or $\gamma, a_1, \ldots, a_m$.

We have

$$f(\eta, \kappa; t) = \epsilon \lambda_0 \kappa_0 (\eta + tv)^\gamma + \sum_{j=1}^m \lambda_j \kappa_j (\eta + tv)^{a_j},$$

where $\epsilon = 0$ or $\epsilon = 1$ depending on whether γ is a scource complex of $\mathcal{N}$.

Steady states of $\mathcal{N}$ correspond to zeros of the function

$$h(\eta, \kappa; t) = \frac{f(\kappa, \eta; t)}{(\eta + tv)^\gamma} = \epsilon \lambda_0 \kappa_0 + \sum_{j=1}^m \lambda_j \kappa_j (\eta + tv)^{e_{i_j}} = \epsilon \lambda_0 \kappa_0 + \sum_{j=1}^m \lambda_j \kappa_j (\eta_{i_j} + t v_{i_j}) = A_0 + A_1 t \tag{20}$$

which is a polynomial in t of degree at most one. Therefore $\mathcal{N}$ has multiple steady states if and only if h is identically zero, in which case all steady states are degenerate. It remains to check that there are choices of $\eta \in \mathbb{R}^n_{>0}$ and of rate constants κ such that h is identically zero. We have

$$A_0 = \epsilon \lambda_0 \kappa_0 + \sum_{j=1}^m \lambda_j \kappa_j \eta_{i_j} \text{ and } A_1 = \sum_{j=1}^m \lambda_j \kappa_j v_{i_j}.$$

For any $s \in S$ the 1D projection of $\mathcal{N}$ on X_s contains at most two source complexes (namely γ_s and $\gamma_s + 1$). Therefore if both arrow patterns $(\rightarrow, \leftarrow)$ and $(\leftarrow, \rightarrow)$ appear on the same 1D projection, then we must have the situation in Figure 5.4(a). But since any source complex differs from γ in at most one coordinate, the two source complexes that project on $\gamma_s + 1$ must be the same, contradiction. It follows that the $(\rightarrow, \leftarrow)$ and $(\leftarrow, \rightarrow)$ patterns must appear in different 1D projections of $\mathcal{N}$, as shown in Figure 5.4(b). Note that the reaction of $\mathcal{N}$ whose source complex projects on X_{s_1} at $\gamma_{s_1} + 1$ is different from the reaction that whose source complex projects on X_{s_2} at $\gamma_{s_2} + 1$, for otherwise that source complex differs from γ in two coordinates. Assume that these two reactions have indexes $j = 1$ and $j = 2$. Suppose the other two reactions whose projections are shown in Figure 5.4(b) have indices $p, q \in R$; p and q may be equal. From (8) and (9) we obtain

$$\lambda_p v_{s_1} > 0,\ \lambda_1 v_{s_1} < 0,\ \lambda_q v_{s_2} < 0,\ \lambda_2 v_{s_2} > 0. \tag{21}$$

The rest of the argument applies the following trivial lemma:

Lemma 5.5. *Suppose $x \in \mathbb{R}^n$ has at least a positive coordinate and at least a negative coordinate. Then*

$$\{x \cdot w | w \in \mathbb{R}^n_{>0}\} = \mathbb{R}.$$

Note that $i_1 = s_1$ and $i_2 = s_2$. It follows from (21) that $x = [\lambda_1 v_{i_1}, \ldots, \lambda_m v_{i_m}]$ has coordinates of mixed signs, and by Lemma 5.5 there exists $\kappa_1, \ldots, \kappa_m$ such that $A_1 = 0$. Fix these values of κ_j. Let $\kappa_0 = \lambda_0 = 1$. Since λ_1 and λ_p have different signs, $x = [\lambda_1 \kappa_1, \ldots, \lambda_m \kappa_m]$ has coordinates of mixed signs, and Lemma 5.5 implies that there exists $w = [\eta_{i_1}, \eta_{i_1}, \ldots, \eta_{i_m}] \in \mathbb{R}^n_{>0}$ such that $x \cdot w = -\epsilon \lambda_0$, in other words $A_0 = 0$. The other coordinates of η (if any) can be chosen arbitrary positive numbers.

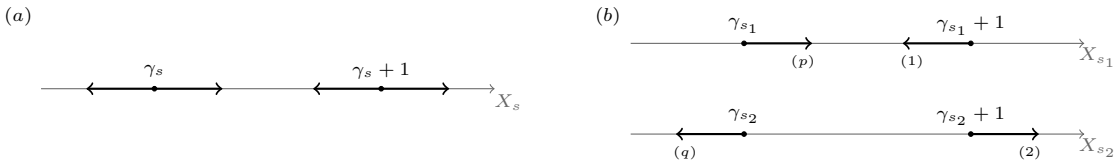


Figure 14: 1D projections of $\mathcal{N}$ that contain 1-alt patterns. Case (a) is impossible, as explained in the text.

5.5 Proof of $2(i)$: capacity for MPNE

We start with a crucial particular case, discussed in the following subsection. The general case is treated in section 5.5.2.

5.5.1 Networks composed of three reactions with pairwise distinct source complexes

We consider networks with $m = 3$ source complexes and one reaction per source complex, in other words $R_0 = \emptyset$. Note that reaction networks of this type cannot be in $\mathcal{S}_1 \cup \mathcal{S}_2^z \cup \mathcal{S}_2^{nz}$. Theorems **??** and 5.13 correspond to cases $\mathcal{N} \in \mathcal{Z}$ and $\mathcal{Z} \notin \mathcal{Z}$ and combine to prove part $2(ii)$ of Theorems 4.1 for $m = 3$ and $R_0 = \emptyset$.

Theorem 5.6. *Let $\mathcal{N}$ be a reaction network with $m = 3$ and $R_0 = \emptyset$. If $\mathcal{N}$ is alt-complete and $\mathcal{N} \notin \mathcal{L} \cup \mathcal{C}$ then $\mathcal{N}$ has the capacity for nondegenerate multiple equilibria.*

We begin with notation and a few lemmas. Let

$$\mathcal{N} = \{a \cdot X \to a' \cdot X, b \cdot X \to b' \cdot X, c \cdot X \to c' \cdot X\}$$

and

$$a' - a = \lambda_1 v,\ b' - b = \lambda_2 v, c' - c = \lambda_3 v.$$

We assume that $\mathcal{N}$ has pairwise distinct source complexes, i.e $a \neq b \neq c \neq a$. Noting that λ_1, λ_2, and λ_3 cannot all have the same sign, we set without loss of generality $\lambda_1 = 1$, $\lambda_2 = -1$, $\lambda_3 = 1$. Therefore

$$f(\eta, \kappa_1, \kappa_2, \kappa_3; t) = \kappa_1(\eta + tv)^a - \kappa_2(\eta + tv)^b + \kappa_3(\eta + tv)^c \tag{22}$$

Define the function g of variable t and depending on parameters η, κ_1, κ_3 :

$$\begin{aligned} g(\eta, \kappa_1, \kappa_3; t) &= \kappa_1(\eta + tv)^{a-b} + \kappa_3(\eta + tv)^{c-b} \\ &= \kappa_1 \prod_{i \in S^+} (\eta_i + t)^{a_i - b_i} \prod_{j \in S^-} (\eta_j - t)^{a_j - b_j} + \kappa_3 \prod_{i \in S^+} (\eta_i + t)^{c_i - b_i} \prod_{j \in S^-} (\eta_j - t)^{c_j - b_j} \end{aligned} \tag{23}$$

Note that g has the same domain $(\alpha^\eta, \beta^\eta)$ as f and that g is positive on this interval.

Clearly, $\eta + t_0 v \in \mathbb{R}^n_{>0}$ is a steady state of $(\mathcal{N}, \kappa)$ if and only if

$$g(\eta, \kappa_1, \kappa_3; t_0) = \kappa_2. \tag{24}$$

Moreover, $\eta + t_0 v$ is a *nondegenerate* steady state of $(\mathcal{N}, \kappa)$ if additionally

$$g'(\eta, \kappa_1, \kappa_3; t) \neq 0. \tag{25}$$

as follows from Proposition 5.1 and Proposition 5.2 with $p(t) = (\eta + tv)^b$ and $q(t) = g(\eta, \kappa_1, \kappa_3; t)) - \kappa_2$. These remarks imply the following proposition, which gives a useful characterization of the capacity for (nondegenerate) multiple steady states using function g.

Proposition 5.7. *1. $\mathcal{N}$ has the capacity for multiple steady states if and only if there exist $\eta \in \mathbb{R}^n_{>0}$ and $\kappa_1, \kappa_3 > 0$ such that $g(\eta, \kappa_1, \kappa_3; t)$ is not injective, i.e. there exist $t_1, t_2 \in (\alpha^\eta, \beta^\eta)$, $t_1 \neq t_2$ such that*

$$g(\eta, \kappa_1, \kappa_3; t_1) = g(\eta, \kappa_1, \kappa_3; t_2).$$

2. $\mathcal{N}$ has the capacity for multiple steady states if and only if there exist $\eta \in \mathbb{R}^n_{>0}$, $\kappa_1, \kappa_3 > 0$ and $t_1, t_2 \in (\alpha^\eta, \beta^\eta)$, $t_1 \neq t_2$ such that

$$g(\eta, \kappa_1, \kappa_3; t_1) = g(\eta, \kappa_1, \kappa_3; t_2)$$

and $g'(\eta, \kappa_1, \kappa_3; t_1), g'(\eta, \kappa_1, \kappa_3; t_2)$ are both nonzero.

Finally, the following easy lemmas give useful tools in applying Proposition 5.7.

Lemma 5.8. *Let $\alpha, \beta \in \mathbb{R} \cup \{\pm\infty\}$ and let $g : (\alpha, \beta) \to \mathbb{R}$ be a non-constant rational function. If $\lim_{t\to\alpha} g(t) = \lim_{t\to\beta} g(t)$ then there exist $t_1, t_2 \in (\alpha, \beta)$, $t_1 \neq t_2$, such that $g(t_1) = g(t_2)$ and $g'(t_1) \neq 0, g'(t_2) \neq 0$.*

Proof. Let $T \in (\alpha, \beta)$ be such that $g(T) \neq \lim_{t\to\alpha} =: L$. Suppose that $g(T) < L$ (the other case is similar). For each $y \in (g(T), L)$ there exist $t_1 \in (\alpha, T)$ and $t_2 \in (T, \beta)$ such that $g(t_1) = g(t_2) = y$. There is an infinite number of choices for y (and therefore an infinite number of pairs t_1, t_2 as above), but only a finite number of roots of g', which is a nonzero rational function. Therefore we can find t_1, t_2 that satisfy the conclusion of the lemma. □

Lemma 5.9. *Let $\alpha, \beta \in \mathbb{R} \cup \{\pm\infty\}$ and let $g : (\alpha, \beta) \to \mathbb{R}$ be a non-constant rational function. Denote $\lim_{t\to\alpha} = A$, $\lim_{t\to\beta} = B$ and let $T \in (\alpha, \beta)$ be such that $g(T) < \min\{A, B\}$ or $g(T) > \max\{A, B\}$. Then there exist $t_1, t_2 \in (\alpha, \beta)$, $t_1 \neq t_2$, such that $g(t_1) = g(t_2)$ and $g'(t_1) \neq 0, g'(t_2) \neq 0$.*

Proof. Suppose $A < B$ and $g(T) < A$ (the other cases are treated similarly). Then there exists $\beta' \in (T, \beta)$ such that $g(\beta') = A$. Lemma 5.8 applies on the interval (α, β') and the conclusion follows. □

Theorem 5.10. *Let $\mathcal{N}$ be a network with one-dimensional stoichiometric subspace composed of three reactions with pairwise distinct source complexes. If $\mathcal{N} \in \mathcal{Z} \setminus (\mathcal{L} \cup \mathcal{C})$ then $\mathcal{N}$ has the capacity for MPNE.*

Proof. If $\mathcal{N} \in \mathcal{Z} \setminus \mathcal{Z}_{-1}$ then $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria by Corollary 4.11. Moreover, letting $\mathcal{N}_1 = \{a \to a', b \to b'\}$ and $\mathcal{N}_2 = \{b \to b', c \to c'\}$ if either $\mathcal{N}_1$ or $\mathcal{N}_2$ belong to $\mathcal{Z}_{-1} \setminus \mathcal{L}$ then by Corollary 4.12 $\mathcal{N}$ admits nondegenerate multistationarity. For the remainder of the proof we assume that $\mathcal{N} \in \mathcal{Z}_{-1} \setminus \mathcal{L}$ and that $\mathcal{N}_1, \mathcal{N}_1 \notin \mathcal{Z}_{-1} \setminus \mathcal{L}$.

Since $\mathcal{N} \in \mathcal{Z}$ at least one of $\mathcal{N}_1$ or $\mathcal{N}_2$ are zigzag networks. Assume $\mathcal{N}_1 \in \mathcal{Z}_{-1}$, and therefore $\mathcal{N}_1 \in \mathcal{L}$. Suppose without loss of generality that the projection of $\mathcal{N}_1$ on $(1, 2)$ is a zigzag of slope -1. Without loss of generality we let $a_1 < b_1$ and $v_1 = v_2 = 1$. Denote $d = a_2 - b_2 = b_1 - a_1 > 0$. $\mathcal{N}_1 \in \mathcal{L}$ implies that $a_i = b_i$ for all $i \in S \setminus \{1, 2\}$ and therefore

$$(\eta + tv)^{a-b} = (\eta_1 + t)^{a_1-b_1}(\eta_2 + t)^{a_2-b_2} = \left(\frac{\eta_2 + t}{\eta_1 + t}\right)^d.$$

Letting $u = c - b$ we rewrite (24) as

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + t}{\eta_1 + t}\right)^m + \kappa_3 \prod_{i\in S^+} (\eta_i + t)^{u_i} \prod_{j\in S^-} (\eta_j - t)^{u_j}. \tag{26}$$

We note that

$$u_i u_j \leq 0 \text{ for all } i \in S^+ \text{ and } j \in S^-. \tag{27}$$

Indeed, otherwise $u_i u_j > 0$, $v_i v_j u_i u_j < 0$ and so the projection of $\mathcal{N}_2$ into (i, j) is a zigzag of positive slope, contradicting $\mathcal{N} \notin \mathcal{Z} \setminus \mathcal{Z}_{-1}$. Moreover,

$$\text{if } u_i u_j < 0 \text{ for some } i, j \in S^+ \text{ or } i, j \in S^- \text{ then } u_i = -u_j \text{ and } u_s = 0 \text{ for all } s \in S \setminus \{i, j\}. \tag{28}$$

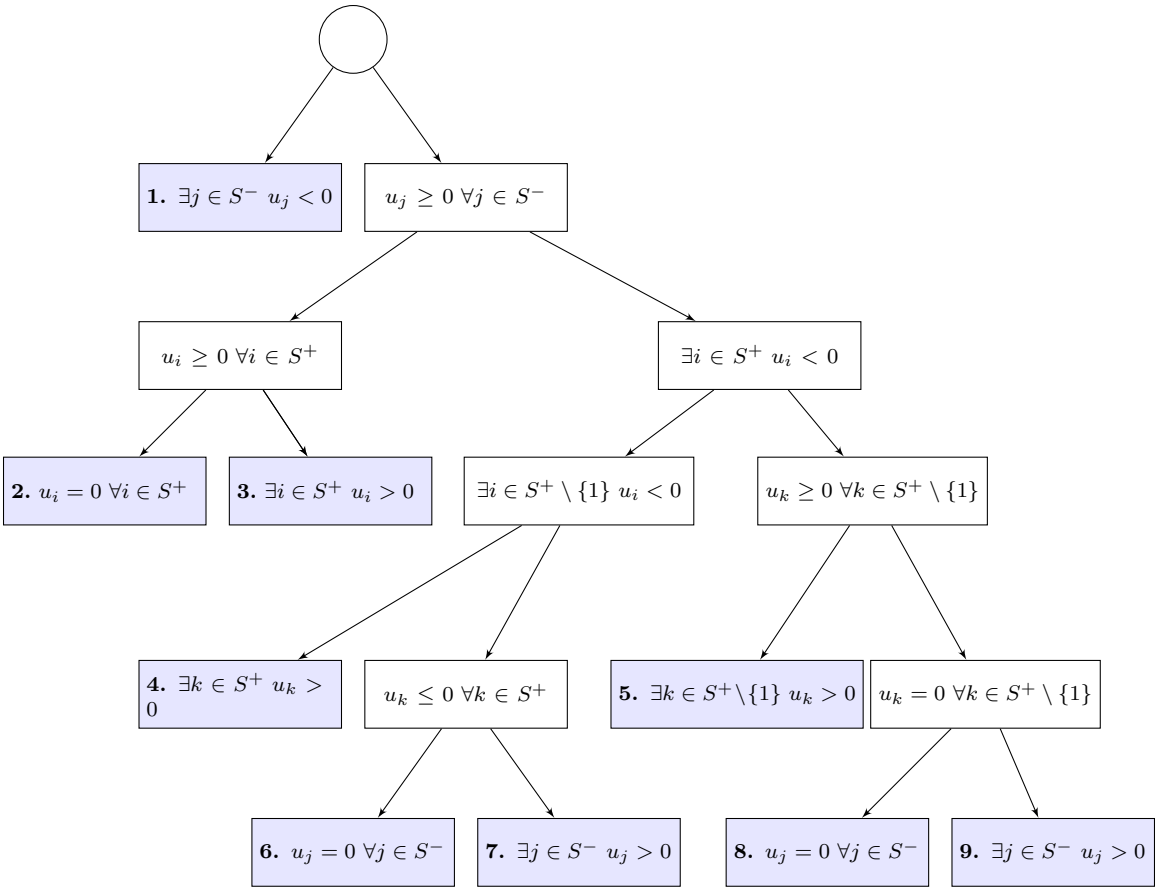


Figure 15: Exhaustive cases for the proof of Theorem 5.10. The cases 1–8 marked by shaded rectangles inherit the assumptions from all ancestor nodes. The symbols $\exists$ and $\forall$ mean "there exists" and "for all" respectively.

Indeed, in this case $v_i v_j u_i u_j < 0$, so $\mathcal{N}_2$ has a zigzag on its (i,j) projection. Therefore $\mathcal{N}_2 \in \mathcal{Z}_{-1}$, which implies $\mathcal{N}_2 \in \mathcal{L}$ and (28) follows.

The proof splits into cases that give various forms for function g. Leaves 1–8 of the tree in Figure 15 (marked by shaded nodes) exhaust all possible cases. Each of the cases 1–8 inherit all assumptions from their ancestor nodes. We note that under our setup $1, 2 \in S^+$.

Case **1**. Fix $j \in S^-$ with $u_j < 0$, and let $\eta \in \mathbb{R}^n_{>0}$ be such that $\eta_1 < \eta_i$ for all $i \in S^+ \setminus \{1\}$ and $\eta_j < \eta_s$ for all $s \in S^- \setminus \{j\}$. Then (see 7) $\alpha^\eta = -\eta_1$, $\beta^\eta = \eta_j$. Equation (27) gives $u_i \geq 0$ for all $i \in S^+$ and applying limits to (26) we obtain $\lim_{t\to\alpha^\eta} g(\eta, \kappa_1, \kappa_3; t) = \lim_{t\to\beta^\eta} g(\eta, \kappa_1, \kappa_3; t) = \infty$. It now follows from Lemma 5.8 and Proposition 5.7 that $\mathcal{N}$ admits nondegenerate multistationarity.

Case **2.** Pick $\eta \in \mathbb{R}^n_{>0}$ with $\eta_j = 1$ for all $j \in S^-$ and $\eta_2 < \eta_i$ for all $i \in S^+ \setminus \{2\}$. Then $\alpha^\eta = -\eta_2$ and $\beta^\eta = 1$ and

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + t}{\eta_1 + t}\right)^d + \kappa_3 (1-t)^L$$

where $L = \sum_{j\in S^-} u_j$. Since $u \neq 0$ and $u_i = 0$ for all $i \in S^+$ we must have $u_j > 0$ for some $j \in S^-$, and therefore $L \geq 1$. We have

$$\lim_{t\to\alpha^\eta} g(\eta, \kappa_1, \kappa_3; t) = \kappa_3 (1+\eta_2)^L,\ \lim_{t\to\beta^\eta} g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + 1}{\eta_1 + 1}\right)^d$$

and we choose positive κ_1, κ_3 such that $\lim_{t\to\alpha^\eta} g(\eta,\kappa_1,\kappa_3;t) = \lim_{t\to\beta^\eta} g(\eta,\kappa_1,\kappa_3;t)$. Lemma 5.8 and Proposition 5.7 apply, and $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

Case **3.** Fix $i \in S^+$ with $u_i > 0$. Equation (27) implies that $u_j \leq 0$ for all $j \in S^-$. Since we have assumed $u_j \geq 0$ for all $j \in S^-$ in this case we have $u_j = 0$ for all $j \in S^-$ and so

$$g(\eta,\kappa_1,\kappa_3;t) = \kappa_1\left(\frac{\eta_2+t}{\eta_1+t}\right)^d + \kappa_3\prod_{k\in S^+}(\eta_k+t)^{u_k}.$$

We pick $\eta \in \mathbb{R}^n_{>0}$ such that $\eta_1 < \eta_i$ for all $i \in S\setminus\{1\}$, and so $\alpha^\eta = -\eta_1$.

Note that regardless of η the function g is defined on (α^η,∞) and we have $\lim_{t\to\alpha^\eta} g(t) = \lim_{t\to\infty} g(t) = \infty$. By Lemma 5.8 we can find $t_1, t_2 \in (\alpha^\eta,\infty)$ such that $g(\eta,\kappa_1,\kappa_3;t_1) = g(\eta,\kappa_1,\kappa_3;t_2)$ and $g'(\eta,\kappa_1,\kappa_3;t_1)$, $g'(\eta,\kappa_1,\kappa_3;t_2)$ are both nonzero. If $S^- = \emptyset$ then $\beta^\eta = \infty$ and it follows from Proposition 5.7 that $\mathcal{N}$ admits nondegenerate multistationarity. If $S^- \neq \emptyset$ we let $\beta > \max\{t_1,t_2\}$, and noting that g does not depend on η_j, $j \in S^-$, we may let $\eta_j = \beta$ for all $j \in S^-$. Then $\beta^\eta = \beta$ and it follows from Proposition 5.7 that $\mathcal{N}$ admits nondegenerate multistationarity.

Remark 5.11. Although we are ultimately interested in showing that g is not injective on the domain (α^η,β^η) of f, we note that g may be defined on $(\alpha^e ta,\infty)$. In some of the cases in this proof we use limits of g at infinity, like we did in Case 3. The approach used here to define β and then η will reoccur in some of the remaining cases.

Case **4**. Fix $i \in S^+\setminus\{1\}$ and $k \in S^+$ such that $u_i < 0$ and $u_k > 0$. With the assumptions in this case (27) implies $u_j = 0$ for all $j \in S^-$ and (28) implies that $u_i = -u_k$ and $u_s = 0$ for all $s \in S^+\setminus\{i,k\}$. Therefore

$$g(\eta,\kappa_1,\kappa_3;t) = \kappa_1\left(\frac{\eta_2+t}{\eta_1+t}\right)^d + \kappa_3\left(\frac{\eta_k+t}{\eta_i+t}\right)^{u_k}.$$

We pick η such that $\eta_i < \eta_s$ for all $s \in S^+\setminus\{i\}$ and $\eta_2 < \eta_1$ (the latter is possible since $i \neq 1$). Then $\alpha^\eta = -\eta_i$ and we have $\lim_{t\to\alpha^\eta} g(t) = \infty$, $\lim_{t\to\infty} g(t) = \kappa_1 + \kappa_3$ and

$$g(\eta,\kappa_1,\kappa_3;0) = \kappa_1\left(\frac{\eta_2}{\eta_1}\right)^d + \kappa_3\left(\frac{\eta_k}{\eta_i}\right)^{u_k}$$

Since $(\frac{\eta_2}{\eta_1})^d < 1$ and $(\frac{\eta_k}{\eta_i})^{u_k} > 1$ we can choose κ_1 and κ_3 such that

$$\kappa_3\left(\left(\frac{\eta_k}{\eta_i}\right)^{u_k} - 1\right) < \kappa_1\left(1 - \left(\frac{\eta_2}{\eta_1}\right)^d\right)$$

which gives $g(\eta,\kappa_1,\kappa_3;0) < \kappa_1+\kappa_3$. From Lemma 5.9 there exist $t_1, t_2 \in (\alpha^\eta,\infty)$ such that $g(\eta,\kappa_1,\kappa_3;t_1) = g(\eta,\kappa_1,\kappa_3;t_2)$ and $g'(\eta,\kappa_1,\kappa_3;t_1)$, $g'(\eta,\kappa_1,\kappa_3;t_2)$ are both nonzero. If $S^- = \emptyset$ then $\beta^\eta = \infty$; otherwise we choose $\beta > 0$ such that $\beta > \max\{t_1,t_2\}$ and since g does not depend on η_j, $j \in S^-$, we may choose $\eta_j = \beta$ for all $j \in S^-$. Then $\beta^\eta = \beta$. In both cases it follows from Proposition 5.7 that $\mathcal{N}$ admits nondegenerate multistationarity.

Case **5**. In this case we have $u_1 < 0$. Fix $k \in S^+\setminus\{1\}$ such that $u_k > 0$. Once again (27) implies that $u_j = 0$ for all $j \in S^-$ and (28) implies that $u_s = 0$ for all $s \in S\setminus\{1,k\}$ and $u_k = -u_1$. Therefore

$$g(\eta,\kappa_1,\kappa_3;t) = \kappa_1\left(\frac{\eta_2+t}{\eta_1+t}\right)^d + \kappa_3\left(\frac{\eta_k+t}{\eta_1+t}\right)^{u_k}$$

Note that $k > 2$, for otherwise we have $a_s = b_s = c_s$ for all $s \in S\setminus\{1,2\}$ and so $\mathcal{N}$ is in $\mathcal{L}$, contradiction. Moreover, we cannot have $d = u_k = 1$: indeed, in that case letting $\gamma = [a_1, b_2, b_3, \ldots, b_n]$ we have $a-\gamma = e_2$, $b-\gamma = e_1$ and $c-\gamma = e_k$ and so $\mathcal{N} \in \mathcal{C}$ contradiction. Therefore $d > 1$ or $u_k > 1$.

We choose η such that $\eta_1 = 2$, $\eta_2 = 1$, $\eta_k = 3$ and $\eta_s > 1$ for all $s \in S^+$. Then $\alpha^\eta = -1$ and g is a non-constant function on $(\alpha^\eta, \beta^\eta)$. Setting $\kappa_1 = 2^d(4^{u_k} - 3^{u_k})$ and $\kappa_3 = 2^{u_k}$ we get

$$\lim_{t\to\alpha^\eta} g(\eta, \kappa_1, \kappa_3; t) = g(\eta, \kappa_1, \kappa_3; 0) = 4^{u_k}$$

and Lemma 5.8 applies on the interval $(\alpha^\eta, 0)$. It follows from Proposition 5.7 that $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

Case **6**. Here we have

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + t}{\eta_1 + t}\right)^d + \kappa_3 \prod_{k\in S^+} (\eta_k + t)^{u_k}$$

where $u_k \le 0$ for all $k \in S^+$. Fix $i \in S^+ \setminus \{1\}$ with $u_i < 0$ and choose η such that $\eta_i < \eta_k$ for all $k \in S^+ \setminus \{i\}$ to obtain $\alpha^\eta = -\eta_i$. Then $\lim_{t\to\alpha^\eta} g(\eta, \kappa_1, \kappa_3; t) = \infty$ and $\lim_{t\to\infty} g(\eta, \kappa_1, \kappa_3; t) = \kappa_1$. Moreover

$$g(\eta, \kappa_1, \kappa_3; 0) = \kappa_1 \left(\frac{\eta_2}{\eta_1}\right)^d + \kappa_3 \prod_{k\in S^+} \eta_k^{u_k}$$

Since $i \neq 1$ we may choose $\eta_2 < \eta_1$. Then $\left(\frac{\eta_2}{\eta_1}\right)^d < 1$ and we can choose κ_1 and κ_3 such that

$$\kappa_3 \prod_{k\in S^+} \eta_k^{u_k} < \kappa_1 \left(1 - \left(\frac{\eta_2}{\eta_1}\right)^d\right)$$

to obtain $g(\eta, \kappa_1, \kappa_3; 0) < \kappa_1$. Lemma 5.9 applies on (α^η, ∞) and the conclusion follows by mimicking the final part of Case 4.

Case **7**. Fix $i \in S^+ \setminus \{1\}$ with $u_i < 0$ and fix $j \in S^-$ with $u_j > 0$. Pick η such that $\eta_i < \eta_k$ for all $k \in S^+ \setminus \{i\}$ and $\eta_1 > \eta_2$. We also let $\eta_j = 1$ for all $j \in S^-$. We therefore have $\alpha^\eta = -\eta_i$ and $\beta^\eta = 1$. Let $L = \sum_{j\in S^-} u_j$ and note that $L \ge 1$. Then

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + t}{\eta_1 + t}\right)^d + \kappa_3 (1-t)^L \prod_{k\in S^+} (\eta_k + t)^{u_k}.$$

We have

$$\lim_{t\to\alpha^\eta} g(\eta, \kappa_1, \kappa_3; t) = \infty, \ \lim_{t\to\beta^\eta} g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + 1}{\eta_1 + 1}\right)^d$$

and

$$g(\eta, \kappa_1, \kappa_3; 0) = \kappa_1 \left(\frac{\eta_2}{\eta_1}\right)^d + \kappa_3 \prod_{k\in S^+} \eta_k^{u_k}$$

Since $\left(\frac{\eta_2 + 1}{\eta_1 + 1}\right)^d > \left(\frac{\eta_2}{\eta_1}\right)^d$ we can choose κ_1 and κ_3 such that

$$\kappa_3 \prod_{k\in S^+} \eta_k^{u_k} < \kappa_1 \left(\left(\frac{\eta_2 + 1}{\eta_1 + 1}\right)^d - \left(\frac{\eta_2}{\eta_1}\right)^d\right)$$

i.e. $g(\eta, \kappa_1, \kappa_3; 0) < \lim_{t\to\beta^\eta} g(\eta, \kappa_1, \kappa_3; t)$. It follows from Lemma 5.9 and Proposition 5.7 that $\mathcal{N}$ admits nondegenerate multistationarity.

Case **8**. In this case

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + t}{\eta_1 + t}\right)^d + \kappa_3 (\eta_1 + t)^{u_1}$$

where $u_1 < 0$. If $d = 1$ and $u_1 = -1$ we let $\gamma = c$ and we have $a - \gamma = e_2$ and $b - \gamma = e_1$. It follows that $\mathcal{N} \in \mathcal{C}$, contradiction. Therefore either $d > 1$ or $u_1 < -1$.

Let $\kappa_1 = \kappa_3 = 1$, $\eta_1 = 2, \eta_2 = 1$, and $\eta_i > 1$ for all $i \in S^+ \setminus \{2\}$, so that $\alpha^\eta = -1$. g is defined on (α^η, ∞) and $\lim_{t\to\alpha^\eta} g(\eta, k_1, k_3; t) = \lim_{t\to\infty} g(\eta, k_1, k_3; t) = 1$. With such choice $g = (\frac{t+1}{t+2})^d + (t+2)^{u_1}$ and since either $d > 1$ or $u_1 < -1$ we have g is non constant. But since either $d > 1$ or $u_1 < -1$ we have

$$g(\eta, k_1, k_3; 0) = \left(\frac{1}{2}\right)^d + 2^{u_1} < 1.$$

Lemma 5.9 applies and the conclusion follows by mimicking the final part of Case **4**.

Case **9**. Fix $j \in S^-$ such that $u_j > 0$. We have

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{\eta_2 + t}{\eta_1 + t}\right)^d + \kappa_3(\eta_1 + t)^{u_1} \prod_{k\in S^-} (\eta_k - t)^{u_k}$$

where $u_1 < 0$.

Suppose $d = 1$, $u_1 = -1$, and $L := \sum_{k\in S^-} u_k = 1$. Note that $L = 1$ is equivalent to saying that $u_j = 1$ and all other coordinates of u are zero. Letting $\gamma = [a_1, b_2, b_3, \ldots, b_n]$ we have $a - \gamma = e_2$, $b - \gamma = e_1$ and $c - \gamma = e_j$, which implies that $\mathcal{N} \in \mathcal{C}$ contradiction. So $d > 1$, or $u_1 < -1$, or $L > 1$.

Choosing $\eta_k = 1$ for all $k \in S^-$, $\eta_2 = 1$ and $\eta_i = 2$ for all $i \in S^+ \setminus \{2\}$ we obtain $\alpha^\eta = -\eta_2 = -1$ and $\beta^\eta = 1$ and

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 \left(\frac{1 + t}{2 + t}\right)^d + \kappa_3(2 + t)^{u_1}(1 - t)^L$$

It is easy to see that under the assumptions on d, u_1 and L, g is non-constant. Letting $\kappa_1 = 3^d$ and $\kappa_3 = 2^{d-L}$ we get $\lim_{t\to\alpha^\eta} g(\eta, \kappa_1, \kappa_3; t) = \lim_{t\to\beta^\eta} g(\eta, \kappa_1, \kappa_3; t) = 2^d$. Once again, Lemma 5.8 applies and Proposition 5.7 concludes that $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

□

Remark 5.12. Although we assume that d and u_k are integers, this fact wasn't used in our proof. The crucial was to know sign of d, sign of components of u_i, and in some cases compare $d\,|u_i|$ with one. As d and u defined, $d = b_2 - a_2 > 0$ and $u = b - c$, the same conclusion can be obtained assuming that $a, b, c \in \mathbb{R}^n_{ge0}$. It follows that the restriction on source complexes to be integers can be eliminated.

Theorem 5.13. *Let $\mathcal{N}$ be a network with one-dimensional stoichiometric subspace composed of three reactions with pairwise distinct source complexes. If $\mathcal{N} \in \mathcal{A}_c \setminus (\mathcal{Z} \cup \mathcal{C})$ then $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.*

Proof. Without loss of generality suppose that $\lambda_1 = \lambda_3 = 1$, $\lambda_2 = -1$, and that a 1D projection of $\mathcal{N}_1 = \{a \to a', b \to b'\}$ has the arrow diagram $(\to, \leftarrow)$. Since $\mathcal{N}_1 \notin \mathcal{Z}$ (11) implies

$$v_i(a_i - b_i) \le 0 \text{ for all } i \in S \tag{29}$$

where at least one such product is nonzero and so

$$v \cdot (a - b) < 0. \tag{30}$$

Since $\{a \to a', b \to b'\}$ is not a zigzag network, the 1D projection of $\mathcal{N}$ containing the pattern $(\leftarrow, \to)$ must come from $\mathcal{N}_2 = \{b \to b', c \to c'\}$. Then (10) implies

$$v_j(c_j - b_j) \ge 0 \text{ for all } j \in S \tag{31}$$

and so

$$v \cdot (b - c) < 0. \tag{32}$$

Combining (30) and (32) we obtain

$$v \cdot (a - c) < 0. \tag{33}$$

The equation

$$g(\eta, \kappa_1, \kappa_3; t_1) = g(\eta, \kappa_1, \kappa_3; t_2)$$

corresponding to multiple steady states of $\mathcal{N}$ (see Proposition 5.7) can be viewed as the following linear system in κ_1, κ_3:

$$\begin{bmatrix} (\eta + t_1 v)^{a-b} & (\eta + t_1 v)^{c-b} \\ (\eta + t_2 v)^{a-b} & (\eta + t_2 v)^{c-b} \end{bmatrix} \begin{bmatrix} \kappa_1 \\ \kappa_3 \end{bmatrix} = \begin{bmatrix} \kappa_2 \\ \kappa_2 \end{bmatrix}. \tag{34}$$

To be precise, $\eta + t_1 v, \eta + t_2 v \in \mathbb{R}^n_{>0}$ are equilibria of $\mathcal{N}$ if there exist κ_2 such that (34) has solutions satisfying $\kappa_1, \kappa_3 > 0$. We show that this is the case under the additional simplifications $\eta = [p, p, \ldots, p]$ for some $p > 1$ and $t_1 = -t_2 = t_0$ where $t_0 = \sqrt{p^2 - 1}$. Note that $p - t_0 = \frac{1}{p + t_0}$.

We let $v_{S^+} = \frac{1}{2}(v + 1)$ and $v_{S^-} = [1, 1, \ldots, 1] - v_{S^+}$. In other words, v_{S^+} has all S^+ coordinates equal to 1 and all S^- coordinates equal to 0, while v_{S^-} has all S^+ coordinates equal to 0 and all S^- coordinates equal to 1. We have

$$v = v_{S^+} - v_{S^-}.$$

The system (34) has determinant

$$\begin{aligned}
\det M =& (\eta + t_0 v)^{a-b} (\eta - t_0 v)^{c-b} - (\eta + t_0 v)^{c-b} (\eta - t_0 v)^{a-b} \\
=& (p + t_0)^{(a-b)\cdot v_{S^+}} (p - t_0)^{(a-b)\cdot v_{S^-}} (p - t_0)^{(c-b)\cdot v_{S^+}} (p + t_0)^{(c-b)\cdot v_{S^-}} \\
& - (p + t_0)^{(c-b)\cdot v_{S^+}} (p - t_0)^{(c-b)\cdot v_{S^-}} (p - t_0)^{(a-b)\cdot v_{S^+}} (p + t_0)^{(a-b)\cdot v_{S^-}} \\
=& (p + t_0)^{(a-b)\cdot v_{S^+} - (a-b)\cdot v_{S^-} - (c-b)\cdot v_{S^+} + (c-b)\cdot v_{S^-}} \\
& - (p + t_0)^{(a-b)\cdot v_{S^-} - (a-b)\cdot v_{S^+} - (c-b)\cdot v_{S^-} + (c-b)\cdot v_{S^+}} \\
=& (p + t_0)^{(a-b)\cdot v - (c-b)\cdot v} - (p + t_0)^{-(a-b)\cdot v + (c-b)\cdot v} \\
=& (p + t_0)^{(a-c)\cdot v} - (p + t_0)^{(c-a)\cdot v}
\end{aligned}$$

which is nonzero – this follows since $p + t_0 > 1$ and (33). For any $\kappa_2 > 0$ the solution of (34) is computed using Cramer's rule:

$$\begin{aligned}
\kappa_1 &= \kappa_2 \frac{(p + t_0)^{(b-c)\cdot v} - (p + t_0)^{-(b-c)\cdot v}}{(p + t_0)^{(a-c)\cdot v} - (p + t_0)^{-(a-c)\cdot v}} \\
\kappa_3 &= \kappa_2 \frac{(p + t_0)^{(a-b)\cdot v} - (p + t_0)^{-(a-b)\cdot v}}{(p + t_0)^{(a-c)\cdot v} - (p + t_0)^{(a-c)\cdot v}}
\end{aligned} \tag{35}$$

Since $(a - b) \cdot v$, $(b - c) \cdot v$ and $(a - c) \cdot v$ have the same sign (see (30), (32), (33)) we have $\kappa_1 > 0$ and $\kappa_3 > 0$ for any choice of $\kappa_2 > 0$ and for any $p > 1$.

It remains to check that the resulting equilibria are nondegenerate. To this end we have

$$g(\eta, \kappa_1, \kappa_3; t) = \kappa_1 (p + t)^{(a-b)\cdot v_{S^+}} (p - t)^{(a-b)\cdot v_{S^-}} + \kappa_3 (p + t)^{(c-b)\cdot v_{S^+}} (p - t)^{(c-b)\cdot v_{S^-}}$$

and therefore

$$\begin{aligned}
g'(t) =& \kappa_1 [(a - b) \cdot v_{S^+} (p + t)^{(a-b)\cdot v_{S^+} - 1} (p - t)^{(a-b)\cdot v_{S^-}} \\
& - (a - b) \cdot v_{S^-} (p + t)^{(a-b)\cdot v_{S^+}} (p - t)^{(a-b)\cdot v_{S^-} - 1}] \\
& + \kappa_3 [(c - b) \cdot v_{S^+} (p + t)^{(c-b)\cdot v_{S^+} - 1} (p - t)^{(c-b)\cdot v_{S^-}} \\
& - (c - b) \cdot v_{S^-} (p + t)^{(c-b)\cdot v_{S^+}} (p - t)^{(c-b)\cdot v_{S^-} - 1}]
\end{aligned}$$

Using $p - t_0 = (p + t_0)^{-1}$ and plugging in (35) we obtain

$$\frac{\det M}{\kappa_2} g'(t_0) = Q(p + t_0)$$

where

$$\begin{aligned} Q(y) =& A_1 y^{E_1} - A_2 y^{E_1+2} - A_3 y^{E_3} + A_4 y^{E_3+2} \\ & - (A_1 - A_3) y^{E_5} + (A_2 - A_4) y^{E_5+2} \end{aligned}$$

with

$$A_1 = (a-b) \cdot v_{S^+},\ A_2 = (a-b) \cdot v_{S^-},\ A_3 = (c-b) \cdot v_{S^+},\ A_4 = (c-b) \cdot v_{S^-}.$$

and

$$E_1 = (a-c) \cdot v - 1,\ E_3 = (c-a) \cdot v - 1,\ E_5 = (a+c-2b) \cdot v - 1.$$

Since any choice of $p > 1$ gives two positive equilibria, it remains to argue that for some value of $p > 1$ these equilibria are nondegenerate, in other words $Q(p + \sqrt{p^2-1}) \neq 0$ and $Q(p - \sqrt{p^2-1}) \neq 0$. Indeed, unless Q is identically zero, Q has a finite number of zeros (Q multiplied with a monomial of large enough exponent is a polynomial). We conclude the proof by showing that Q cannot be identically zero. Suppose it is; it can be seen from (30) and (32) that the following inequalities hold between exponents of Q:

$$E_1 < E_1 + 2 \leq E_5 < E_5 + 2 \leq E_3 < E_3 + 2. \tag{36}$$

Since the the exponents E_1 and $E_3 + 2$ appear only once in the expression of Q, we have $A_1 = A_4 = 0$. Since $A_1 - A_2 = (a-b) \cdot v < 0$ we have $A_2 \neq 0$ and therefore a term with exponent $E_1 + 2$ must appear elsewhere. The inequalities (36) then imply $E_1 + 2 = E_5$, in other words $(c-b) \cdot v = 1$. The aggregate coefficient of this exponent is $-A_2 - A_1 + A_3 = 0$, so $A_2 = A_3$. Therefore $A_3 \neq 0$ and we must have $E_3 = E_5 + 2$, in other words $(b-a) \cdot v = 1$. The combined coefficient of the E_3 exponent equals $-A_3 + A_2 - A_4 = 0$, so $A_4 = 0$. Therefore we have

$$(a-b) \cdot v_{S^+} = 0,\ (a-b) \cdot v = -1,\ (c-b) \cdot v_{S^-} = 0,\ (c-b) \cdot v = 1,$$

and so

$$(a-b) \cdot v_{S^-} = 1 \text{ and } (c-b) \cdot v_{S^+} = 1. \tag{37}$$

Since every term in the dot products above are non-negative integers by (29) and (**??**) it follows that it follows that $a - b$ and $c - b$ are elements of the standard basis of $\mathbb{R}^n$, and so $\mathcal{N} \in \mathcal{C}$ (with $\gamma = b$), contradiction.

Therefore Q is not identically zero and the proof is complete. □

Remark 5.14. Inequality 36 is obtained under the assumption that $|(a-b) \cdot v| \geq 1$, $|(c-b) \cdot v| \geq 1$ and $|(a-c) \cdot v| \geq 1$. Suppose this assumption is lifted. Then we have $E_1 < E_5 < E_3 < E_3 + 2$. The same arguments to get $A_1 = A_4 = 0$ which implies that $A_2 \neq 0$ and $A_3 \neq 0$. Note, that any three of the remaining four exponents cannot be equal. The only possibility to get zero is when $E_1 + 2 = E_5$ and $E_3 = E_5 + 2$. It is the case covered by the theorem.

We conclude the discussion on networks with three reactions with the following useful result.

Lemma 5.15. *Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace consisting of three reactions. If $\mathcal{N}$ has a 1D projection that contains both $(\rightarrow, \leftarrow)$ and $(\leftarrow, \rightarrow)$ patterns (i.e. is alt-complete) then $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.*

Proof. Networks of class $\mathcal{L}$ and $\mathcal{C}$ do not have 1D projections that are alt-complete, so $\mathcal{N} \in \mathcal{A}_c \setminus (\mathcal{L} \cup \mathcal{C})$. The conclusion follows from case $m = 3$ of Theorem 5.6 2(i). □

5.5.2 The general case

combine! **Networks with more than three reactions** combine this into the general case Throughout this section $\mathcal{N}$ denotes a reaction network with one-dimensional stoichiometric subspace, composed of m reactions

$$a_k \to a'_k,\ k \in\ R.$$

Lemma 5.16. *Suppose $\mathcal{N}$ is a reaction net alt-complete reaction network composed of $m \geq 4$ reactions with pairwise distinct source complexes. Then $\mathcal{N}$ has an alt-complete subnetwork composed of three reactions.*

We start with two lemmas:

Lemma 5.17. *Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace with at least three source complexes. If $\mathcal{N} \in \mathcal{A}_c$ then $\mathcal{N}$ has an alt-complete subnetwork composed of three reactions with pairwise distinct source complexes.*

Proof. does this work? True when $\mathcal{N}$ composed of three reactions.

Let $\mathcal{N}' = \{a_1 \to a'_1, a_2 \to a'_2, a_3 \to a'_3, a_4 \to a'_4\}$ be an alt-complete subnetwork of $\mathcal{N}$.

Without loss of generality assume that a 1D projection of $\{a_1 \to a'_1, a_2 \to a'_2\}$ contains the $(\to, \leftarrow)$ pattern and a 1D projection of $\{a_3 \to a'_3, a_4 \to a'_4\}$ contains the $(\leftarrow, \to)$ pattern. Additionally, suppose that $\lambda_1 > 0,\ \lambda_2 < 0$, and $\lambda_3 > 0,\ \lambda_4 < 0$. Then (11) implies that $v_i(a_{1i} - a_{2i}) < 0$ for some $i \in S$, and (10) implies that $v_j(a_{3j} - a_{4j}) > 0$ for some $j \in S$ (it is possible to have $i = j$). If $a_1 \neq a_4$,then there exists $s \in S$ such that $v_s(a_{1s} - a_{4s}) \neq 0$. Additionally, $\lambda_1\lambda_4 < 0$. Hence, $\{a_1 \to a'_1, a_4 \to a'_4\} \in \mathcal{A}_1$. If $v_s(a_{1s} - a_{4s}) > 0$, then $\{a_1 \to a'_1, a_2 \to a'_2, a_4 \to a'_4\} \in \mathcal{A}_c$. Otherwise $\{a_1 \to a'_1, a_3 \to a'_3, a_4 \to a'_4\} \in \mathcal{A}_c$. If $a_1 = a_4$ and $a_2 \neq a_3$ by applying the same arguments we get that $\{a_1 \to a'_1, a_2 \to a'_2, a_3 \to a'_3\} \in \mathcal{A}_c$ or $\{a_2 \to a'_2, a_3 \to a'_3, a_4 \to a'_4\} \in \mathcal{A}_c$. If $a_1 = a_4$, $a_2 = a_3$, and since $\mathcal{N} \notin \mathcal{S}_2^z \cup \mathcal{S}_2^{nz}$ then there exist $a_5 \to a'_5$ with $a_5 \neq a_1$ and $a_5 \neq a_2$. Assume that $\lambda_5 > 0$ (similar arguments when $\lambda_5 < 0$). If reactions 2,5 and 4,5 have different patterns $(\to, \leftarrow)$ or $(\leftarrow, \to)$ on 1D projections, then 2,4,5 form an alt-complete subnetwork. If they have the same pattern on all 1D projections, then one we choose a pair from 1,2 or 3,4 that has different pattern. We get that reactions 1,2,5 or 3,4,5 form an alt-complete network. If $a_1 = a_2 = a_3 = a_4$, then $\mathcal{N}' \notin \mathcal{A}_c$. □

case Z, just do the not in Z case.

Lemma 5.18. *Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace composed of three reactions. If $\mathcal{N} \in \mathcal{A}_c \setminus \mathcal{Z}$ then $\mathcal{N}$ has pairwise distinct source complexes.*

Proof. Let $\mathcal{N} = \{a \to a', b \to b', c \to c'\}$, and set $a \to a'$ and $c \to c'$ to have the same direction, the opposite of that of $b \to b'$.

Since $\mathcal{N}$ is alt-complete not all a, b, c can be equal. Recall that each source complex has at most one reaction for each direction, so $a \neq c$. Suppose $a = b$; then the $(\to, \leftarrow)$ and $(\leftarrow, \to)$ patterns of $\mathcal{N}$ must come from projections of $\mathcal{N}' = \{b \to b', c \to c'\}$, which is a zigzag network; it follows that $\mathcal{N} \in \mathcal{Z}$, contradiction. We conclude that a, b, c are pairwise distinct. □

Proof. check Let $\mathcal{N} = \{a_1 \to a'_1, a_2 \to a'_2, a_3 \to a'_3, a_4 \to a'_4\} \in \mathcal{A}_c$ be a network with pairwise distinct source complexes. By way of contradiction, assume that $\mathcal{N}$ does not have an alt-complete subnetwork composed of three reactions. Without loss of generality assume that a 1D projection of $\{a_1 \to a'_1, a_2 \to a'_2\}$ contains the $(\to, \leftarrow)$ pattern and a 1D projection of $\{a_3 \to a'_3, a_4 \to a'_4\}$ contains the $(\leftarrow, \to)$ pattern. Additionally, suppose that $\lambda_1 > 0,\ \lambda_2 < 0$, and $\lambda_3 > 0,\ \lambda_4 < 0$. Then (11) implies that $v_i(a_{1i} - a_{2i}) < 0$ for some $i \in S$, and (10) implies that $v_j(a_{3j} - a_{4j}) > 0$ for some $j \in S$ (it is possible to have $i = j$). Since $a_1 \neq a_4$, there exists $s \in S$ such that $v_s(a_{1s} - a_{4s}) \neq 0$. Additionally, $\lambda_1\lambda_4 < 0$. Hence, $\{a_1 \to a'_1, a_4 \to a'_4\} \in \mathcal{A}_1$. If $v_s(a_{1s} - a_{4s}) > 0$, then $\{a_1 \to a'_1, a_2 \to a'_2, a_4 \to a'_4\} \in \mathcal{A}_c$. Otherwise $\{a_1 \to a'_1, a_3 \to a'_3, a_4 \to a'_4\} \in \mathcal{A}_c$. The result contradicts the assumption. □

Lemma 5.19. *Let $\mathcal{N}$ be a reaction network with one-dimensional stoichiometric subspace. Asssume that $\mathcal{N} \notin \mathcal{L} \cup \mathcal{C}$ and that there exists subnetwork*

$$\mathcal{N}' = \{a \to a',\ b \to b', c \to c'\}$$

of $\mathcal{N}$ that has a 2D projection forming one of the patterns in Figure 16 (in particular, for (i) $a - c, b - c \in \{e_1, \ldots, e_n\}$). Then $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

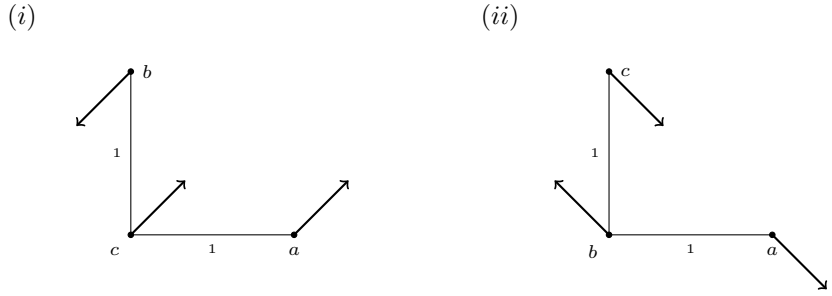


Figure 16: Special 2D patterns that imply the capacity for multiple nondegenerate equilibria (see Lemma 5.19).

Proof. Note that for both (i) and (ii) the subnetwork $\mathcal{N}' = \{a \to a', b \to b', c \to c'\}$ of $\mathcal{N}$ is not in $\mathcal{L}$. If it's also not in $\mathcal{C}$ then $\mathcal{N}$ has multiple nondegenerate equilibria from case $m = 3$ of Theorem 5.6 and Theorem 2.7. It remains to treat the case when $\mathcal{N}' \in \mathcal{C}$.

Pattern (i). Let $a = c + e_1$, $b = c + e_2$. Let $d \to d'$ be an arbitrary reaction in $\mathcal{N} \setminus \mathcal{N}'$. The subnetwork

$$\mathcal{N}'' = \{a \to a', b \to b', d \to d'\}$$

is alt-complete.

If $\mathcal{N}'' \notin \mathcal{L} \cup \mathcal{C}$ then it follows from case $m = 3$ of Theorem 5.6 2(i) that $\mathcal{N}''$ has the capacity for multiple nondegenerate equilibria, and therefore so does $\mathcal{N}$.

If $\mathcal{N}'' \in \mathcal{L}$ then the projection of d on $(1, 2)$ must lie on the line ab and be different from a and b. One checks easily from Figure 17 that in this case the subnetwork $\{b \to b', c \to c', d \to d'\}$ of $\mathcal{N}$ is alt-complete, but not in $\mathcal{L} \cup \mathcal{C}$, and therefore it has the capacity for multiple nondegenerate equilibria and so does $\mathcal{N}$.

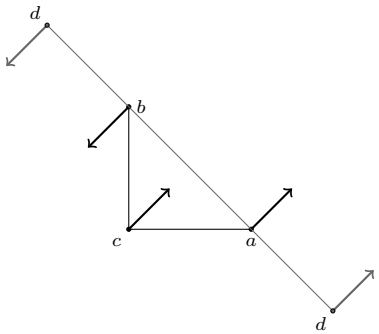


Figure 17: Possible locations for the projection of d on $(1, 2)$ when $\mathcal{N}' \in \mathcal{L}$. The direction of $d \to d'$ is not important.

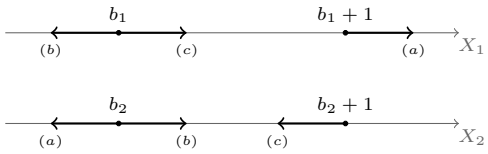


Figure 18: 1D projections of pattern (ii) in Lemma 5.19.

If $\mathcal{N}'' \in \mathcal{C}$, let γ' denote its corner. Since $a - b \notin \{e_1, \ldots, e_n\}$ we have $\gamma' \neq a$, $\gamma' \neq b$ and therefore for some $i, j \in S$ we have $a = \gamma + e_1 = \gamma' + e_i$ and $b = \gamma + e_2 = \gamma' + e_j$. It follows that $\gamma - \gamma' = e_i - e_1 = e_j - e_2$, and we must have $i = 1$, $j = 2$, and $\gamma = \gamma'$, and so

$$d - \gamma \in \{e_1, \ldots, e_n\}. \tag{38}$$

We have shown that if not all source complexes $d \notin \{a, b, c\}$ of $\mathcal{N}$ satisfy (38) then $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria. On the other hand, if all source complexes $d \notin \{a, b, c\}$ satisfy (38) then $\mathcal{N} \in \mathcal{C}$, contradiction.

Pattern (ii). Let $a = b + e_1$, $c = b + e_2$, and $d \to d'$ be an arbitrary reaction in $\mathcal{N} \setminus \mathcal{N}'$. First suppose that $d \to d'$ has the same direction as $a \to a'$. By inspecting the 1D projections of pattern (ii) in Figure 18 we note that if $d_1 < b_1$ then $\mathcal{N}$ has both patterns $(\to, \leftarrow)$ and $(\leftarrow, \to)$ on its X_1 projection, and therefore has the capacity for multiple nondegenerate equilibria by Lemma 5.15. The same is true if $d_2 < b_2$.

If $d_1 > b_1$ and $d_2 > b_2$ then the projection of $\{b \to b', d \to d'\}$ on $(1, 2)$ is a zigzag of positive slope, and therefore $\mathcal{N} \in \mathcal{Z} \setminus \mathcal{Z}_{-1}$ has the capacity for multiple nondegenerate equilibria by Corollary 4.11.

If $d_1 = b_1$ and $d_2 > b_2$ then the network $\mathcal{N}'' = \{a \to a', b \to b', d \to d'\}$ is alt-complete but not in $\mathcal{L}$. We next argue that $\mathcal{N}''$ is also not in $\mathcal{C}$. Indeed, otherwise we must have $d_2 = b_2 + 1$ and in fact $d = b + e_2 = c$, contradiction. So $\mathcal{N}'' \notin \mathcal{L} \cup \mathcal{C}$ and $\mathcal{N}''$ (and therefore $\mathcal{N}$) has the capacity for multiple nondegenerate equilibria. If $d_2 = b_2$ then there exists $s \notin \{1, 2\}$ such that $d_s \neq b_s$. Since b and d have different directions, $\{b \to b', d \to d'\}$ form one of the $(\to, \leftarrow)$ or $(\leftarrow, \to)$ patterns on the X_s 1D projection of $\mathcal{N}$. The remaining pattern is formed by $\{a \to a', b \to b'\}$ on X_1 or by $\{b \to b', c \to c'\}$ on X_2. Therefore either $\mathcal{N}'' = \{a \to a', b \to b', d \to d'\}$ or $\mathcal{N}''' = \{b \to b', c \to c', d \to d'\}$ is alt-complete. Suppose $\mathcal{N}'' \in \mathcal{A}_c$ (the other case is similar). Note that $\mathcal{N}' \notin \mathcal{L}$. If $\mathcal{N}'' \notin \mathcal{C}$ then it has the capacity for multiple nondegenerate equilibria by case $m = 3$ of Theorem 5.6, and so does $\mathcal{N}$ by Theorem 2.7. If $\mathcal{N}'' \in \mathcal{C}$ then b must be the corner of this network and therefore

$$d - b \in \{e_3, \ldots, e_n\}. \tag{39}$$

We have shown that if any reaction $d \in \mathcal{N} \setminus \mathcal{N}'$ does not satisfy (39) then $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria. On the other hand if all reactions $d \in \mathcal{N} \setminus \mathcal{N}'$ does obey (39) then $\mathcal{N} \in \mathcal{C}$, contradiction.

Now assume that $d \to d'$ has the same direction as $b \to b'$. If $d_1 \notin \{b_1, b_1 + 1\}$ or $d_2 \notin \{b_2, b_2 + 1\}$ $d_1 > b_1 + 1$ or $d_2 > b_2 + 1$ then the projection of $\mathcal{N}$ on X_1 or X_2 has both $(\to, \leftarrow)$ and $(\leftarrow, \to)$ patterns if $d_1 < b_1$ and $d_2 < b_2 + 1$, then $\{a \to a', d \to d'\} \in \mathcal{Z} \setminus \mathcal{Z}_{-1}$ and $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria by Lemma 5.15.

If $[d_1, d_2] = [b_1, b_2]$ then the subnetwork $\{a \to a', c \to c', \to d'\}$ of $\mathcal{N}$ is alt-complete and not in $\mathcal{C}$it can be in $\mathcal{C}$, but like (i) . If this network is in $\mathcal{C}$ then we must have $c = d$, contradiction. Therefore the subnetwork has the capacity for multiple nondegenerate equilibria, and so does $\mathcal{N}$.

If $[d_1, d_2] = [b_1 + 1, b_2 + 1]$ then $\{a \to a', c \to c', d \to d'\} \notin \mathcal{L} \cup \mathcal{C}$ is alt-complete, and so $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

If $[d_1, d_2] = [b_1, b_2 + 1] = [c_1, c_2]$ then there exists $s \in S \setminus \{1, 2\}$ such that $d_s \neq c_s = a_s$. If $(a \to a', d \to d')$ form the $(\to, \leftarrow)$ pattern on X_s then the subnetwork $\{a \to a', c \to c', d \to d'\}$ of $\mathcal{N}$ is alt-complete and not in $\mathcal{L}$; it is also not in $\mathcal{C}$ since that would imply $d = c$imply $a_2 = d_2$, contradiction. Therefore $\mathcal{N}$ has the capacity for multiple equilibria. If $(a \to a', d \to d')$ form the $(\leftarrow, \to)$ pattern on X_s then as above the

subnetwork $\{a \to a', b \to b', d \to d'\}$ of $\mathcal{N}$switch a for c is alt-complete and not in $\mathcal{L} \cup \mathcal{C}$, and therefore $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

The case $[d_1, d_2] = [b_1 + 1, b_2]$ is similar to the one above. □

Now we proceed to the proof of Theorem 5.6 part $2(i)$, using notation introduced in 3.2. The cases $m = 2$ and $m = 3$ were settled in sections **??** and **??**. We assume $m \geq 4$. According to Lemma 5.17 there exists an alt-complete subnetwork

$$\mathcal{N}' = \{a \to a',\ b \to b', c \to c'\}$$

of $\mathcal{N}$. Assume without loss of generality that $a = a_1$, $b = a_2$, $c = a_3$ and (see Remark 5.4) that $\lambda_1 = \lambda_3 = -\lambda_2$. If $\mathcal{N}' \notin \mathcal{L} \cup \mathcal{C}$ then $\mathcal{N}'$ has the capacity for multiple nondegenerate equilibria by Theorems 5.10 and 5.13. It follows from Theorem 2.7 that $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

1. Case $\mathcal{N}' \in \mathcal{L}$ We may assume that the projection of $\mathcal{N}'$ on $(1, 2)$ is a zigzag network, and we have

$$\begin{bmatrix} a_1 \\ a_2 \end{bmatrix} = \delta + p_1 \begin{bmatrix} 1 \\ -1 \end{bmatrix}, \quad \begin{bmatrix} b_1 \\ b_2 \end{bmatrix} = \delta + p_2 \begin{bmatrix} 1 \\ -1 \end{bmatrix}, \quad \begin{bmatrix} c_1 \\ c_2 \end{bmatrix} = \alpha + p_3 \begin{bmatrix} 1 \\ -1 \end{bmatrix}, \tag{40}$$

where $\delta \in \mathbb{R}^2_{>0}$, p_1 and p_3 have the same sign and p_2 the opposite sign. Permuting X_1 and X_2 we may choose without loss of generality $p_3 < p_1 < 0$. We also set $v_1 > 0, v_2 > 0$ and choose $\delta \notin \{[a_{j1}, a_{j2}]^t | j \in R\}$ (i.e. δ is different from all projections of source complexes of $\mathcal{N}$ on $(1, 2)$). The projection of $\mathcal{N}'$ on $(1, 2)$ is illustrated in Figure 19 (i).

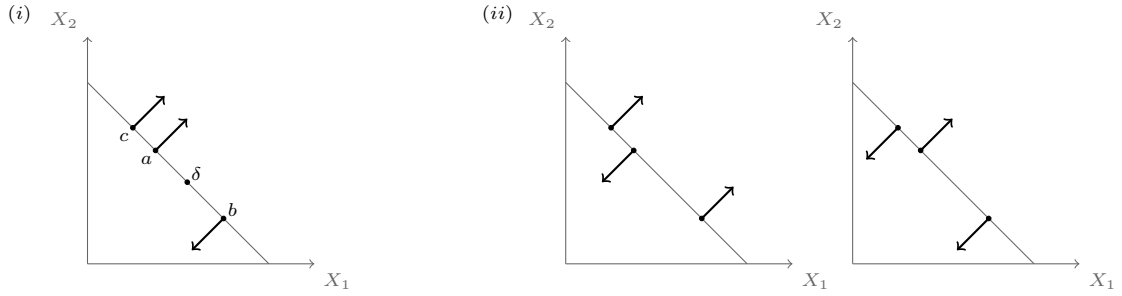


Figure 19: Case $\mathcal{N}' \in \mathcal{L}$

.

Let $d \to d'$ be an arbitrary reaction in $\mathcal{N} \setminus \mathcal{N}'$. The subnetwork $\mathcal{N}'' = \{a \to a',\ b \to b',\ d \to d'\}$ of $\mathcal{N}$ is alt-complete and not of class $\mathcal{C}$. This can be seen by computing $b - c = (p_2 - p_3)[1, -1]^t$ and noting that $p_1 - p_3 \geq 2$; but differences of source complexes of $\mathcal{C}$ networks may only have coordinates equal to $0, 1$ or -1. Therefore if $\mathcal{N}''$ is not in $\mathcal{L}$ then $\mathcal{N}''$ has capacity for multiple nondegenerate equilibria, and so does $\mathcal{N}$.

It remains to discuss the case when $\mathcal{N}'' \in \mathcal{L}$ for any reaction $d \to d' \in \mathcal{N} \setminus \mathcal{N}'$. For any such source complex d, $[d_1, d_2]$ is collinear with $[a_1, a_2]$ and $[b_1, b_2]$. Since $\mathcal{N} \notin \mathcal{L}$ the directions of the reactions on the $(1, 2)$ projection must alternate, in other words $\mathcal{N}$ must contain a subnetwork $\mathcal{N}'''$ whose projection on $(1, 2)$ falls within one of the patterns in Figure 19 (ii). But $\mathcal{N}'''$ is composed of three reactions is not in $\mathcal{L} \cup \mathcal{C}$ and therefore has the capacity for multiple nondegenerate equilibria. It follows that $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria as well.

2. Case $\mathcal{N}' \in \mathcal{C}$. There are two cases, depending on whether or not the corner γ of $\mathcal{N}$ is a source complex, see Definition 3.12.

2.1. γ is a source complex. Assume without loss of generality that $a - \gamma, b - \gamma, c - \gamma \in \{0, e_1, e_2\}$. Up to replacing every reaction vector with its negative (i.e. replacing λ with $-\lambda$), permuting a and c, and up to reflection about the $X_1 = X_2$ diagonal (i.e. permuting X_1 and X_2) there are two possibilities for $\mathcal{N}_{(1,2)}$, namely those illustrated in Figure 16. It follows from Lemma 5.19 that $\mathcal{N}$ has the capacity for multiple nondegenerate equilibria.

2.2: γ is not a source complex. Suppose without loss of generality that $a = \gamma + e_1$, $b = \gamma + e_2$, $c = \gamma + e_3$ and set $v_1 > 0$.

If $v_2 > 0$ then the projection of $\mathcal{N}'$ on $(1, 2)$ has the pattern in Figure 16(i) and the conclusion follows from Lemma 5.19. Likewise, if $v_2 < 0$ and $v_3 < 0$ then after replacing λ with $-\lambda$ and a reflection about the $X_2 = X_3$ axis the projection of $\mathcal{N}'$ on $(2, 3)$has the pattern in Figure 16(i), and the conclusion follows.

Finally, if $v_2 < 0$ and $v_1 > 0$ then the $(\rightarrow, \leftarrow)$ pattern is missing from all 1D projections of $\mathcal{N}'$ (Figure 10) and $\mathcal{N}'$ is not alt-complete, contradiction.

Proof of $2(i)$: sufficient conditions for nondegenerate multistationarity

Case $\mathcal{N} \in \mathcal{Z}$. Without loss of generality suppose that $1 \in R^+$, $2 \in R^-$ and the projection of $\mathcal{N}' = \{a_1 \rightarrow a_1', a_2 \rightarrow a_2'\}$ on $(1, 2)$ is a zigzag with $a_{11} < a_{21}$. Let $\mathcal{N}_{ds}$ be a subnetwork of $\mathcal{N}$ obtained by keeping a single reaction out of each source complex, including $a_1 \rightarrow a_1'$ and $a_2 \rightarrow a_2'$. If $\mathcal{N}_{ds} \notin \mathcal{L} \cup \mathcal{C}$ then $\mathcal{N}_{ds}$ has the capacity for multiple nondegenerate equilibria by Theorem 5.6, and therefore so does $\mathcal{N}$ by Theorem 2.7. Note that since $\mathcal{N} \notin \mathcal{C}$ we have $\mathcal{N}_{ds} \notin \mathcal{C}$

If $\mathcal{N}_{ds} \in \mathcal{L}$ we differentiate two cases. When $\mathcal{N}_{ds}$ has no other source complexes than a_1 and a_2 then $\mathcal{N}$ is either equal to $\mathcal{N}_{ds}$ or has one or two additional reactions, picked from the negatives of the reactions in $\mathcal{N}'$. If both negatives are in $\mathcal{N}$ then $\mathcal{N} \in \mathcal{S}_2^{nz}$, and otherwise $\mathcal{N} \in \mathcal{L}$, contradiction.

Suppose $\mathcal{N}_{ds}$ has three or more source complexes. We show that in this case $\mathcal{N} \in \mathcal{L}$, a contradiction. Indeed, if $\mathcal{N} \notin \mathcal{L}$ then

$$a_{\bar{k}1} = \max_{k \in R^+} a_{k1} > \min_{l \in R^-} a_{l1} = a_{\bar{l}1}. \tag{41}$$

We may refine our choice of $\mathcal{N}_{ds}$ by choosing reactions from sources $a_{\bar{k}}$ and $a_{\bar{l}}$ that satisfy $\lambda_{\bar{k}} > 0$ and $\lambda_{\bar{l}} < 0$. Then (41) implies that $\mathcal{N}_{ds} \notin \mathcal{L}$, contradiction.

Case $\mathcal{N} \notin \mathcal{Z}$. In this case $\mathcal{N}$ must have at least three source complexes, otherwise $\mathcal{N} \in \mathcal{S}_2^{nz}$, contradiction. Lemma 5.17 implies that there exists a subnetwork $\mathcal{N}'$ of $\mathcal{N}$ with three pairwise distinct source complexes which is alt-complete. Consider a subnetwork $\mathcal{N}_{ds}$ of $\mathcal{N}$ obtained by keeping only one reaction for each source complex of $\mathcal{N}$ and making sure that $\mathcal{N}' \subset \mathcal{N}_{ds}$. If $\mathcal{N}_{ds} \notin \mathcal{C}$ then it follows from Theorem 5.6 that $\mathcal{N}_{ds}$ has the capacity for MPNE, and therefore so does $\mathcal{N}$ by Theorem 2.7. If on the other hand $\mathcal{N}_{ds} \in \mathcal{C}$ then it follows that $\mathcal{N} \in \mathcal{C}$, contradiction.

References

[1] Uri Alon. Network motifs: theory and experimental approaches. *Nature Reviews Genetics*, 8(6):450–461, 2007.

[2] David Angeli, James E Ferrell, and Eduardo D Sontag. Detection of multistability, bifurcations, and hysteresis in a large class of biological positive-feedback systems. *Proceedings of the National Academy of Sciences*, 101(7):1822–1827, 2004.

[3] M. Banaji and C. Pantea. Some results on injectivity and multistationarity in chemical reaction networks. *SIAM J. Appl. Dyn. Syst.*, 15(2):807–869, 2016.

[4] M. Banaji and C. Pantea. The inheritance of nondegenerate ultistationarity in chemical reaction networks. *SIAM J.Appl. Dyn. Syst.*, 78(2):1105–1130, 2018.

[5] Murad Banaji, Balázs Boros, and Josef Hofbauer. Adding species to chemical reaction networks: Preserving rank preserves nondegenerate behaviours. *Applied Mathematics and Computation*, 426:127109, aug 2022.

[6] Katherine C Chen, Attila Csikasz-Nagy, Bela Gyorffy, John Val, Bela Novak, and John J Tyson. Kinetic analysis of a molecular model of the budding yeast cell cycle. *Molecular biology of the cell*, 11(1):369–391, 2000.

[7] Carsten Conradi, Elisenda Feliu, Maya Mincheva, and Carsten Wiuf. Identifying parameter regions for multistationarity. *PLoS computational biology*, 13(10):e1005751, 2017.

[8] Carsten Conradi and Maya Mincheva. Graph-theoretic analysis of multistationarity using degree theory. *Mathematics and Computers in Simulation*, 133:76–90, 2017.

[9] G. Craciun. Polynomial dynamical systems, reaction networks, and toric differential inclusions. *SIAM J. Appl. Algebra Geometry*, 3(1):87–106, 2019.

[10] G. Craciun and M. Feinberg. Multiple equilibria in complex chemical reaction networks: I. The injectivity property. *SIAM J. Appl. Math.*, 65(5):1526–1546, 2005.

[11] G. Craciun and M. Feinberg. Multiple equilibria in complex chemical reaction networks: Extensions to entrapped species models. *IEE Proceedings-Systems Biology*, 153:179–186, 2006.

[12] G. Craciun and M. Feinberg. Multiple equilibria in complex chemical reaction networks: II. The species-reaction graph. *SIAM J. Appl. Math.*, 66(4):1321–1338, 2006.

[13] G. Craciun, F. Nazarov, and C. Pantea. Persistence and permanence of mass-action and power-law dynamical systems. *SIAM J. Appl. Math.*, 73(1):305–329, 2013.

[14] Gheorghe Craciun, Badal Joshi, Casian Pantea, and Ike Tan. Multistationarity in cyclic sequestration-transmutation networks. *Bulletin of Mathematical Biology*, 84(6):1–22, 2022.

[15] Gheorghe Craciun, Yangzhong Tang, and Martin Feinberg. Understanding bistability in complex enzyme-driven reaction networks. *Proceedings of the National Academy of Sciences*, 103(23):8697–8702, 2006.

[16] James E Ferrell Jr. Self-perpetuating states in signal transduction: positive feedback, double-negative feedback and bistability. *Current opinion in cell biology*, 14(2):140–148, 2002.

[17] J. Helton, I. Klep, and R. Gomez. Determinant expansions of signed matrices and of certain jacobians. *SIAM J. Matrix Anal. Appl.*, 31:732–754, June 2009.

[18] K. Ho and H. Harrington. Bistability in apoptosis by receptor clustering. *PLoS computational biology*, 6(10):e1000956, 2010.

[19] B. Joshi. Complete characterization by multistationarity of fully open networks with one non-flow reaction. *J. Appl. Math. Comput.*, 219(12):6931–6945, 2013.

[20] B. Joshi and A. Shiu. Atoms of multistationarity in chemical reaction networks. *J. Math. Chem.*, 51(1):153–178, 2013.

[21] B. Joshi and A. Shiu. Which small reaction networks are multistationary? *SIAM J. Appl. Dyn. Syst.*, 6(2):802–833, 2017.

[22] Badal Joshi and Anne Shiu. Simplifying the Jacobian Criterion for precluding multistationarity in chemical reaction networks. *SIAM Journal on Applied Mathematics*, 72(3):857–876, 2012.

[23] K. Lin, X. Tang, and Z. Zhang. Multistationarity of reaction networks with one-dimensional stoichiometric subspaces. *CSIAM Transactions on Applied Mathematics*, 2022.

[24] Nick I. Markevich, Jan B. Hoek, and Boris N. Kholodenko. Signaling switches and bistability arising from multisite phosphorylation in protein kinase cascades. *The Journal of Cell Biology*, 164(3):353–359, 2004.

[25] Stefan Müller, Elisenda Feliu, Georg Regensburger, Carsten Conradi, Anne Shiu, and Alicia Dickenstein. Sign conditions for injectivity of generalized polynomial maps with applications to chemical reaction networks and real algebraic geometry. *Foundations of Computational Mathematics*, 16(1):69–97, 2016.

[26] Andrew W Murray. Creative blocks: cell-cycle checkpoints and feedback controls. *Nature*, 359(6396):599–601, 1992.

[27] Joseph R Pomerening, Eduardo D Sontag, and James E Ferrell. Building a cell cycle oscillator: hysteresis and bistability in the activation of cdc2. *Nature cell biology*, 5(4):346–351, 2003.

[28] M. Savageau. Comparison of classical and autogenous systems of regulation in inducible operons. *Nature*, 252(5484):546–549, 1974.

[29] M. Savageau. Allometric morphogenesis of complex systems: Derivation of the basic equations from first principles. *Proceedings of the National Academy of Sciences*, 76(12):6023–6025, 1979.

[30] M. Savageau. Introduction to s-systems and the underlying power-law formalism. *Mathematical and Computer Modelling*, 11:546–551, 1988.

[31] A. Shiu and T. de Wolff. Nondegenerate multistationarity in small reaction networks. *Discrete Continuous Dyn. Syst. Ser. B*, 24(6):2683–2700, 2019.

[32] X. Tang and H. Xu. Multistability of small reaction networks. *SIAM J. Appl. Dyn. Syst.*, 20(2):608–635, 2021.

[33] X. Tang and Z. Zhang. Multistability of reaction networks with one-dimensional stoichiometric subspaces. *SIAM J. Appl. Dyn. Syst.*, 21(2):1426–1454, 2022.

[34] A. Vol'pert. Differential equations on graphs. *Mathematics of the USSR-Sbornic*, 17(4):571–581, 1972.

[35] Carsten Wiuf and Elisenda Feliu. Power-law kinetics and determinant criteria for the preclusion of multistationarity in networks of interacting species. *SIAM Journal on Applied Dynamical Systems*, 12(4):1685–1721, 2013.

[36] Wen Xiong and James E Ferrell. A positive-feedback-based bistable 'memory module'that governs a cell fate decision. *Nature*, 426(6965):460–465, 2003.