Uniqueness of feasible equilibria for mass action law (MAL) kinetic systems

Antonio A. Alonso[*1] and Gábor Szederkényi [†2]

[1]Process Engineering Group, IIM-CSIC. Spanish Council for Scientific Research.
Eduardo Cabello 6, 36208 Vigo, Spain
[2]Pazmany Peter Catholic University, Faculty of Information Technology and Bionics,
Prater u. 50/a, H-1083 Budapest, Hungary

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Abstract

This paper studies the relations among system parameters, uniqueness, and stability of equilibria, for kinetic systems given in the form of polynomial ODEs. Such models are commonly used to describe the dynamics of nonnegative systems, with a wide range of application fields such as chemistry, systems biology, process modeling or even transportation systems. Using a flux-based description of kinetic models, a canonical representation of the set of all possible feasible equilibria is developed.

The characterization is made in terms of strictly stable compartmental matrices to define the so-called family of solutions. Feasibility is imposed by a set of constraints, which are linear on a log-transformed space of complexes, and relate to the kernel of a matrix, the columns of which span the stoichiometric subspace. One particularly interesting representation of these constraints can be expressed in terms of a class of monotonous decreasing functions. This allows connections to be established with classical results in CRNT that relate to the existence and uniqueness of equilibria along positive stoichiometric compatibility classes.

In particular, monotonicity can be employed to identify regions in the set of possible reaction rate coefficients leading to complex balancing, and to conclude uniqueness of equilibria for a class of positive deficiency networks. The latter result might support constructing an alternative proof of the well-known deficiency one theorem. The developed notions and results are illustrated through examples.

Keywords: Chemical reaction networks, kinetic systems, mass action law, network deficiency, feasible equilibrium, complex balanced equilibrium

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[*]Author to whom correspondence should be addressed. E-mail: antonio@iim.csic.es
[†]szederkenyi@itk.ppke.hu

Nomenclature

Notation	Description	Defining/introducing eqn. or (sub)section
$\mathbb{R}^n$	n-dimensional real space	
$\mathbb{R}^n_{>0}$ ($\mathbb{R}^n_{<0}$)	n-dimensional positive (resp. negative) orthant	
$\mathbb{R}^n_{\geq 0}$ ($\mathbb{R}^n_{\leq 0}$)	n-dimensional non-negative (resp. non-positive) orthant	
$\mathbf{x} > 0$ ($\mathbf{x} < 0$)	each element of the vector $\mathbf{x}$ is positive (resp. negative)	
$\mathbf{x} \geq 0$ ($\mathbf{x} \leq 0$)	each element of the vector $\mathbf{x}$ is non-negative (resp. non-positive)	
$\mathbf{1}_n \in \mathbb{R}^n$	The n-dimensional vector with each element being one	
$\boldsymbol{\varepsilon}_i$	the ith standard basis vector in $\mathbb{R}^n$	sec. 2, sec.3
$\mathcal{D}(\mathbf{x})$	diagonal matrix $\mathcal{D}(\mathbf{x}) \in \mathbb{R}^{n \times n}$ with components of $\mathbf{x}$ in the diagonal	eq. (28),(73)
m	number of species	sec. 2
n	number of complexes	sec. 2
ρ	number irreversible chemical reaction steps in the network	sec. 2
R_{ij}	rate of the reaction from complex i to complex j	eq. (1)
k_{ij}	rate coefficient of the reaction from complex i to complex j	eq. (1)
ℓ	the number of linkage classes	sec. 2
λ	integer for indexing linkage classes	sec. 2
$\mathcal{L}_\lambda$	the λth linkage class	sec. 2
N_λ	the number of complexes in linkage class no. λ	sec. 2 (footnote 1)
j_λ	index of the reference complex in linkage class no. λ	subsec. 2.1
$\mathbf{c}$	vector of concentrations (state variables)	sec. 2
Y	$m \times n$ dimensional molecularity matrix	eq. (4)
$\boldsymbol{\psi} : \mathbb{R}^m \to \mathbb{R}^n$	monomial function of the kinetic dynamics, $\psi_i(c) = \prod_{j=1}^m c_j^{Y_{ji}}$	eq. (1)
ϕ_i	net reaction rate corresponding to complex i	eq. (6)
Δ	subspace containing $\mathrm{im}(A_k)$	eq. (10)
Ξ	stoichiometric subspace	eq. (11)
s	dimension of the stoichiometric subspace	subsec. 2.2
δ	deficiency of the reaction network	eq. (13)

1 Introduction

Deterministic reaction networks obeying mass action law (MAL) kinetics form an important subclass of kinetic systems, which in spite of their apparent simplicity, are able to describe a rich variety of dynamical behavior, that includes multiple equilibria conditions, oscillations or even chaos [19, 9]. Such networks are typically employed to describe the dynamics of open or closed chemical reaction systems, but over the last years they proved useful in modeling other system classes as well.

Reaction networks belong to the class of nonnegative (or positive) systems, the main characteristics of which being that the non-negative orthant is invariant for the dynamics. The application field of nonnegative systems extends far beyond chemistry, and includes dynamical models whose state variables are naturally nonnegative, as it is the case of biological systems in their many scales (from cells to ecological systems), or systems that can be transformed to be nonnegative, such as certain process models (e.g. heat exchangers, distillation columns, convection networks), economic, transportation or stochastic models [20]. With an appropriate selection of coordinates, even many classical mechanical and electrical models can be described

in the nonnegative framework.

The main specialty of reaction networks within nonnegative polynomial models is the lack of so-called cross-effects, what defines an additional constraint between the monomial coefficients and exponents [19]. Still, the class of reaction network models is quite wide, and many non-chemical models can be brought into a kinetic form using simple transformations [9, 48]. Widely used examples of kinetic systems are compartmental systems [31] and Lotka-Volterra models into which most smooth nonlinear ODEs can be embedded [33]. These facts, clearly underline the importance of reaction network models and motivate us to attempt to look at general dynamical models through the glasses of kinetic systems.

The study of the relationships between chemical reaction structure and dynamic behaviour is the purpose of Chemical Reaction Network Theory (CRNT), a program formally proposed and developed in [4, 5, 40]. One of the earliest results on the relation between the solutions of nonlinear dynamical systems (including kinetic systems) and their associated directed graphs is published in [52]. Important cycle-related conditions on the stability of kinetic systems were given in [10]. An extensive stability analysis of reaction networks using algebraic and graph-theoretical tools can be found in [11]. Thermodynamically motivated Lyapunov-function-based stability analysis of kinetic systems, considering certain frequently applied model-simplification steps, is proposed in [32].

The seminal works in [35, 21] (collected in their most comprehensive form in [23]) explored the dynamic properties of MAL complex chemical systems, and contributed to equip CRNT with a mathematical formalism that has prevailed to present. It is important to remark here, that several different network structures may correspond to the same kinetic differential equations [35, 18]. Therefore, important network properties such as deficiency, weak reversibility or complex balancing, may vary among the possible reaction structures belonging to the same ODE model (see, e.g. [50, 36]).

One fundamental problem in CRNT is to decide from the structure or parameters of the network, whether it can exhibit or not multiple equilibria. An important early result in this field is the rigorous proof of the existence and uniqueness of thermodynamic equilibrium in a mixture of chemically reacting ideal gases [53]. The motivation in [49] was the computational analysis of large thermodynamical models. The work contains fundamental results about the existence and uniqueness of compositions minimizing the free energy.

In answering the questions about the properties of equilibria, the concept of network deficiency (a number that relates to reaction network structure and stoichiometry) has become central to characterize the network behavior. Two essential results of CRNT are the well-known deficiency zero and deficiency one theorems [23, 24] which (besides other important results) establish conditions for networks to have exactly one equilibrium point in each positive stoichiometric

compatibility class [23]. This suggests network robustness with respect to parameter variability, and underlines the importance of the kinetic system class in general nonlinear systems theory.

CRNT has received renewed interest over the last years, particularly in the area of systems biology, because of its potential to explore and to analyse complex behavior and functionality in biological systems (e.g. [13, 42, 12, 45]). Most efforts were dedicated to investigate the relationships between reaction network structure and dynamic behaviour. In this regard, special mention should be made of the so-called injectivity property, investigated as a condition that relates to the singularity (or not) of the determinant of the Jacobian associated to a given dynamic system [16]. Algebraic and graph theoretical methods have been devised to check injectivity, and therefore uniqueness of equilibria [16, 17]. In the same direction, extensions to cope with instabilities have been developed in [42]. From different perspectives, a number of necessary and sufficient conditions for a given network structure and stoichiometry to accommodate multiple equilibria have been also recently proposed in [12, 45].

A particularly interesting class of chemical networks are the reversible ones, either in the strict thermodynamic sense, in which every elementary reaction step is reversible, or in a weak reversibility context. Reversibility leads to a particular set of positive equilibria which is known as detailed balance if each reaction step is equilibrated by a reverse one, or complex balanced if the network is weakly reversible.

At this point, it must be remarked that equilibrium should be understood along the sequel in the sense given in dynamic systems, irrespectively of whether it corresponds to thermodynamic equilibrium or to a particular steady-state on a chemical reactor. Note, however, that in agrement with thermodynamics, instabilities in the dynamics of reaction systems (when taking place on a homogeneous medium in isothermal conditions) require the reaction domain to be open to mass exchange with the environment.

Because of microreversibility, most chemical systems, when closed to mass and energy exchanges with the environment, satisfy the principle of detailed balance equilibrium, resulting into stable equilibria [29]. As discussed in [30] and [28], irreversibility can be allowed within a reaction network, as limit cases of reversible steps under a thermodynamic consistency condition (known as the Wegscheider condition) which necessarily assumes microreversibility.

The notion of complex balancing (also known as cyclic balancing or semi-detailed balancing), on the other hand, generalizes the detailed balance condition to any weakly reversible network. The structure of complex balanced systems has been explored in [15] and shown to be a toric variety with unique and stable equilibrium points (see also [51]). Extensions to cope with more general classes of kinetic systems have been investigated in [43, 46].

It is important to mention here the recent fundamental results on the proof of the Global

Attractor Conjecture which says that any equilibrium point of a complex balanced mass action system is globally stable. A proof for the single linkage class case was given in [3], while a possible general proof based on differential inclusions was described in [14].

CRNT, as it stands nowadays within the field of applied mathematics, offers an extraordinary potential in system's theory for analysis and design of complex dynamic systems of polynomial type, what in turn may cover a wide spectrum of chemical and biological systems. Unfortunately, many of its results remain at a large extent unexploited, when not unnoticed, in the fields of process systems and engineering.

Among the reasons that hamper application might be certain advanced mathematical tools and the intensive use of graph theory that are often not well-enough known to engineers. Some practical questions that demand attention relate to the link between dynamic behavior of a given mechanism and parameter sets (reaction rate coefficients), or to the design of a chemical/biochemical network with some pre-specified behaviour (e.g bistable, oscillatory, etc).

In this contribution we present some conditions that ensure feasibility of equilibrium solutions for weakly reversible mass action law (MAL) systems. They are linked to the notion of family of solutions, a concept originally derived in [44, 45] to study multiplicity phenomena as a function of network parameters.

In deriving what it will be referred in the sequel as feasibility conditions, we exploit a flux-based form of the model equation. Within such structure, the time evolution of the species concentration vector is expressed as the product of a matrix denoted by S, whose columns span the stoichiometric subspace of the reaction system, and a vector function that is related to concentrations through a class of stable Metzler matrices [6].

As we will show, feasibility relates to the orthogonality between a log-transformed vector function of reaction complexes and the kernel of matrix S. Based on this observation, feasibility conditions will be expressed in terms of certain functions that can be employed to identify admissible equilibria within the positive orthant of the concentration space. It will be shown that such functions are monotonous in their respective argument and take the zero within their domain, what will allow us to establish links with existence and uniqueness of equilibria along positive stoichiometric compatibility classes for MAL kinetic systems. In this context, connections between monotonicity and two classical results in CRNT theory that relate to complex balanced equilibrium [34, 35], and to a class of positive deficiency networks [22, 23, 24], will be discussed.

Finally, it must be remarked that the potential interest of the notion of complex balancing in the context of process control is to characterize stable operation regimes in open systems, where the principle of detailed balance does not necessarily hold. This may allow, for instance, the selection or manipulation of exchange fluxes so to preserve stability of the resulting (open to the

environment) reaction system, via appropriate process optimization and/or feed-back control (see e.g. [41]). Future directions may also involve the detection or design of networks having multiple equilibria.

The paper is organized as follows: Section 2 introduces a formal description of chemical reaction networks. The graph structure underlying a reaction network, and its algebraic counterpart, will be described in Section 3. Section 4 presents a flux-based form canonical representation of the equilibrium set, that includes some feasibility conditions. Relationships between network structure and monotonicity of feasibility conditions will be established in Section 5. Connections between monotonicity of feasibility functions and some classical results on uniqueness and stability of equilibria will be discussed in Section 6.

2   Preliminaries: Reaction Network Structure and Dynamics

Let m be the number of chemical species which react by ρ irreversible chemical reaction steps, and $\mathbf{c} \in \mathbb{R}^m$ the corresponding vector of species concentrations, defined as mole number per unit of volume. Each reaction step transforms some set of chemicals, usually referred to as reactants, into a set of reaction products. In CRNT, reactants and reaction products receive the name of *reaction complexes*. Complexes and reaction steps describe a graph where complexes correspond to nodes and reaction steps to directed edges.

Formally, a graph involving n complexes $\{\mathcal{C}_1, \ldots, \mathcal{C}_n\}$ linked by irreversible reaction steps can be constructed by associating to each complex i a set $\mathcal{I}_i$ with n integer elements, and a vector $\boldsymbol{y}_i$. The elements of the set $\mathcal{I}_i$ are the indices of the complexes that are directly reachable (i.e. by one reaction step) from $\mathcal{C}_i$. From now on, we will refer to each complex $\mathcal{C}_i$ by the corresponding index i. Vector $\boldsymbol{y}_i \in \mathbb{R}^m$ has as entries the (positive) stoichiometric coefficients of the molecular species that participate in complex i.

The graph structure is then built by linking every complex i to $j \in \mathcal{I}_i$. This process results in a number ℓ of connected components known in CRNT as *linkage classes*. For each linkage class $\lambda = 1, ..., \ell$, we define the set $\mathcal{L}_\lambda$ which contains as elements the indexes of the complexes that belong to that linkage class[1].

Complexes are connected within a linkage class by sequences of irreversible reaction steps that define *directed paths*. Two complexes are strongly linked if they can be mutually reached from each other by directed paths (trivially, every complex is strongly linked to itself). A maximal set of pairwise strongly linked complexes defines a *strong terminal linkage class* if no other complex

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[1]To be precise, the set $\mathcal{L}_\lambda$ is that containing as elements $\mathcal{L}_\lambda = \{i_1, i_2, ..., i_{N_\lambda}\}$, with $N_\lambda = \mathcal{N}(\mathcal{L}_\lambda)$, being i_j the cardinality associated to complex $\mathcal{C}_{i_j}$, and $\mathcal{N}(\cdot)$ the operator which indicates the number of elements in the set.

can be reached from its nodes. In this work we will consider only networks in which every linkage class contains just one strong terminal linkage class.

A linkage class $\mathcal{L}_\lambda$ is said to be *weakly reversible* if any pair of its complexes is strongly linked. Weakly reversible networks are those composed by weakly reversible linkage classes. A particular type of weakly reversible linkage class is a reversible linkage class if each reaction step is itself reversible, so that for every i and $j \in \mathcal{I}_i$, we have that $i \in \mathcal{I}_j$. The rate R_{ij}, at which a set of reactants in complex i is transformed into a set of products in complex j, will be assumed to be mass action, so that:

$$R_{ij}(\mathbf{c}) = k_{ij}\psi_i(\mathbf{c}), \quad \text{with} \quad \psi_i(\mathbf{c}) = \prod_{j=1}^{m} c_j^{y_{ji}} \equiv \mathbf{c}^{\boldsymbol{y}_i}, \tag{1}$$

where $\boldsymbol{y}_i$ is the stoichiometric vector corresponding to complex $\mathcal{C}_i$. The reaction systems we consider in this work will take place under isothermal conditions, what makes any reaction rate parameter $k_{ij}(>0)$ constant. Whenever $\mathbf{c}$ is a strictly positive vector, the following alternative representation for $\psi_i(c)$ may be more convenient:

$$\ln \psi_i(\mathbf{c}) = \boldsymbol{y}_i^{\mathrm{T}} \ln \mathbf{c}, \tag{2}$$

where the natural logarithm operator $\ln(\cdot)$ acts on any vector element-wise. Let $\boldsymbol{\psi} : \mathbb{R}_{>0}^m \to \mathbb{R}_{>0}^n$ be the vector containing as entries the monomials described in (1), then the previous expression can be written in matrix form as:

$$\ln \boldsymbol{\psi}(\mathbf{c}) = Y^{\mathrm{T}} \ln \mathbf{c}, \tag{3}$$

where $Y \in \mathbb{R}^{m \times n}$ is the so-called *molecularity matrix* which collects as columns the stoichiometric vectors $\boldsymbol{y}_i \in \mathbb{R}^m$ associated to the complexes of the network.

2.1 The dynamics of reaction networks

Following the classical work by Feinberg [21], the time evolution of species concentrations on a well-mixed reaction medium at constant temperature can be described by a set of ordinary differential equations that we write as:

$$\dot{\mathbf{c}} = Y \cdot A_k(\boldsymbol{\psi}(\mathbf{c})) = Y \cdot \sum_\lambda A_k^\lambda(\boldsymbol{\psi}(\mathbf{c})), \tag{4}$$

where $A_k^\lambda : \mathbb{R}^n \to \mathbb{R}^n$ is a linear operator defined as:

$$A_k^\lambda(\boldsymbol{\psi}) \equiv \sum_{i \in \mathcal{L}_\lambda} \psi_i \sum_{j \in \mathcal{I}_i} k_{ij} \cdot (\boldsymbol{\varepsilon}_j - \boldsymbol{\varepsilon}_i), \tag{5}$$

with $\boldsymbol{\varepsilon}_i \in \mathbb{R}^n$ denoting the ith standard unit vector employed to represent axes on a cartesian coordinate system. Let us define the net reaction rate flux around a complex i, as the signed

sum of in- and out-flowing fluxes, i.e. as a function $\phi_i : \mathbb{R}_{\geq 0}^n \to \mathbb{R}$ of the form:

$$\phi_i(\boldsymbol{\psi}) = \sum_{\{j|i \in \mathcal{I}_j\}} R_{ji}(\boldsymbol{\psi}) - \sum_{j \in \mathcal{I}_i} R_{ij}(\boldsymbol{\psi}), \tag{6}$$

where the first summation at the right hand side extends to all source complexes j in the network from which there exists a reaction step to product complex i, and is represented by $\{j|i \in \mathcal{I}_j\}$.

We can express $A_k^\lambda(\boldsymbol{\psi})$ in (5) in terms of fluxes (6), by selecting any reference complex $j_\lambda \in \mathcal{L}_\lambda$, and adding and subtracting $\boldsymbol{\varepsilon}_{j_\lambda}$ from the right hand side of (5) so that:

$$A_k^\lambda(\boldsymbol{\psi}) = \sum_{i \in \mathcal{L}_\lambda} \psi_i \sum_{j \in \mathcal{I}_i} k_{ij} \cdot (\boldsymbol{\varepsilon}_j - \boldsymbol{\varepsilon}_{j_\lambda}) - \sum_{i \in \mathcal{L}_\lambda} \left(\sum_{j \in \mathcal{I}_i} k_{ij} \psi_i \right) \cdot (\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_{j_\lambda}).$$

After switching subindexes, re-ordering the summations for the first term at the right hand side and making use of (6), we get the following equivalent expressions:

$$\begin{aligned}
A_k^\lambda(\boldsymbol{\psi}) &= \sum_{i \in \mathcal{L}_\lambda} \left(\sum_{\{j|i \in \mathcal{I}_j\}} k_{ji} \psi_j \right) \cdot (\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_{j_\lambda}) - \sum_{i \in \mathcal{L}_\lambda} \left(\sum_{j \in \mathcal{I}_i} k_{ij} \psi_i \right) \cdot (\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_{j_\lambda}) \\
&= \sum_{i \in \mathcal{L}_\lambda} \phi_i(\boldsymbol{\psi}) \cdot (\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_{j_\lambda}). \tag{7}
\end{aligned}$$

For convenience, the reference complex will be chosen from the corresponding strong terminal linkage class. Since vectors $\boldsymbol{\varepsilon}_i$ are orthogonal, by using (7), we have that $\phi_i(\boldsymbol{\psi}) = \boldsymbol{\varepsilon}_i^{\mathrm{T}} A_k^\lambda(\boldsymbol{\psi})$ for every $i \in \mathcal{L}_\lambda$. Let $\boldsymbol{\omega}_\lambda = \sum_{i \in \mathcal{L}_\lambda} \boldsymbol{\varepsilon}_i$, then we also have that $\boldsymbol{\omega}_\lambda^T A_k^\lambda(\boldsymbol{\psi}) = 0$ and therefore:

$$\sum_{i \in \mathcal{L}_\lambda} \phi_i(\boldsymbol{\psi}) = \left(\sum_{i \in \mathcal{L}_\lambda} \boldsymbol{\varepsilon}_i \right)^T A_k^\lambda(\boldsymbol{\psi}) = 0. \tag{8}$$

Note that fluxes in (6) (as well as the linear operator in (5)) are implicitly dependent on the reaction rate coefficients associated to the reaction steps in the linkage class. By inspection of (7), it can be concluded that the image of $A_k(\boldsymbol{\psi})$ lies on the subspace Δ defined as follows:

$$\Delta = \Delta_1 + \cdots + \Delta_\lambda + \cdots + \Delta_\ell, \tag{9}$$

where

$$\Delta_\lambda = \mathrm{span}\{\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_{j_\lambda} \mid i \in \mathcal{L}_\lambda\} \quad \text{for} \quad \lambda = 1, \cdots, \ell . \tag{10}$$

and the sum of vector spaces V_1 and V_2 is defined as:

$$V_1 + V_2 = \{v_1 + v_2 \mid v_1 \in V_1, \ v_2 \in V_2\}.$$

Since vectors in $\{\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_{j_\lambda} \mid i \in \mathcal{L}_\lambda\}$ are linearly independent, they form a basis for the subspace Δ_λ, thus $\dim(\Delta_\lambda) = N_\lambda - 1$. In addition, since the subspaces Δ_λ are orthogonal:

$$\dim(\Delta) = \sum_\lambda (N_\lambda - 1) = n - \ell.$$

This implies that $A_k(\boldsymbol{\psi}) = 0$ if and only if $\phi_i(\boldsymbol{\psi}) = 0$ for all $i \in \cup_\lambda \mathcal{L}_\lambda$. Consequently, if a positive concentration vector $\mathbf{c}$ exists compatible with a zero flux condition for every complex in the network, that vector should be an equilibrium for system (4). Such equilibrium condition, known as *complex balanced* [34], is formally defined as follows:

Definition 2.1 (Complex Balanced Equilibrium) *Any vector $\mathbf{c}^* > 0$ such that $\phi_i(\boldsymbol{\psi}(\mathbf{c}^*)) = 0$ (Eqn (6)) for every $i = 1, \cdots, n$ is called a complex balanced equilibrium solution.*

A subclass of complex balanced equilibrium, particularly meaningful from a thermodynamic point of view as it relates to microreversibility ([37, 29]), is the detailed balance equilibrium which we define next:

Definition 2.2 (Detailed Balance Equilibrium) *If the network is reversible (i.e. for every i and $j \in \mathcal{I}_i$, we have that $i \in \mathcal{I}_j$) any vector $\mathbf{c}^* > 0$ such that $R_{ij}(\mathbf{c}^*) = R_{ji}(\mathbf{c}^*)$ (where $R_{ij}(\boldsymbol{c})$ is of the form (1)) is called as a detailed balance equilibrium solution.*

2.2 The stoichiometric subspace

Similarly to the subspace Δ, we define the stoichiometric subspace Ξ as:

$$\Xi = \Xi_1 + \cdots + \Xi_\lambda + \cdots + \Xi_\ell,$$

where:

$$\Xi_\lambda = \mathrm{span}\{\boldsymbol{y}_i - \boldsymbol{y}_{j_\lambda} \mid i \in \mathcal{L}_\lambda\} \quad \text{for} \quad \lambda = 1, \cdots, \ell \ . \tag{11}$$

In what follows it will be more convenient to collect the elements from each of the sets $\{\boldsymbol{y}_i - \boldsymbol{y}_{j_\lambda} \mid i \in \mathcal{L}_\lambda\}$ and their union, column-wise in matrices $S_\lambda \in \mathbb{R}^{m \times (N_\lambda - 1)}$ and $S \in \mathbb{R}^{m \times (n - \ell)}$, respectively, so that:

$$S = [\ S_1 \quad \cdots \quad S_\lambda \quad \cdots \quad S_\ell\ ]. \tag{12}$$

Let $s = \dim(\Xi)$, which eventually coincides with the rank of S, then it follows from the rank-nullity theorem that the dimension of the kernel (null space) of S will be:

$$\delta = n - \ell - s. \tag{13}$$

This number is known in CRNT as the *deficiency* of the network. In a similar way, we can define the deficiency of each linkage class as the dimension of the kernel of S_λ so that $\delta_\lambda = N_\lambda - 1 - s_\lambda$, where $s_\lambda = \dim(\Xi_\lambda)$. Since $s \leq \sum_\lambda s_\lambda$, it is not difficult to conclude that linkage class and network deficiencies relate as:

$$\delta \geq \sum_\lambda \delta_\lambda. \tag{14}$$

Let $\{\mathbf{g}^r \mid r = 1, \ldots, \delta\}$ be a basis for the kernel of S, and express each vector $\mathbf{g}^r \in \mathbb{R}^{n-\ell}$ in terms of ℓ sub-vectors $\mathbf{g}_\lambda^r \in \mathbb{R}^{N_\lambda - 1}$ (one per linkage class), so that:

$$(\mathbf{g}^r)^T = [\ (\mathbf{g}_1^r)^T \quad \cdots \quad (\mathbf{g}_\lambda^r)^T \quad \cdots \quad (\mathbf{g}_\ell^r)^T\ ], \text{ for } r = 1, \cdots, \delta. \tag{15}$$

Using the above description, equation $S\mathbf{g}^r = 0$ can be re-written as:

$$\sum_\lambda S_\lambda \mathbf{g}_\lambda^r = 0 \text{ for } r = 1, \ldots, \delta. \tag{16}$$

We will be particularly interested in solutions of system (4) on the convex region resulting from the intersection of the non-negative (respectively positive) orthant in the concentration space and a certain linear variety associated to the stoichiometric subspace Ξ, the result known in CRNT as a stoichiometric (respectively, positive stoichiometric) compatibility class. Given a reference concentration vector $\mathbf{c}_0$, the stoichiometric compatibility class can be formally defined as:

$$\Omega(\mathbf{c}_0) = \{\mathbf{c} \in \mathbb{R}^m \mid \mathbf{c} \geq 0, P^T(\mathbf{c} - \mathbf{c}_0) = 0\}, \tag{17}$$

where $P \in \mathbb{R}^{m \times (m-s)}$ is a full rank matrix whose columns span the orthogonal complement $\Xi^\perp$. The corresponding positive stoichiometric compatibility class can expressed as $\Omega^+(\mathbf{c}_0) = \Omega(\mathbf{c}_0) \cap \mathbb{R}_{>0}^n$. In passing, let us define the function $\boldsymbol{\sigma} : \mathbb{R}^m \to \mathbb{R}^{m-s}$ as $\boldsymbol{\sigma}(\mathbf{c}) = P^T \mathbf{c}$. Such function is constant along trajectories (4), since by combining (7) and (4) we have that:

$$\dot{\mathbf{c}} = \sum_\lambda \sum_{i \in \mathcal{L}_\lambda} \phi_i(\boldsymbol{\psi}(\mathbf{c}))(\boldsymbol{y}_i - \boldsymbol{y}_{j_\lambda}), \tag{18}$$

and the columns of P are orthogonal to S, hence $\dot{\boldsymbol{\sigma}} = P^T \dot{\mathbf{c}} = 0$. In other words, $\boldsymbol{\sigma}$ is an invariant of motion for system (4). From this observation it is not difficult to conclude that any trajectory that starts in a compatibility class $\Omega(\mathbf{c}_0)$ will remain there.

2.3 Some examples of chemical reaction networks

A reversible chemical reaction network

Let us consider a reaction network involving $m = 6$ molecular species we label as $\{M_1, ..., M_6\}$, each of them constituted by a combination of three types of functional groups (or atoms) we denote as A, B and C. The (reversible) chemical reaction steps that take place are:

$$\begin{aligned} A_2B + C &\leftrightarrows AC + AB \\ AB + 2C &\leftrightarrows AC_2B \\ AC_2B &\leftrightarrows AC + CB \end{aligned} \tag{19}$$

Molecular species and functional groups are related as follows: $M_1 \equiv A_2B$, $M_2 \equiv AC$, $M_3 \equiv AB$, $M_4 \equiv C$, $M_5 \equiv AC_2B$, $M_6 \equiv CB$. The network consists of $n = 5$ complexes:

$$\{\mathcal{C}_1, \mathcal{C}_2, \mathcal{C}_3, \mathcal{C}_4, \mathcal{C}_5\} \equiv \{M_1 + M_4, M_2 + M_3, M_3 + 2M_4, M_5, M_2 + M_6\}.$$

Making use of the formal description previously discussed, the sets $\mathcal{I}_i$ that indicate which complexes are reached from complex i become, for this example:

$$\mathcal{I}_1 = \{2\} \quad \mathcal{I}_2 = \{1\} \quad \mathcal{I}_3 = \{4\} \quad \mathcal{I}_4 = \{3,5\} \quad \mathcal{I}_5 = \{4\}. \tag{20}$$

The corresponding stoichiometric vectors $\boldsymbol{y}_i$ associated to each complex are written as columns in the molecularity matrix Y:

$$Y = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & 0 \\ 1 & 0 & 2 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}. \tag{21}$$

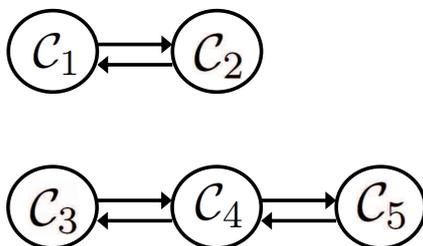The graph representation is depicted in Figure 1, and comprises two linkage classes $\mathcal{L}_1 = \{1,2\}$

Figure 1: Graph representation for the reaction network described by reversible steps (19).

and $\mathcal{L}_2 = \{3,4,5\}$. The net reaction fluxes (6) around each complex are:

$$\begin{aligned} \phi_1(\boldsymbol{\psi}) &= k_{21}\psi_2 - k_{12}\psi_1 \\ \phi_2(\boldsymbol{\psi}) &= k_{12}\psi_1 - k_{21}\psi_2 \\ \phi_3(\boldsymbol{\psi}) &= k_{43}\psi_4 - k_{34}\psi_3 \\ \phi_4(\boldsymbol{\psi}) &= k_{34}\psi_3 + k_{54}\psi_5 - (k_{43} + k_{45})\psi_4 \\ \phi_5(\boldsymbol{\psi}) &= k_{45}\psi_4 - k_{54}\psi_5 \end{aligned} \tag{22}$$

Note that if $j_1 = 1$ and $j_2 = 3$ are chosen as reference complexes, by relation (8), the fluxes associated to the reference become:

$$\phi_1(\boldsymbol{\psi}) = -\phi_2(\boldsymbol{\psi}) \qquad \text{and} \qquad \phi_3(\boldsymbol{\psi}) = -(\phi_4(\boldsymbol{\psi}) + \phi_5(\boldsymbol{\psi})).$$

The image of A_k coincides with subspace Δ (Eqn (9)) with Δ_1 and Δ_2 of the form:

$$\begin{aligned} \Delta_1 &= \text{span}\{(\boldsymbol{\varepsilon}_2 - \boldsymbol{\varepsilon}_1)\} \\ \Delta_2 &= \text{span}\{(\boldsymbol{\varepsilon}_4 - \boldsymbol{\varepsilon}_3), (\boldsymbol{\varepsilon}_5 - \boldsymbol{\varepsilon}_3)\} \end{aligned} . \tag{23}$$

Matrices S_λ, employed in Section 2.2 to define (column-wise) the corresponding stoichiometric subspaces (11), are of the form:

$$S_1 = \begin{bmatrix} -1 \\ 1 \\ 1 \\ -1 \\ 0 \\ 0 \end{bmatrix}, \quad S_2 = \begin{bmatrix} 0 & 0 \\ 0 & 1 \\ -1 & -1 \\ -2 & -2 \\ 1 & 0 \\ 0 & 1 \end{bmatrix}.$$

The dimension of the stoichiometric subspace, which coincides with the rank of matrix $S = \begin{bmatrix} S_1 & S_2 \end{bmatrix}$, is $s = 3$. Hence, network deficiency is $\delta = 5 - 2 - 3 \equiv 0$ what means that no vector $\mathbf{g}^r$ other than the zero vector exists such that $S\mathbf{g}^r = 0$.

The numbers of atoms (or functional groups) A-C remain constant, provided that reactions take place on a closed domain (i.e. no mass exchanges with the environment occur). Let $([A]_0, [B]_0, [C]_0)$ be total concentrations for A, B and C on the closed and homogeneous domain. Mole-number balances result in the following set of linear relations:

$$[A]_0 = 2[A_2B] + [AC] + [AB] + [AC_2B]$$
$$[B]_0 = [A_2B] + [AB] + [AC_2B] + [CB]$$
$$[C]_0 = [AC] + [C] + 2[AC_2B] + [CB]$$

where brackets indicate chemical species concentrations. Previous relations can be written in matrix form as follows:

$$P^{\mathrm{T}}(\mathbf{c} - \mathbf{c}_0) = 0 \quad \text{with} \quad P = \begin{bmatrix} 2 & 1 & 1 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 2 & 1 \end{bmatrix}^T,$$

where $\mathbf{c}$ is the vector of chemical species concentrations and $P^T\mathbf{c}_0$ is the (constant) concentration of functional groups/atoms. It must be noted that the above expression is employed in (17) to characterize the set of compatibility classes. As discussed in Section 2.2, because $\mathrm{rank}(P) \equiv m - s = 3$ (full rank), the columns of P define a basis for the orthogonal complement of the stoichiometric subspace.

An irreversible network

Let us consider the following set of irreversible reactions:

$$
\begin{aligned}
S + I &\rightarrow 2I \\
I &\leftrightarrows R \rightarrow S
\end{aligned}
\tag{24}
$$

This network can be interpreted as an extension of the SIR epidemic model [38] which describes the effect of a disease on a large population. Individuals on the population are classified either as those susceptible to the disease (S), infected (I) or those recovered from the disease (R). In this extension, individuals under recovering may evolve either to those susceptible to the disease or directly infected again. In the CRNT formalism, the network comprises three species, with concentrations $[S]$, $[I]$ and $[R]$, and 5 complexes, numbered as:

$$\{\mathcal{C}_1, \mathcal{C}_2, \mathcal{C}_3, \mathcal{C}_4, \mathcal{C}_5\} \equiv \{2I, S + I, S, R, I\}.$$

Graph structure is depicted in Figure 2. Molecularity matrix Y for this network reads:

$$Y = \begin{bmatrix} 0 & 1 & 1 & 0 & 0 \\ 2 & 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix}. \tag{25}$$

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Choosing as reference complexes $j_1 = 1$ and $j_2 = 3$, the S_λ matrices become:

$$S_1 = \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix}, \quad S_2 = \begin{bmatrix} -1 & -1 \\ 0 & 1 \\ 1 & 0 \end{bmatrix}.$$

Because both matrices are full rank, the dimension of Ξ_1 and Ξ_2 is $s_1 = 1$ and $s_2 = 2$,
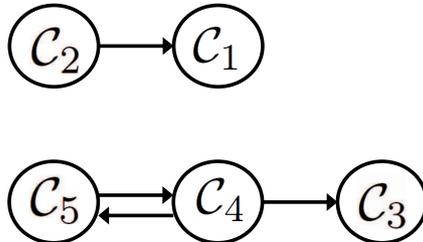

Figure 2: Graph representation for the two linkage class, irreversible reaction network (24).

respectively. Thus $\delta_1 = N_1 - 1 - s_1 = 0$ and $\delta_2 = N_2 - 1 - s_2 = 0$. However, matrix $S = \begin{pmatrix} S_1 & S_2 \end{pmatrix}$ is rank deficient since vector S_1 is parallel to the vector in the second column of S_2. Consequently $s = 2$, and $\delta = 5 - 2 - 2 = 1$, verifying inequality (14). A basis for the kernel of S is given by the vector $\mathbf{g}^1 = \begin{pmatrix} 1 & 0 & 1 \end{pmatrix}^T$.

For this network, the basis that spans the orthogonal complement of the stoichiometric subspace corresponds to $P = \begin{pmatrix} 1 & 1 & 1 \end{pmatrix}^T$. Each compatibility class is given by $\Omega(\mathbf{c}_0)$ (see (17)), the region of non-negative concentrations ($\mathbf{c} \geq 0$) satisfying:

$$[S] + [I] + [R] = P^T \mathbf{c}_0,$$

with $\mathbf{c}_0 \geq 0$ being a constant vector. A representation of a compatibility class for the reaction network considered is presented in Figure 3, with $\mathbf{c} = ([S], [I], [R])^T$.

3 Linkage classes, Graphs and Compartmental Matrices

The nature of equilibrium solutions in chemical reaction networks (e.g. positivity, instability of equilibrium points, or the possibility of multiple equilibria) is at a large extent determined by the graph structure of each linkage class and the properties of some matrices associated to it, that belong to the class of compartmental matrices [26].

In this section, we describe such matrices and discuss their properties, with emphasis on invertibility and non-negativity of their inverses. The main results, summarized in Lemma 3.1, will be extensively employed in the sequel. For the sake of completeness, we introduce a derivation from scratch, while establishing connections with known facts in the field of positive linear systems and non-negative matrices.
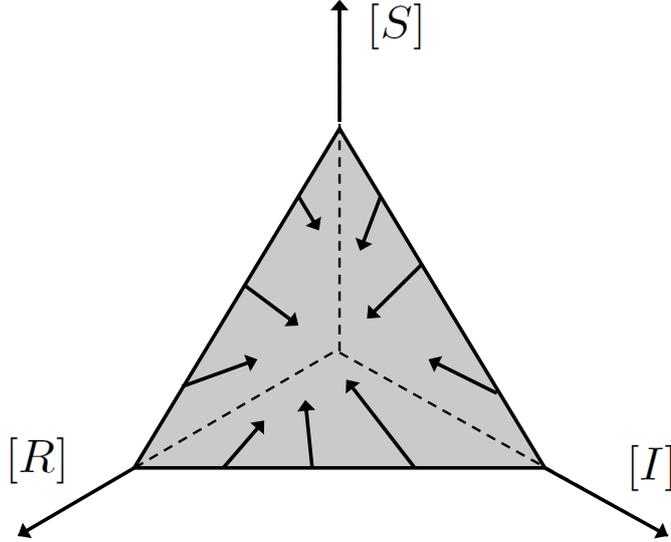
Figure 3: Representation of a compatibility class for the network example (24).

To that purpose, we introduce a graph related to the graph description of a linkage class, and a matrix associated to it. The properties of this matrix will be studied by constructing an auxiliary linear dynamic system and examining the corresponding equilibrium.

A directed graph $\mathcal{G} = \{(\mathcal{V} \bigcup v_E), \mathcal{E}\}$ is constructed by a set of vertices containing a distinguished vertex v_E and a set $\mathcal{E}$ of edges. The first set of vertices $\mathcal{V} = \{v_1, v_2, \ldots, v_n\}$, with indexes $\mathcal{L} = \{1, \ldots, n\}$ will be referred to as nodes, while the remaining vertex v_E will represent the 'environment'. To any directed edge $v_i \to v_j$ for $i, j \in \mathcal{L}$ and $i \neq j$ in $\mathcal{G}$ (i.e. $(v_i, v_j) \in \mathcal{E}$) there corresponds a scalar weight $V_{ij} > 0$. In addition, for every $i \in \mathcal{L}$, such that $(v_i, v_E) \in \mathcal{E}$ or $(v_E, v_i) \in \mathcal{E}$, we associate scalar weights $b_i > 0$ and $a_i > 0$, respectively. Such weights will be collected as entries in (non-negative) vectors $\mathbf{a}, \mathbf{b} \in \mathbb{R}^n$, with $a_i = 0$ (respectively, $b_i = 0$) if there is no directed edge $v_E \to v_i$ (respectively, $v_i \to v_E$). As in the description of linkage classes (Section 2) we say that two nodes are strongly linked if they can be reached from each other by directed paths. The maximal set of strongly linked nodes (not passing through the environment) in $\mathcal{L}$ from which there are no outgoing edges to other nodes, defines a strong terminal set, we will refer to as $\mathcal{L}_{\mathrm{p}}$.

Since in this work we are interested in linkage classes with just one strong terminal linkage class, the graphs we consider will only contain one strong terminal set. The set of non-terminal nodes is defined as $\mathcal{L}_{\mathrm{q}} = \mathcal{L} \setminus \mathcal{L}_{\mathrm{p}}$. Some examples of directed graphs are illustrated in Figure 4. We associate to the graph $\mathcal{G}$ a state vector $\mathbf{z} \in \mathbb{R}^n$, where each component z_i corresponds to a node. For each node $i = 1, \ldots, n$, we define an internal net flux $\phi_i : \mathbb{R}^n \to \mathbb{R}$ and a net exchange with the environment $\varphi_i : \mathbb{R} \to \mathbb{R}$. Each flux is of the form:

$$\phi_i(\mathbf{z}) = \sum_{\{j | i \in \mathcal{I}_j\}} V_{ji} z_j - z_i \sum_{j \in \mathcal{I}_i} V_{ij}, \tag{26}$$
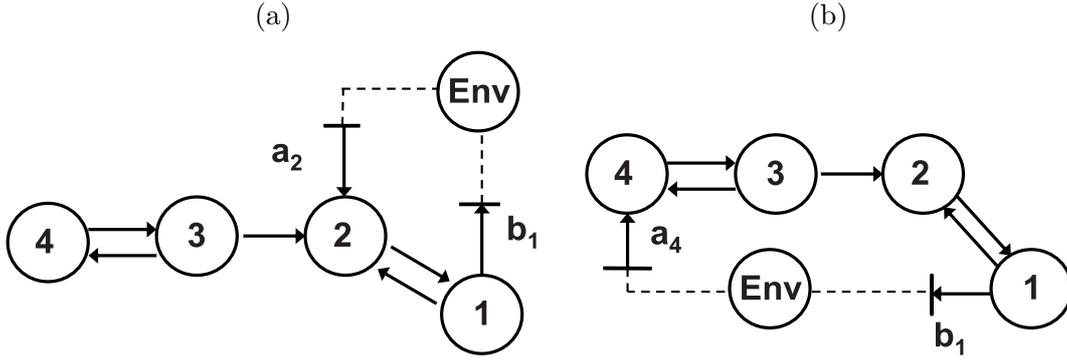
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Figure 4: Some typical examples of directed graphs. For both cases, the terminal set is $\mathcal{L}_{\mathrm{p}} = \{1, 2\}$ whereas the set of non-terminal nodes is $\mathcal{L}_{\mathrm{q}} = \{3, 4\}$. (a) Exchange with the environment takes place in the strong terminal set through input a_2 (second coordinate of vector $\mathbf{a}$) and output b_1 (first coordinate of vector $\mathbf{b}$). Node **Env** represents the environment. (b) The input from the environment enters the system through a non-terminal node (coordinate a_4 of vector $\mathbf{a}$) while the output to the environment leaves from a terminal node (coordinate b_1 of vector $\mathbf{b}$).

where as in Section 2, the indexes of the nodes that are directly reached from node i are grouped in a set $\mathcal{I}_i$, and $\{j | i \in \mathcal{I}_j\}$ refers to all nodes j with edges directed to i. In addition, the net exchange with the environment is expressed as $\varphi_i(z_i) = a_i - b_i z_i$. From (26), and similarly to expression (8), it is straightforward to see that:

$$\sum_{i \in \mathcal{L}} \phi_i(\mathbf{z}) = 0. \tag{27}$$

We consider that for each node i, the state z_i will evolve in time as a function of the corresponding internal and external net fluxes, so that $\dot{z}_i = \phi_i(\mathbf{z}) + \varphi_i(z_i)$. Combining this expression with (27), the dynamics of the system can be described as:

$$\dot{\mathbf{z}} = \sum_{i=1}^{n} \phi_i(\mathbf{z})(\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_1) - B\mathbf{z} + \mathbf{a}, \tag{28}$$

where $B = \mathcal{D}(\mathbf{b})$, a diagonal matrix with the components of $\mathbf{b}$ in the diagonal. Equation (28) can be re-written in the alternative form:

$$\dot{\mathbf{z}} = W\mathbf{z} + \mathbf{a} \tag{29}$$

where matrix $W = V^T - B$, and $V \in \mathbb{R}^{n \times n}$ is the matrix that contains as off-diagonal components the coefficients in (26), with $V_{ij} = 0$ if there is no directed edge $v_i \to v_j$. The diagonal elements for V are of the form:

$$V_{ii} = - \sum_{\substack{j=1 \\ j \neq i}}^{n} V_{ij}.$$

Both matrices V^T and W are compartmental [26], [2] and belong to the class of Metzler matrices [6]. It is known from e.g. [7], that the eigenvalues of a compartmental matrix are either zero or they have negative real parts. Such conclusion can be also reached from the structure of compartmental matrices by applying the Gershgorin disc theorem [27].

Definition 3.1 *We say that the matrix $W \in \mathbb{R}^{n \times n}$ associated to the system (29) is C-Metzler if its entries are of the form:*

$$
\begin{aligned}
W_{ij} &\geq 0 &&\text{for} \quad i \neq j \\
W_{ii} &= -(b_i + \textstyle\sum_{j \neq i} W_{ji}) &&\text{with} \quad b_i \geq 0 \quad \text{and} \quad W_{ii} < 0,
\end{aligned}
\tag{30}
$$

with at least one positive b_i associated to the strong terminal set (i.e. $i \in \mathcal{L}_{\mathrm{p}}$).

Proposition 3.1 *Consider system (29) with $\boldsymbol{a} \geq 0$ and nonnegative initial conditions $\mathbf{z}(0) \geq 0$. Then $\mathbf{z}(t) \geq 0$ for every $t > 0$.* [3]

Proof: In order to prove the statement all we need is to show that the flow associated to the differential system on the boundary of the positive orthant is either aligned to the boundary or oriented to the interior of the orthant. Before we compute the flow, let us define the set $H_k = \{\mathbf{z} \geq 0 \mid \varepsilon_k^{\mathrm{T}} \mathbf{z} = 0\}$ which characterizes the k-th facet of the positive orthant. The inner product between the flow induced by (28) (equivalently (29)) on any element $\mathbf{z} \in H_k$, and the unit vector orthogonal to H_k takes the form:

$$
\varepsilon_k^{\mathrm{T}} \dot{\mathbf{z}} = \phi_k(\mathbf{z}) - b_k z_k + a_k = \sum_{\{j \mid k \in \mathcal{I}_j\}} V_{jk} z_j + a_k \geq 0
\tag{31}
$$

where the equivalence at the right hand side holds since $z_k = 0$ in H_k. Thus, at the boundary of H_k, the flow associated to the differential system will be either aligned to the boundary ($\varepsilon_k^{\mathrm{T}} \dot{\mathbf{z}} = 0$) or oriented to the interior of the positive orthant (i.e. $\varepsilon_k^{\mathrm{T}} \dot{\mathbf{z}} > 0$). Repeating the argument for all values of k completes the proof. $\qquad\square$

Next, we will study the equilibrium of system (29) that results from some constant non-negative vectors $\mathbf{a}$ and $\mathbf{b}$. To that purpose, let $\mathcal{L}_\ell \subset \mathcal{L}_{\mathrm{q}}$ be the set containing those non-terminal nodes that are directly linked to any node in the strong terminal set (the different partitions are illustrated in Figure 5). Let us introduce functions $\sigma_{\mathrm{p}}(\mathbf{z}) = \boldsymbol{\omega}_{\mathrm{p}}^T \mathbf{z}$, $\sigma_{\mathrm{q}}(\mathbf{z}) = \boldsymbol{\omega}_{\mathrm{q}}^T \mathbf{z}$ and $\sigma(\mathbf{z}) = \sigma_{\mathrm{p}}(\mathbf{z}) + \sigma_{\mathrm{q}}(\mathbf{z})$, where:

$$
\boldsymbol{\omega}_{\mathrm{p}} = \sum_{i \in \mathcal{L}_{\mathrm{p}}} \boldsymbol{\varepsilon}_i, \quad \boldsymbol{\omega}_{\mathrm{q}} = \sum_{i \in \mathcal{L}_{\mathrm{q}}} \boldsymbol{\varepsilon}_i.
\tag{32}
$$

---

[2] A matrix $A \in \mathbb{R}^{n \times n}$ is compartmental if: (i) $A_{ij} \geq 0$, for $i, j = 1, \ldots, n$, $i \neq j$, (ii) $\sum_{i=1}^{n} A_{ij} \leq 0$, for $j = 1, \ldots, n$.

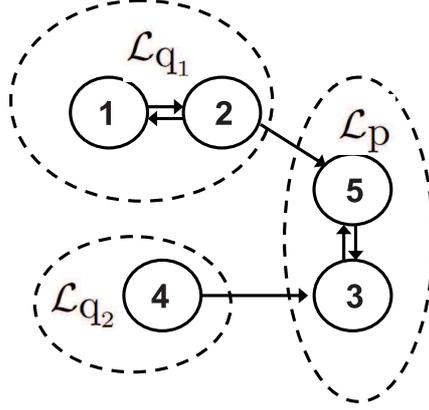[3] This result is actually a special case of Theorem 2 in [20] (page 14).

Figure 5: Example of a graph with $\mathbf{a}, \mathbf{b} = 0$, partitioned into a terminal set $\mathcal{L}_{\mathrm{p}}$ and nonterminal sets $\mathcal{L}_{\mathrm{q}_1}$ $\mathcal{L}_{\mathrm{q}_2}$. In this case set $\mathcal{L}_\ell$ comprises nodes 2 and 4.

The time derivative of σ_{q} along system (28) is of the form:

$$\dot{\sigma}_{\mathrm{q}} = \boldsymbol{\omega}_{\mathrm{q}}^T \mathbf{a} - \sum_{i \in \mathcal{L}_{\mathrm{q}}} b_i z_i - \sum_{i \in \mathcal{L}_\ell} \sum_{j \in \mathcal{I}_i} V_{ij} z_i \tag{33}$$

$$\dot{\sigma}_{\mathrm{p}} = \boldsymbol{\omega}_{\mathrm{p}}^T \mathbf{a} - \sum_{i \in \mathcal{L}_{\mathrm{p}}} b_i z_i + \sum_{i \in \mathcal{L}_\ell} \sum_{j \in \mathcal{I}_i} V_{ij} z_i \tag{34}$$

Proposition 3.2 *Consider system (29) with $\mathbf{a} = 0$ and W C-Metzler (Definition 3.1). Then, for any $\mathbf{z}(0) \geq 0$, $\mathbf{z}^* = 0$ is the only equilibrium solution of (29).*

Proof: Since $\mathbf{z}(0) \geq 0$, by Proposition 3.1 we have that $\mathbf{z}(t)$ will remain in the positive orthant, $\sigma_{\mathrm{p}}(\mathbf{z})$ and $\sigma_{\mathrm{q}}(\mathbf{z})$ will be non-negative, and $\sigma(\mathbf{z}) = \sigma_{\mathrm{q}}(\mathbf{z}) + \sigma_{\mathrm{p}}(\mathbf{z}) \geq 0$.

For every node $i \in \mathcal{L}_\ell$ it is clear that $z_i^* = 0$ is the only possible equilibrium. Otherwise, from (33), it follows that $\dot{\sigma}_{\mathrm{q}} < 0$ for all times, what would make $\sigma_{\mathrm{q}}(\mathbf{z})$ to become negative. In addition, note that for $z_i^* = 0$ to be an equilibrium point for node $i \in \mathcal{L}_\ell$, requires the equilibrium states for all nodes j linked to i (thus $j \in \mathcal{L}_{\mathrm{q}}$) to be zero as well, otherwise $\dot{z}_i = \phi_i(\mathbf{z}) + \varphi_i(z_i) > 0$. Repeating the argument upstream to the nodes linked to j, we conclude that zero is the only possible equilibrium for every node in $\mathcal{L}_{\mathrm{q}}$.

Since W is C-Metzler (i.e. there exists at least one index $i \in \mathcal{L}_{\mathrm{p}}$ for which $b_i > 0$), zero is also the only possible equilibrium for every node in the terminal set. Suppose, on the contrary, that there exists a positive equilibrium z_i^* for some $i \in \mathcal{L}_{\mathrm{p}}$. In the limit, expression (34) would become:

$$\lim_{t \to \infty} \dot{\sigma}_{\mathrm{p}} = - \sum_{i \in \mathcal{L}_{\mathrm{p}}} b_i z_i^* < 0,$$

but $\sigma_{\mathrm{p}}(\mathbf{z})$ cannot become negative, thus $z_i^* = 0$. Finally, since $z_i^* = 0$ is an equilibrium point for $i \in \mathcal{L}_{\mathrm{p}}$ such that $b_i > 0$, the equilibrium states for all nodes j linked to i must be zero as

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well, otherwise $\dot{z}_i = \phi_i(\mathbf{z}) + \varphi_i(z_i) > 0$. repeating the argument for every $j \in \mathcal{L}_\mathrm{p}$ we have that $\lim_{t \to \infty} \mathbf{z}(t) = \mathbf{z}^* = 0$. $\qquad\square$

Remark 3.1 *Using the terminology of [26], V^T defines a compartmental system with one trap, where the notion of trap is equivalent to the definition of strong terminal set used in this paper. Therefore, zero is an eigenvalue of V^T with multiplicity 1. W is also a compartmental matrix, and due to the choice of b_i, the compartmental system corresponding to W contains no traps. Therefore, W is of full rank and thus, assuming $\mathbf{a} = 0$, the only equilibrium of (29) is $\mathbf{z}^* = 0$.*

Proposition 3.3 *Consider system (29), with matrix W being C-Metzler (Definition 3.1). Equilibrium $\mathbf{z}^*$ will be non-negative and globally asymptotically stable. Moreover, let some entry k of vector $\mathbf{a}$ positive (i.e. $a_k > 0$). Then, for all nodes $j \in \mathcal{L}$ reached from node k by directed paths, we have that $z_j^* > 0$.*

Proof: First note that because matrix W in (29) is compartmental, its eigenvalues are either zero or they have negative real parts. Thus, to show that the equilibrium is globally asymptotically stable it only remains to prove that no zero eigenvalue exists. Actually, this is the case, since from Proposition 3.2, the only equilibrium solution for which $W\mathbf{z}^* = 0$ is $\mathbf{z}^* = 0$. Since all eigenvalues have negative real part, W is invertible and the equilibrium $\mathbf{z}^* = -W^{-1}\mathbf{a}$ is globally asymptotically stable.

In proving the second part of the statement, we have that since $a_k > 0$, the equilibrium in node k must be:

$$z_k^* = \frac{\sum_{\{j|k \in \mathcal{I}_j\}} V_{jk} z_j^* + a_k}{b_k + \sum_{j \in \mathcal{I}_k} V_{kj}} > 0$$

and so is the case for all j reached from k, so that $z_j^* > 0$, what completes the proof. $\qquad\square$

Remark 3.2 *The full rank property of W and the uniqueness of the equilibrium $\mathbf{z}^* = 0$ for $\mathbf{a} = 0$ are equivalent, since this latter means that the dimension of the kernel of W is zero. From this, it follows that W cannot have zero eigenvalues, and from the compartmental property of W we obtain that all the real parts of its eigenvalues are negative. This means that W is a stability matrix. Since $\mathbf{a}$ can be considered as a bounded input, $\mathbf{z}^* = W^{-1}(-\mathbf{a})$ is a unique asymptotically stable equilibrium point of (29). Since $-W$ is a full-rank M-matrix, it is inverse-nonnegative [47], i.e. all entries of W^{-1} are non-positive. This implies that $\mathbf{z}^*$ is a nonnegative vector.*

Lemma 3.1 *Any C-Metzler matrix W is non-singular and its inverse W^{-1} non-positive. Let its associated graph be numbered so that the first p nodes are in $\mathcal{L}_\mathrm{p}$ (thus, the remaining $\mathrm{q} = n - \mathrm{p}$ are in $\mathcal{L}_\mathrm{q}$). Then $N = W^{-1}$ can be partitioned as:*

$$N = \left[\begin{array}{c|c} N_\mathrm{p} & N_\mathrm{pq} \\ \hline \emptyset & N_\mathrm{q} \end{array} \right], \tag{35}$$

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with $\emptyset \in \mathbb{R}^{q \times p}$ the zero matrix, $N_p \in \mathbb{R}^{p \times p}$ and $N_{pq} \in \mathbb{R}^{p \times q}$ strictly negative matrices, and $N_q \in \mathbb{R}^{q \times q}$ non-positive. Moreover, for each node $j \in \mathcal{L}_q$, every node i not reached from j by directed paths will correspond with an entry $N_{ij} = 0$.

Proof: That W (being C-Metzler) is non-singular and therefore invertible has been shown in the proof of Proposition 3.3 (see also Remark 3.2). In addition, note that the equilibrium solution can be written as $\mathbf{z}^* = -N\mathbf{a}$, and choose $\mathbf{a} = \boldsymbol{\varepsilon}_j$. For each $j \in \mathcal{L}$, the corresponding equilibrium will be $\mathbf{z}^* = -(N)_j$, where $(N)_j$ represents the j-th column of matrix N.

According to Proposition 3.3, the equilibrium state for all nodes $i \in \mathcal{L}$ reached from j by directed paths must be positive, and thus the corresponding entries N_{ij} must be negative. This holds for all $i, j \in \mathcal{L}_p$. Thus, using the order given in the statement of the Lemma, we can conclude that N_p is strictly negative. In addition, every $i \in \mathcal{L}_p$ can be reached from $j \in \mathcal{L}_q$ what makes N_{pq} strictly negative as well. The zero matrix $\emptyset$ appears since none of the nodes $i \in \mathcal{L}_q$ can be reached from nodes $j \in \mathcal{L}_p$. Finally, zero entries in N_q will correspond to those i not reachable from j, with $i, j \in \mathcal{L}_q$. $\square$

Lemma 3.1 will be invoked along the sequel on a linkage class basis to study positive equilibrium solutions of chemical reaction networks. The possibility of positive equilibria is at a large extent connected with Proposition 4.1 in Lecture 4 of Feinberg [22] (see also proofs in [34] and [25]) on the structure of the kernel of A_k defined in (4). In this regard, it is noted that the arguments behind Proposition 3.3 and Lemma 3.1 can serve as a basis to prove the result in Feinberg Lectures.

Example: The graphs in Figure 4 depict two different scenarios. In Figure 4a, input a_2 enters a node in the strong terminal set thus forcing the states z_i^* in that set to be strictly positive, while leaving those that belong to the non-terminal set to reach zero. Figure 4b, describes the case in which the input enters a non-terminal node that communicates with the remaining nodes of the graph (non-terminal and terminal), forcing the system to reach a strictly positive equilibrium state $\mathbf{z}^* > 0$.

Since $b_1 > 0$ leaves a node from the strong terminal set, the associated matrix W is C-Metzler (Definition 3.1). The sign patterns for the first two columns $(N)_1$ and $(N)_2$ of its corresponding inverse N are of the form: $(\; - \quad - \quad 0 \quad 0\;)^T$. For the 3rd and 4th columns, the sign patterns are $(\; - \quad - \quad - \quad - \;)^T$, since every node can be reached from either node 3 or 4. The sign pattern of the negative inverse will then be:

$$(-N) = \begin{bmatrix} + & + & + & + \\ + & + & + & + \\ 0 & 0 & + & + \\ 0 & 0 & + & + \end{bmatrix}.$$

$\triangle$

4 A Canonical Representation of the Equilibrium Set

The time evolution of the concentration vector (18) can be re-written in terms of the S_λ matrices associated to the stoichiometric subspace Ξ, already discussed in Section 2.2, so that:

$$\dot{\mathbf{c}} = \sum_\lambda S_\lambda \boldsymbol{\phi}_\lambda(\psi_{j_\lambda}(\mathbf{c}), \boldsymbol{\psi}_\lambda(\mathbf{c})), \tag{36}$$

where $\psi_{j_\lambda} : \mathbb{R}^m_{>0} \to \mathbb{R}_{>0}$, corresponds to the monomial associated to the reference complex, and $\boldsymbol{\psi}_\lambda : \mathbb{R}^m_{>0} \to \mathbb{R}^{N_\lambda - 1}_{>0}$ is the vector function that includes as coordinate functions the monomials associated to the remaining complexes. Finally, vector function $\boldsymbol{\phi}_\lambda : \mathbb{R}^{N_\lambda}_{\geq 0} \to \mathbb{R}^{N_\lambda - 1}$ contains the corresponding fluxes. Element-wise, monomials relate to fluxes by expression (6), that in matrix form can be written as:

$$\begin{pmatrix} \phi_{j_\lambda}(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda) \\ \boldsymbol{\phi}_\lambda(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda) \end{pmatrix} = M_\lambda \begin{pmatrix} \psi_{j_\lambda} \\ \boldsymbol{\psi}_\lambda \end{pmatrix}, \tag{37}$$

where the fluxes and monomials are ordered such that for each linkage class, the first elements correspond to the reference complex j_λ (i.e. $\phi_{j_\lambda}(\mathbf{c}), \psi_{j_\lambda}(\mathbf{c})$). Matrix $M_\lambda \in \mathbb{R}^{N_\lambda \times N_\lambda}$ is a compartmental matrix that has as off-diagonal entries the corresponding reaction constants. An explicit description of its structure can be given as follows:

Let $\mathcal{L}_\lambda(i)$ denote the i-th element in the set $\mathcal{L}_\lambda$ for $i = 1, \ldots, N_\lambda$. Without loss of generality, we can assume that the first element of $\mathcal{L}_\lambda$ is the index of the reference complex, i.e. $\mathcal{L}_\lambda(1) = j_\lambda$. In addition, let $k_{\mathcal{L}_\lambda(i), \mathcal{L}_\lambda(j)}$ denote the reaction rate coefficient associated to a possible reaction step from complex $\mathcal{L}_\lambda(i)$ to $\mathcal{L}_\lambda(j)$, being 0 if such reaction step does not exist. Then:

$$(M_\lambda)_{ij} = k_{\mathcal{L}_\lambda(j), \mathcal{L}_\lambda(i)} \quad \text{for} \quad i, j = 1, \ldots, N_\lambda, \ i \neq j \tag{38}$$

$$(M_\lambda)_{ii} = - \sum_{l=1, l \neq i}^{N_\lambda} k_{\mathcal{L}_\lambda(i), \mathcal{L}_\lambda(l)} \quad \text{for} \quad i = 1, \ldots, N_\lambda. \tag{39}$$

Note that because of (8), we have that:

$$\phi_{j_\lambda}(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda) + \mathbf{1}^T_{N_\lambda - 1} \boldsymbol{\phi}_\lambda(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda) = 0, \tag{40}$$

so that M_λ is a Kirchoff (i.e. column conservation) matrix, which for convenience we re-write as:

$$M_\lambda = \left[\begin{array}{c|c} -(\mathbf{1}^T_{N_\lambda - 1} \mathbf{a}_\lambda) & \mathbf{b}^T_\lambda \\ \hline \mathbf{a}_\lambda & E_\lambda \end{array} \right], \tag{41}$$

with $\mathbf{a}_\lambda, \mathbf{b}_\lambda \in \mathbb{R}^{N_\lambda - 1}$, $E_\lambda \in \mathbb{R}^{(N_\lambda - 1) \times (N_\lambda - 1)}$, and $\mathbf{b}^T_\lambda = -\mathbf{1}^T_{N_\lambda - 1} E_\lambda$. By construction, the off-diagonal elements of the first column and row in M_λ correspond to the rate coefficients for reaction steps leaving and entering, respectively, the reference complex j_λ. Such reference has

been chosen to be in the terminal linkage class, what ensures $\mathbf{b}_\lambda$ to be non-zero, since at least one reaction step is directed to the reference complex. The off-diagonal elements of matrix E_λ collect the remaining rate coefficients.

Proposition 4.1 E_λ *in expression (41) is C-Metzler, therefore invertible, and its inverse non-positive.*

Proof: First, we note that E_λ complies with Definition 3.1 (C-Metzler matrices). This is so because it is associated to a directed graph which coincides with the linkage class (the environment corresponds with the reference complex). By construction, the off-diagonal elements of E_λ are either zero or positive. In addition, since $\mathbf{b}_\lambda^T = -\mathbf{1}^T E_\lambda$, for each diagonal element we have that:

$$(E_\lambda)_{ii} = -[(\mathbf{b}_\lambda)_i + \sum_{j \neq i} (E_\lambda)_{ji}],$$

where at least one component of $\mathbf{b}_\lambda$ associated to the reference complex (linked to the strong terminal set) is positive. Thus, E_λ is C-Metzler and the result then follows by applying Lemma 3.1. $\qquad\square$

Inspection of Eqn (36) suggests that apart from complex balanced equilibrium solutions (i.e. those satisfying Definition 2.1), non-zero flux combinations can lead to equilibrium, if the corresponding flux vector $\boldsymbol{\phi}(\boldsymbol{\psi}) = [\ \boldsymbol{\phi}_1^T(\psi_{j_1}, \boldsymbol{\psi}_1)\ \ \cdots\ \ \boldsymbol{\phi}_\lambda^T(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda)\ \ \cdots\ \ \boldsymbol{\phi}_\ell^T(\psi_{j_\ell}, \boldsymbol{\psi}_\ell)\ ]^T$ lies in the kernel of S (12). In other words, if the network has non-zero deficiency, vector $\boldsymbol{\phi}(\boldsymbol{\psi})$ can be written as a linear combination of the set of vectors $\{\mathbf{g}^r \mid r = 1, \ldots, \delta\}$ that define a basis for the kernel of S, so that:

$$\boldsymbol{\phi}(\boldsymbol{\psi}) = \sum_r \nu_r \mathbf{g}^r, \tag{42}$$

for some given scalars ν_r. Making use of (15) in the above summation to express each element r of the basis in terms of the sub-vectors $\mathbf{g}_\lambda^r$, for $\lambda = 1, \cdots, \ell$, the flux vector for each linkage class can be written as:

$$\boldsymbol{\phi}_\lambda(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda) = \sum_r \nu_r \mathbf{g}_\lambda^r. \tag{43}$$

Note that such fluxes lead in fact to an equilibrium solution. This can be verified by substituting (43) into (36) and re-grouping summations, so that:

$$\dot{\mathbf{c}} = \sum_\lambda S_\lambda \sum_r \nu_r \mathbf{g}_\lambda^r = \sum_r \nu_r \sum_\lambda S_\lambda \mathbf{g}_\lambda^r, \tag{44}$$

where the right hand side is zero because of (16).

Example: Let us consider the network depicted in Figure 6. Since $\ell = 1$, there is just one matrix M_1 (41) that consists of the following sub-matrix components:

$$E_1 = \begin{bmatrix} -(k_{21} + k_{23}) & k_{32} & 0 & 0 \\ k_{23} & -k_{32} & k_{43} & 0 \\ 0 & 0 & -(k_{43} + k_{45}) & k_{54} \\ 0 & 0 & k_{45} & -k_{54} \end{bmatrix}, \quad \mathbf{a}_1 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ k_{15} \end{bmatrix}, \quad \mathbf{b}_1 = \begin{bmatrix} k_{21} \\ 0 \\ 0 \\ 0 \end{bmatrix}. \tag{45}$$
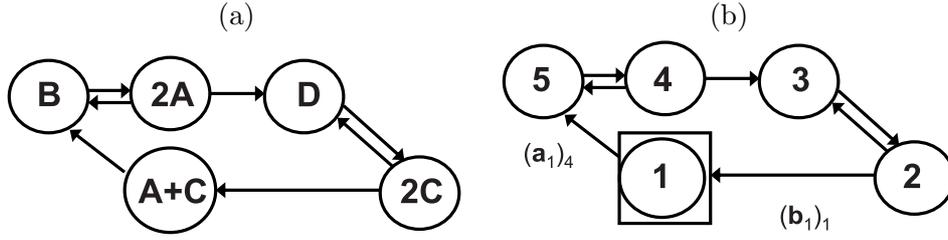
Figure 6: A one linkage class weakly reversible network consisting of 4 chemical species $\{A, B, C, D\}$. (a) The graph of complexes with explicit indication of the chemical species. (b) The graph with numbered complexes, including the reference complex in the square box and the graph associated to the C-Metzler matrix with the non-zero coordinates of vectors $\mathbf{a}_1$ and $\mathbf{b}_1$, represented in the diagram as $(\mathbf{a}_1)_4$ and $(\mathbf{b}_1)_1$, respectively.

The Y and S matrices described in Section 2 are, respectively:

$$
Y = \begin{bmatrix} 1 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 1 & 2 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \end{bmatrix} \quad \text{and} \quad S = \begin{bmatrix} -1 & -1 & 1 & -1 \\ 0 & 0 & 0 & 1 \\ 1 & -1 & -1 & -1 \\ 0 & 1 & 0 & 0 \end{bmatrix}, \tag{46}
$$

Since $rank(S) = 3$, the network has deficiency $\delta = 1$. Thus, equilibrium solutions would correspond to fluxes satisfying relation (43) with $\mathbf{g}^1 \equiv \mathbf{g}_1^1 = \begin{pmatrix} 1 & 0 & 1 & 0 \end{pmatrix}^T$ defining a one-dimensional subspace. $\triangle$

In computing the set of positive equilibrium solutions, we make use of (37) and (41) for every linkage class, to express fluxes $\boldsymbol{\phi}_\lambda$ as:

$$
\boldsymbol{\phi}_\lambda(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda) = \psi_{j_\lambda} \mathbf{a}_\lambda + E_\lambda \boldsymbol{\psi}_\lambda. \tag{47}
$$

Combining the right hand sides of (43) and (47) we get:

$$
E_\lambda \boldsymbol{\psi}_\lambda + \psi_{j_\lambda} \mathbf{a}_\lambda = \sum_r \nu_r \mathbf{g}_\lambda^r. \tag{48}
$$

Let $\boldsymbol{\nu} = [\nu_1 \ \ldots \nu_\delta]^T$, and define a vector $\boldsymbol{\chi} \in \mathbb{R}^\delta$ on the unit sphere as $\boldsymbol{\chi} = \frac{1}{\|\boldsymbol{\nu}\|} \boldsymbol{\nu}$. Since any positive equilibrium solution requires $\psi_{j_\lambda} > 0$ and $\boldsymbol{\psi}_\lambda > 0$, we can multiply both sides of Eqn (48) by $1/\psi_{j_\lambda}$ to obtain, after some re-arrangement:

$$
E_\lambda \mathbf{f}_\lambda + \mathbf{a}_\lambda = x_\lambda G_\lambda \boldsymbol{\chi}, \quad \text{with} \ \mathbf{f}_\lambda \equiv (1/\psi_{j_\lambda}) \boldsymbol{\psi}_\lambda. \tag{49}
$$

In the above expression, $G_\lambda \in \mathbb{R}^{(N_\lambda - 1) \times \delta}$ is a matrix of the form $G_\lambda = [\mathbf{g}_\lambda^1 \cdots \mathbf{g}_\lambda^r \cdots \mathbf{g}_\lambda^\delta]$, and $x_\lambda \equiv \frac{\|\boldsymbol{\nu}\|}{\psi_{j_\lambda}}$ a scalar variable. It must be noted that because $\|\nu\| = x_\lambda \psi_{j_\lambda}$ for every $\lambda = 1, \ldots \ell$, variables x_λ are not independent but related to each other through the following equalities:

$$
x_1 \psi_{j_1} = \cdots = x_\lambda \psi_{j_\lambda} = \cdots = x_\ell \psi_{j_\ell}. \tag{50}
$$

Since E_λ is invertible (Proposition 4.1), we can solve (49) to get a vector function $\mathbf{f}_\lambda : \mathbb{R} \times \mathbb{R}^\delta \to \mathbb{R}^{(N_\lambda - 1)}$ of the form:

$$
\mathbf{f}_\lambda(x_\lambda; \boldsymbol{\chi}) = \mathbf{f}_\lambda^* + x_\lambda \mathbf{h}_\lambda(\boldsymbol{\chi}), \tag{51}
$$

where $\mathbf{f}_\lambda^* = -E_\lambda^{-1}\mathbf{a}_\lambda$ and $\mathbf{h}_\lambda(\boldsymbol{\chi}) = E_\lambda^{-1}\mathbf{g}_\lambda(\boldsymbol{\chi})$, with $\mathbf{g}_\lambda(\boldsymbol{\chi}) = G_\lambda\boldsymbol{\chi}$. Vector fluxes in (47) can be expressed as a function of (51) for each linkage class so that:

$$\boldsymbol{\phi}_\lambda(\psi_{j_\lambda}, x_\lambda; \boldsymbol{\chi}) = \psi_{j_\lambda}\left[\mathbf{a}_\lambda + E_\lambda\mathbf{f}_\lambda(x_\lambda; \boldsymbol{\chi})\right]. \tag{52}$$

In this way, for each $\boldsymbol{\chi}$ in the unit sphere and $\mathbf{x} = (x_1, \cdots, x_\lambda, \cdots, x_\ell)^T$, constrained by (50) to be either zero or to belong to the interior of the positive orthant $\mathbb{R}_{>0}^\ell$, the right hand side of (36) vanishes. This follows since for each $\boldsymbol{\chi}$ on the unit sphere, the corresponding fluxes (52) become:

$$\boldsymbol{\phi}_\lambda(\psi_{j_\lambda}, x_\lambda; \boldsymbol{\chi}) = x_\lambda \psi_{j_\lambda} G_\lambda\boldsymbol{\chi}.$$

Substituting the above expressions in (36) and making use of (50) we get:

$$\dot{\mathbf{c}} = \left(\sum_\lambda x_\lambda \psi_{j_\lambda} S_\lambda G_\lambda\right)\boldsymbol{\chi} = x_1 \psi_{j_1}\left(\sum_\lambda S_\lambda G_\lambda\right)\boldsymbol{\chi}, \tag{53}$$

where the right hand side is zero because from (16) we have that:

$$\sum_\lambda S_\lambda G_\lambda = 0.$$

Note that for a vector $\boldsymbol{\chi}' = -\boldsymbol{\chi}$ we have that $\mathbf{x} \in \{0\} \cup \mathbb{R}_{<0}^\ell$, so it is enough to study vector functions (51) for $\mathbf{x} \in \{0\} \cup \mathbb{R}_{>0}^\ell \cup \mathbb{R}_{<0}^\ell$ and $\boldsymbol{\chi}$ in the set:

$$\mathbf{U} = \{\boldsymbol{\chi} \in \mathbb{R}^\delta \mid \|\boldsymbol{\chi}\| = 1, \ \boldsymbol{\varepsilon}_1^T\boldsymbol{\chi} \geq 0\}. \tag{54}$$

Definition 4.1 (Family of Solutions[4]) *Let $\mathbb{D}_0 \subset \mathbb{R}^\ell$ be the domain $\{0\} \cup \mathbb{R}_{>0}^\ell \cup \mathbb{R}_{<0}^\ell$, and $\mathbf{f}_{\boldsymbol{\eta}} : \mathbb{D}_0 \times \mathbf{U} \to \mathbb{R}^{(n-\ell)}$ a vector function:*

$$\mathbf{f}_{\boldsymbol{\eta}}^T(\mathbf{x}; \boldsymbol{\chi}) = \left[\begin{array}{ccccc} \mathbf{f}_1^T(x_1; \boldsymbol{\chi}) & \cdots & \mathbf{f}_\lambda^T(x_\lambda; \boldsymbol{\chi}) & \cdots & \mathbf{f}_\ell^T(x_\ell; \boldsymbol{\chi}) \end{array}\right], \tag{55}$$

with $\mathbf{x} = (x_1, \cdots, x_\ell)^T$ and $\mathbf{f}_\lambda(x_\lambda; \boldsymbol{\chi})$ for $\lambda = 1, \cdots, \ell$ as in (51). We will refer to $\mathbf{f}_{\boldsymbol{\eta}}(\boldsymbol{x}; \boldsymbol{\chi})$ as the family of solutions.

In order to comply with positive equilibrium solutions in the concentration space, each vector function $\mathbf{f}_\lambda(x_\lambda; \boldsymbol{\chi})$ in (51) must be strictly positive, and related to the reaction monomials by the expression:

$$\mathbf{f}_\lambda = \exp\left(\ln\frac{1}{\psi_{j_\lambda}}\boldsymbol{\psi}_\lambda\right). \tag{56}$$

In what follows, and at the risk of some abuse of notation, when referring to a given linkage class, we will drop subscript λ, and re-write (51) as:

$$\mathbf{f}(x; \boldsymbol{\chi}) = \mathbf{f}^* + x\mathbf{h}(\boldsymbol{\chi}). \tag{57}$$

---

[4]A closely related notion has been proposed in [45]

If in addition, the discussion concerns a particular vector $\chi \in \mathbf{U}$, the following simplified expression for Eqn (57) will be employed:

$$\mathbf{f}(x) = \mathbf{f}^* + x\mathbf{h}. \tag{58}$$

Lemma 4.1 *If the linkage class is weakly reversible, $\mathbf{f}^*$ in (58) is strictly positive. If the linkage class is irreversible, $\mathbf{f}^*$ will be non-negative with zero entries that correspond to the non-terminal complexes.*

Proof: If the linkage class is weakly reversible, every complex in the linkage class can be reached from the reference (equivalently, from the complexes associated to positive entries $\mathbf{a}$ in (41)). Thus from Lemma 3.1, $\mathbf{f}^* = -E^{-1}\mathbf{a} > 0$.

If the linkage class is irreversible, let $\mathbf{a}^T = [\mathbf{a}_p^T \ \mathbf{a}_q^T]$ where sub-indexes p and q denote the terminal and non-terminal complexes of the linkage class. Since the reference belongs to the strong terminal linkage class, positive components of vector $\mathbf{a}$ only enter terminal complexes so that $\mathbf{a}_q^T = \mathbf{0}_q$. Using the inverse (35) from Lemma 3.1, $\mathbf{f}^* = -N\mathbf{a}$ can be written as:

$$\mathbf{f}^* = \left[\begin{array}{c} \mathbf{f}_p^* \\ \mathbf{f}_q^* \end{array} \right] = \left[\begin{array}{c} -N_p\mathbf{a}_p \\ \mathbf{0}_q \end{array} \right],$$

where $\mathbf{f}_p^*$ is strictly positive because, by Lemma 3.1, N_p is strictly negative. Thus $\mathbf{f}^* \geq 0$, with zero entries $\mathbf{f}_q^*$ that correspond to the non-terminal complexes. $\qquad\square$

Next we present some conditions that ensure positivity of vector functions (51) and the corresponding family of solutions (Definition 4.1).

4.1 Positivity conditions for the family of solutions

At this point, it should be clear that positivity of the family of solutions in Definition 4.1 is a necessary condition for positive equilibrium in the concentration space. Next, we discuss how such condition relates to the structure of the network and give some indications on how to construct the domain where (55) remains positive.

Proposition 4.2 *If a given linkage class is weakly reversible, then for every $\chi \in \mathbf{U}$ there exists an interval $\mathbb{X}(\chi) \subset \mathbb{R}$ (which includes the zero) where the vector function (57) remains positive. If the linkage class is irreversible, and there exists a positive vector function (57) on $\mathbb{X}(\chi)$, such interval cannot contain the zero.*

Proof: If the linkage class is weakly reversible, by Lemma 4.1 we have that $\mathbf{f}^* > 0$, so the values of the scalar x for which $\mathbf{f}(x)$ in (58) remains strictly positive will depend on the signs of the

entries in $\mathbf{h}$. For every such entry i, define $p_i = h_i/\mathrm{f}_i^*$ and introduce two index sets $\mathcal{I}^+$ and $\mathcal{I}^-$ so that:

$$
\begin{aligned}
i \in \mathcal{I}^+, & \quad \text{if } h_i > 0, \quad \text{thus } p_i > 0 \\
i \in \mathcal{I}^-, & \quad \text{if } h_i < 0, \quad \text{thus } p_i < 0.
\end{aligned} \tag{59}
$$

It is straightforward to see that $\mathbf{f}(x)$ will be strictly positive for every x in the open interval:

$$
\mathbb{X} = (L^-, L^+), \text{ with } L^- = \max_{i \in \mathcal{I}^+}\{-1/p_i\} \text{ and, } L^+ = \min_{i \in \mathcal{I}^-}\{-1/p_i\}. \tag{60}
$$

Note that $L^- = -\infty$ (respectively, $L^+ = +\infty$) provided that $\mathcal{I}^+ = \emptyset$ (respectively, $\mathcal{I}^- = \emptyset$). In any case, because $\mathbf{f}^* > 0$, the interval $\mathbb{X}$ includes the zero. If the linkage class is irreversible, by using Lemma 4.1, $\mathbf{f}(x)$ in (58) can be written as:

$$
\begin{aligned}
\mathbf{f}_{\mathrm{p}}(x) &= \mathbf{f}_{\mathrm{p}}^* + x\mathbf{h}_{\mathrm{p}} \\
\mathbf{f}_{\mathrm{q}}(x) &= \mathbf{0}_{\mathrm{q}} + x\mathbf{h}_{\mathrm{q}},
\end{aligned} \tag{61}
$$

where sub-indexes p and q denote the terminal and non-terminal nodes of the linkage class. Since $\mathbf{f}_{\mathrm{p}}^*$ is strictly positive, there exists some domain $\mathbb{X}_{\mathrm{p}}$ that includes the zero, for which $\mathbf{f}_{\mathrm{p}}(x) > 0$. Let $\mathbb{X}_{\mathrm{p}} = \mathbb{X}_{\mathrm{p}}^- \cup \mathbb{X}_{\mathrm{p}}^+ \cup \{0\}$, where $\mathbb{X}_{\mathrm{p}}^-$ and $\mathbb{X}_{\mathrm{p}}^+$ are the intervals containing the negative and positive values, respectively. It is then straightforward to see from (61) that in order for $\mathbf{f}_{\mathrm{q}}(x) > 0$, $\mathbf{h}_{\mathrm{q}}$ must have a definite sign (i.e. all components either positive or negative). If this is the case, i.e. if $\mathbf{h}_{\mathrm{q}} > 0$ (respectively, < 0), we can always find some $x \in \mathbb{X}_{\mathrm{p}}^+$ (respectively, $x \in \mathbb{X}_{\mathrm{p}}^-$), so that $\mathbf{f}(x) > 0$. Otherwise, no positive solution exists. Because $\mathbb{X}_{\mathrm{p}}^+$ (respectively, $\mathbb{X}_{\mathrm{p}}^-$) does not contain the zero, if the linkage class is irreversible, the interval $\mathbb{X}(\chi)$ does not contain the zero. $\square$

Proposition 4.3 *Let $\mathbf{f}_{\boldsymbol{\eta}} : \mathbb{D}_0 \times \mathbf{U} \to \mathbb{R}^{(n-\ell)}$ (with $\mathbb{D}_0 = \{0\} \cup \mathbb{R}_{>0}^{\ell} \cup \mathbb{R}_{<0}^{\ell}$) be the family of solutions as given in Definition 4.1. In addition, for each $\lambda = 1, \cdots, \ell$ and $\boldsymbol{\chi} \in \mathbf{U}$, let $\mathbb{X}_{\lambda}(\boldsymbol{\chi}) \subset \mathbb{R}$ be the interval such that $\mathbf{f}_{\lambda}(x_{\lambda}; \boldsymbol{\chi}) > 0$ for every $x_{\lambda} \in \mathbb{X}_{\lambda}(\boldsymbol{\chi})$, and $\mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) = \mathbb{X}_1(\boldsymbol{\chi}) \times \cdots \mathbb{X}_{\lambda}(\boldsymbol{\chi}) \times \cdots \mathbb{X}_{\ell}(\boldsymbol{\chi})$ an open ℓ-dimensional domain. Then:*

If the network is weakly reversible, for every $\boldsymbol{\chi} \in \mathbf{U}$ there exists a domain $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) = \mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) \cap \mathbb{D}_0$ that contains the zero, such that $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi}) > 0$ for every $\mathbf{x} \in \mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi})$.

If the network is irreversible and the domain $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) = \mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) \cap \mathbb{D}_0$ is non-empty, then $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi}) > 0$ for every $\mathbf{x} \in \mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi})$. Such domain does not contain the zero.

Proof: If the network is weakly reversible, Proposition 4.2 ensures that for every $\lambda = 1, \cdots, \ell$ and $\boldsymbol{\chi} \in \mathbf{U}$, $\mathbf{f}_{\lambda}(x_{\lambda}; \boldsymbol{\chi}) > 0$ for every $x_{\lambda} \in \mathbb{X}_{\lambda}(\boldsymbol{\chi})$, where the interval contains the zero. In consequence, a non-empty domain $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) = \mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) \cap \mathbb{D}_0$ exists, what proves the first assertion.

If the network is irreversible and $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi})$ is non-empty, the second assertion holds. Because at least one linkage class is irreversible, it follows from Proposition 4.2 that $\mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi})$, and therefore $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi})$, does not contain the zero. Finally, note that for irreversible networks it may well happen that $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi})$, as defined above, is empty so no positive family of solutions exists. $\square$

4.2 The set of feasible (equilibrium) solutions

Not all positive elements (vectors) that are part of the family of solutions (55) will necessarily comply with condition (56) but only a particular subset we will refer to as the set of *feasible solutions*, that we formally define next. Using (2) for every complex $i \in \mathcal{L}_\lambda$, we have that $\ln(\psi_i(\mathbf{c})/\psi_{j_\lambda}(\mathbf{c})) = (\boldsymbol{y}_i - \boldsymbol{y}_{j_\lambda})^T \ln \mathbf{c}$. Hence, the logarithm at the right hand side of (56) can be expressed as:

$$\ln \frac{1}{\psi_{j_\lambda}(\mathbf{c})} \psi_\lambda(\mathbf{c}) = S_\lambda^T \ln \mathbf{c}, \tag{62}$$

so that $\ln \mathbf{f}_\lambda(\boldsymbol{\xi}) = S_\lambda^T \boldsymbol{\xi}$ for every $\lambda = 1, ..., \ell$, and $\boldsymbol{\xi} \in \mathbb{R}^m$ ($\boldsymbol{\xi} \equiv \ln \mathbf{c}$).

Definition 4.2 (The set of feasible solutions) *For a given $\boldsymbol{\chi} \in \mathbf{U}$, let us assume that there exists a non-empty domain $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}) \subset \mathbb{D}_0$ such that for every $\mathbf{x} \in \mathbb{D}_{\boldsymbol{\eta}}$, $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi}) > 0$. We say that $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi}) > 0$ is a feasible solution if:*

$$\ln \mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi}) \in \mathrm{Im}(S^T). \tag{63}$$

The set of vectors $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi})$, with $\boldsymbol{\chi} \in \mathbf{U}$ and $\mathbf{x} \in \mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi})$ that satisfy (63), constitutes the set of feasible solutions.

Note that (63) implies that there exists some $\boldsymbol{\xi} \in \mathbb{R}^m$ such that $\ln \mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi}) = S^T \boldsymbol{\xi}$. In this way, each element of the set of feasible solutions relates to a set of equilibrium concentrations of the form $\mathbf{c} = \exp(\boldsymbol{\xi})$ for system (36). The following result gives some conditions to identify the set of feasible equilibrium solutions:

Lemma 4.2 (Feasibility conditions) *Every element $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi})$ of the set of feasible solutions satisfies that:*

$$(\mathbf{g}^r)^T \ln \mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi}) = 0, \quad \text{for} \quad r = 1, ..., \delta. \tag{64}$$

Proof: By Definition 4.2, every element of the set of feasible solutions satisfies Eqn (63). This implies that $\ln \mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}; \boldsymbol{\chi})$ is in the range of S^T, which in turn is orthogonal to the kernel of S. Since $\{\mathbf{g}^r \mid r = 1, \dots, \delta\}$ is a basis for the kernel, expressions in (64) follow. $\qquad\square$

Definition 4.3 (Feasibility function) *Let $\mathrm{F} : \mathbb{X} \times \mathbf{U} \to \mathbb{R}$ (with $\mathbb{X} \subset \mathbb{R}$) be defined as:*

$$\mathrm{F}(x; \boldsymbol{\chi}) = \mathbf{g}^T(\boldsymbol{\chi}) \ln \mathbf{f}(x; \boldsymbol{\chi}), \tag{65}$$

where $\boldsymbol{\chi} \in \mathbf{U}$ and $\mathbb{X}(\boldsymbol{\chi})$ is the interval in which $\mathbf{f}(x; \boldsymbol{\chi})$, of the form (57), remains positive

We make use of the above definition to present an immediate consequence of Lemma 4.2.

Proposition 4.4 *For every element* $\mathbf{f}_\eta(\mathbf{x}; \boldsymbol{\chi})$ *of the set of feasible solutions, the following relation holds:*

$$\sum_\lambda \mathrm{F}_\lambda(x_\lambda; \boldsymbol{\chi}) = 0, \quad \text{where} \quad \mathrm{F}_\lambda(x_\lambda; \boldsymbol{\chi}) = \boldsymbol{g}_\lambda^T(\boldsymbol{\chi}) \ln \mathbf{f}_\lambda(x_\lambda; \boldsymbol{\chi}). \tag{66}$$

Proof: Pre-multiplying each equality in (64) (Lemma 4.2) by the corresponding coordinate χ_r, taking the summation to δ and expanding over linkage classes, we get:

$$\sum_r \chi_r(\mathbf{g}^r)^T \ln \mathbf{f}_\eta(\mathbf{x}; \boldsymbol{\chi}) = 0, \quad \text{and} \quad \sum_\lambda \mathbf{g}_\lambda^T(\boldsymbol{\chi}) \ln \mathbf{f}_\lambda(x_\lambda; \boldsymbol{\chi}) = 0.$$

The result then follows by using Definition 4.3 to re-write the above expression as in (66). $\quad\square$

As we will see in the next sections, feasibility functions $\mathrm{F}_\lambda(x; \boldsymbol{\chi})$ will prove to be fundamental to characterize the structure of equilibrium, allowing in some instances to conclude uniqueness of equilibrium in each positive stoichiometric compatibility class.

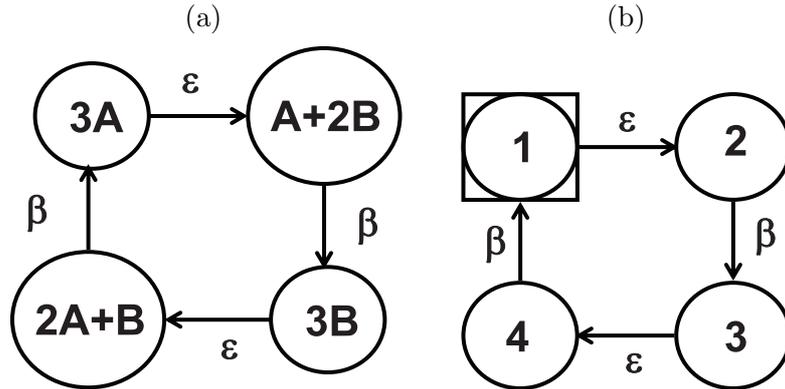## 4.3 Example: feasibility for a one linkage class weakly reversible network

Figure 7: A weakly reversible one-linkage class network with reaction constants $k_{12} = k_{34} = \epsilon$ and $k_{23} = k_{41} = \beta$. (a) The network with explicit indication of the chemical species. (b) The corresponding graph of complexes with the reference complex in the squared box.

Let us consider the weakly reversible reaction network taken from [23] and presented in Figure 7. Matrix (41) for this network takes the form:

$$M = \begin{bmatrix} -k_{12} & 0 & 0 & k_{41} \\ k_{12} & -k_{23} & 0 & 0 \\ 0 & k_{23} & -k_{34} & 0 \\ 0 & 0 & k_{34} & -k_{41} \end{bmatrix}. \tag{67}$$

Substituting the reaction constants given in Figure 7, leads to the following sub-matrices in M:

$$E = \begin{bmatrix} -\beta & 0 & 0 \\ \beta & -\epsilon & 0 \\ 0 & \epsilon & -\beta \end{bmatrix}, \quad \mathbf{a} = \begin{bmatrix} \epsilon \\ 0 \\ 0 \end{bmatrix}, \quad \mathbf{b} = \begin{bmatrix} 0 \\ 0 \\ \beta \end{bmatrix}. \tag{68}$$

For this example, matrix S and a basis for its kernel, expressed as columns of matrix G read:

$$S = \begin{bmatrix} -2 & -3 & -1 \\ 2 & 3 & 1 \end{bmatrix}, \quad G = \begin{bmatrix} 1 & 0 & -2 \\ 0 & 1 & -3 \end{bmatrix}^T.$$

In order to compute the feasibility function (65), we have that:

$$\mathbf{f}^* = -E^{-1}\mathbf{a} = \begin{pmatrix} \epsilon/\beta & 1 & \epsilon/\beta \end{pmatrix}^T, \quad E^{-1} = \begin{bmatrix} -\frac{1}{\beta} & 0 & 0 \\ -\frac{1}{\epsilon} & -\frac{1}{\epsilon} & 0 \\ -\frac{1}{\beta} & -\frac{1}{\beta} & -\frac{1}{\beta} \end{bmatrix}, \qquad (69)$$

and

$$\mathbf{h}(\boldsymbol{\chi}) = E^{-1}\left[\chi_1 \begin{pmatrix} 1 \\ 0 \\ -2 \end{pmatrix} + \chi_2 \begin{pmatrix} 0 \\ 1 \\ -3 \end{pmatrix}\right] = \chi_1 \begin{pmatrix} -1/\beta \\ -1/\epsilon \\ 1/\beta \end{pmatrix} + \chi_2 \begin{pmatrix} 0 \\ -1/\epsilon \\ 2/\beta \end{pmatrix}.$$

For parameters $\beta = 2$ and $\epsilon = 1$ we have that:

$$\mathbf{f}^* = \begin{pmatrix} 1/2 \\ 1 \\ 1/2 \end{pmatrix} \quad \text{and} \quad \mathbf{h}(\boldsymbol{\chi}) = \chi_1 \begin{pmatrix} -1/2 \\ -1 \\ 1/2 \end{pmatrix} + \chi_2 \begin{pmatrix} 0 \\ -1 \\ 1 \end{pmatrix}$$

For $\boldsymbol{\chi}_1 = (1\ 0)^T$, the entries of the vector function $\mathbf{f}(x; \boldsymbol{\chi}_1)$ will remain all positive as long as the values taken by x will lie in the open interval $(-1, +1)$. Hence, its domain $\mathbb{X}(\boldsymbol{\chi}_1) = (-1, +1)$. In the same way, for $\boldsymbol{\chi}_2 = (0\ 1)^T$, $\mathbb{X}(\boldsymbol{\chi}_2) = (-1/2, +1)$. Because the logarithm is defined for positive values, both domains $\mathbb{X}(\boldsymbol{\chi}_1)$ and $\mathbb{X}(\boldsymbol{\chi}_2)$ coincide also with the domains for $F(x; \boldsymbol{\chi}_1)$ and $F(x; \boldsymbol{\chi}_2)$. The explicit expressions become:

$$F(x; \boldsymbol{\chi}_1) = \ln \frac{2(1-x)}{(1+x)^2}, \quad \text{and} \quad F(x; \boldsymbol{\chi}_2) = \ln \frac{8(1-x)}{(1+2x)^3}.$$

Feasibility functions for some vectors $\boldsymbol{\chi}$ in the unit sphere are presented in Figure 8. It must be observed that each vector $\boldsymbol{\chi}$ leads to a different domain $\mathbb{X}(\boldsymbol{\chi})$. Finally note that since $\mathbf{f}^*$ is strictly positive, all possible domains will include the zero. $\triangle$

It must be noted that the functions depicted in the above example are monotonous decreasing in their respective domains. Remarkably, this will be the case for any feasibility function $F(x; \boldsymbol{\chi})$, despite network structure or stoichiometry. Next section provides a formal proof of this fact which will turn out to be central in exploring the nature of equilibrium solutions.

5 Monotonicity of feasibility functions

Here, we study the properties of function (65), presented in Definition 4.3. In particular, it will be shown that it is monotonous decreasing in its domain $\mathbb{X}(\boldsymbol{\chi})$ and crosses the x-axis.

Let us consider a weakly reversible linkage class and a given vector $\boldsymbol{\chi} \in \mathbf{U}$. Without loss of generality, assume that the $N - 1$ components of the vector $\mathbf{h}$ in (58), being m of them positive,
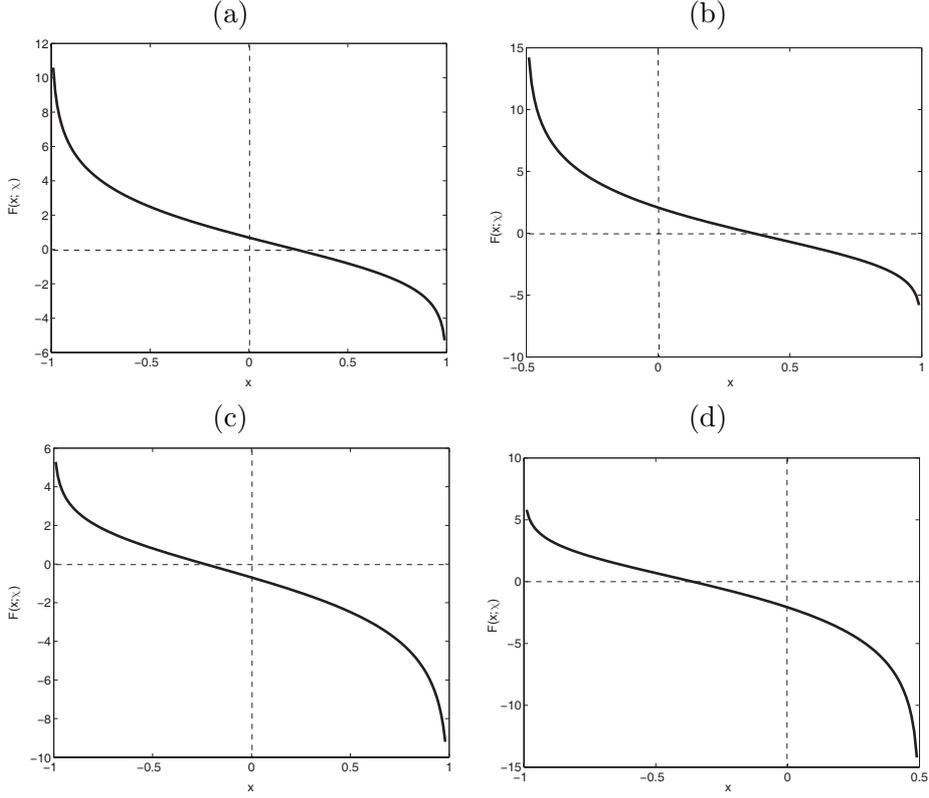
Figure 8: Feasibility functions $F(x; \chi)$ associated to the network presented in Figure 7 for different vectors χ in the unit sphere. (a) $\chi = (1\ 0)^T$, (b) $\chi = (0\ 1)^T$, (c) $\chi = (-1\ 0)^T$, (d) $\chi = (0\ -1)^T$. Note that since vectors in plots (a)-(c), and (b)-(d) relate as $\chi' = -\chi$, the corresponding functions relate as $F(x; \chi) = -F(-x; \chi')$.

r zero and the remaining negative, are ordered so that:

$$h_1 \geq \cdots \geq h_k \geq \cdots \geq h_m > 0 > h_{m+r+1} \geq \cdots \geq h_\ell \geq \cdots \geq h_{N-1},$$
$$h_{m+1} = \cdots = h_{m+r} = 0. \tag{70}$$

Note that such order can always be induced by a suitable row and column permutation in equations $\mathbf{g} = E\mathbf{h}$ and $E\mathbf{f}^* = -\mathbf{a}$. In order to simplify notation, let us re-write function (65) for a fixed χ as:

$$F(x) = \mathbf{g}^T \ln \mathbf{f}(x). \tag{71}$$

The main result on monotonicity is presented in the theorem below.

Theorem 5.1 *Let* $\mathbb{X} \subset \mathbb{R}$ *and consider the function* $F(x) : \mathbb{X} \mapsto \mathbb{R}$ *defined in (71).* $F(x)$ *is monotonous decreasing in the interval* $\mathbb{X}$*, defined as in (60). Moreover,*

$$\lim_{x^+ \to L^-} F(x) = +\infty \quad \text{and} \quad \lim_{x^- \to L^+} F(x) = -\infty. \tag{72}$$

Proof: Function (71) is continuous differentiable in the the interval $\mathbb{X}$ since $\mathbf{f}(x)$ is strictly positive (see Proposition 4.2). Thus, the first part of the proof reduces to computing the first

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derivative with respect to x and studying its sign in the interval $\mathbb{X}$. For every entry i of vectors $\mathbf{h}$ and $\mathbf{f}^*$, let us define $p_i = h_i/f_i^*$ as in the proof of Proposition 4.2, and re-write $\mathbf{h}$ as:

$$\mathbf{h} = \mathcal{D}(\mathbf{f}^*)\mathbf{p}, \tag{73}$$

where vector $\mathbf{p} \in \mathbb{R}^{N-1}$ includes the elements p_i and $\mathcal{D}(\mathbf{f}^*)$ represents a diagonal matrix with the components of $\mathbf{f}^*$ in the diagonal. Let us also re-order the p_i elements so that:

$$p_1 \geq \cdots \geq p_k \geq \cdots \geq p_m > 0 > p_{m+r+1} \geq \cdots \geq p_\ell \geq \cdots \geq p_{N-1},$$
$$p_{m+1} = \cdots = p_{m+r} = 0. \tag{74}$$

Note that the number of positive, negative and zero elements must coincide with those in (70), although not necessarily in the same order. Define functions $Q_i(x) : \mathbb{X} \mapsto \mathbb{R}$ as:

$$Q_i(x) = \frac{p_i}{1 + xp_i}. \tag{75}$$

For every k such that $p_k > 0$ and $x \in \mathbb{X}$, we have that $x > -(1/p_k)$, since from (60):

$$x > \max_{i \in \mathcal{I}^+}\{-1/p_i\}(= -1/p_1).$$

In turns, this implies that $x + (1/p_k) > 0$, and:

$$Q_k(x) = \frac{1}{x + (1/p_k)} > 0.$$

Using the same argument for the negative elements, we have that $x < -1/p_\ell$ so that $Q_\ell(x) < 0$ for any $\ell = m+r+1, \ldots, N-1$. In addition, for any $p_i \geq p_j$ (both, either positive or negative), we have that $Q_i(x) \geq Q_j(x)$. Consequently, from (74), for every $x \in \mathbb{X}$ we have that:

$$Q_1(x) \geq \cdots \geq Q_k(x) \geq \cdots \geq Q_m(x) > 0 > Q_{m+r+1}(x) \geq \cdots \geq Q_\ell(x) \geq \cdots \geq Q_{N-1}(x),$$
$$Q_{m+1}(x) = \cdots = Q_{m+r}(x) = 0. \tag{76}$$

Keeping the order established in (74), the first derivative can be written as:

$$\mathrm{F}'(x) = \sum_{i=1}^{N-1} \frac{g_i h_i}{\mathrm{f}_i(x)}, \tag{77}$$

where g_i is the i coordinate of vector $\mathbf{g} = E\mathbf{h}$, and $\mathrm{f}_i(x)$ represents the i component of vector function (58). The derivative is well defined and continuous on $\mathbb{X}$, since $\mathrm{f}_i(x) > 0$ for every i and $x \in \mathbb{X}$. By dividing every element of the summation by f_i^*, and using $p_i = h_i/f_i^*$, we can re-write (77) in term of functions $Q_i(x)$ (75) as:

$$\mathrm{F}'(x) = \sum_{i=1}^{N-1} g_i Q_i(x). \tag{78}$$

Let us define a matrix $H \in \mathbb{R}^{(N-1)\times(N-1)}$ as:

$$H = E\mathcal{D}(\mathbf{f}^*), \tag{79}$$

which by construction is C-Metzler (Definition 3.1), since E is C-Metzler, and the columns of E are scaled by a positive diagonal matrix. By means of H and Eqn (73), we re-write $E\mathbf{f}^* = -\mathbf{a}$ and $\mathbf{g} = E\mathbf{h}$, respectively, as:

$$H\mathbf{1}_{N-1} = -\mathbf{a}, \quad \text{and} \quad \mathbf{g} = H\mathbf{p}. \tag{80}$$

Because H is C-Metzler, and the relations (76) and (80) hold, we are under the conditions of Lemmas A.1 and A.2 in Appendix A. In particular, the right hand side of (78) has the same structure as $G(x)$ in Lemma A.2. Consequently, the first derivative is strictly negative on the interval $\mathbb{X}$ and monotonicity follows.

In order to prove (72), we note that each entry of $\mathbf{f}(x)$ can be expressed as $\mathrm{f}_i(x) = \mathrm{f}_i^*(1 + xp_i)$, and re-write (71) as:

$$\mathrm{F}(x) = \sum_{i=1}^{N-1} g_i \ln \mathrm{f}_i(x) = \sum_{i=1}^{N-1} g_i \ln \mathrm{f}_i^* + \sum_{i=1}^{N-1} g_i \Pi_i(x), \tag{81}$$

where $\Pi_i(x) = \ln(1 + xp_i)$. In addition, let us re-write the sequence of positive parameters in (74), in the equivalent form:

$$p_1 = \cdots = p_s > p_{s+1} \geq \cdots p_k \geq \cdots \geq p_m > 0,$$

with s being an integer that denotes the first strict inequality in the sequence (counted starting from the largest element), and can take any value between 1 and m. Similarly, let us re-write the sequence of negative parameters in (74) as:

$$0 > p_{m+r+1} \geq \cdots \geq p_\ell \geq \cdots \geq p_{t-1} > p_t = \cdots = p_{N-1},$$

with t being an integer that denotes the first strict inequality in the sequence (counted from the smallest element), and can take any value between $m + r + 1$ and $N - 1$.

The first term at the right hand side of (81) is constant, while the second term can be expanded as in (A.14) (proof of Lemma A.2) with $\Pi_i(x)$ instead of $Q_i(x)$. Taking into account the above sequences, the expansion can be written as:

$$\mathrm{F}(x) = \sum_{i=1}^{N-1} g_i \ln \mathrm{f}_i^* + \mathrm{F}^+(x) + \mathrm{F}^-(x), \tag{82}$$

with:

$$\begin{aligned}
\mathrm{F}^+(x) &= (\Pi_1(x) - \Pi_{s+1}(x)) \sum_{i=1}^{s} g_i + \cdots + (\Pi_k(x) - \Pi_{k+1}(x)) \sum_{i=1}^{k} g_i + \cdots \\
&\quad + \Pi_m(x) \sum_{i=1}^{m} g_i, \tag{83}
\end{aligned}$$

$$\begin{aligned}
\mathrm{F}^-(x) &= \Pi_{m+r+1}(x) \sum_{i=m+r+1}^{N-1} g_i + \cdots + (\Pi_\ell(x) - \Pi_{\ell-1}(x)) \sum_{i=\ell}^{N-1} g_i + \cdots \\
&\quad + (\Pi_{N-1}(x) - \Pi_{t-1}(x)) \sum_{i=t}^{N-1} g_i, \tag{84}
\end{aligned}$$

where terms of the form $\Pi_i(x) - \Pi_j(x)$ such that $p_i = p_j$ have been dropped from the expansion, as they are zero. In computing the left and right limits of $F(x)$, these are the possible scenarios:

1. If $s = m$ or $t = m + r + 1$, expansions (83) or (84) reduce to:

$$F^+(x) = \Pi_m(x) \sum_{i=1}^{m} g_i, \quad \text{or} \quad F^-(x) = \Pi_{m+r+1}(x) \sum_{i=m+r+1}^{N-1} g_i.$$

By Lemma A.1 (Expression in (A.6)), we have that $\sum_{i=1}^{m} g_i < 0$, and $\sum_{i=m+r+1}^{N-1} g_i > 0$. We also have that $p_m = p_1$ and $p_{m+r+1} = p_{N-1}$. Thus, using the limits (A.18) in Proposition A.2 we obtain (72).

2. If $s < m$ and $t > m + r + 1$, there are both, positive, zero and negative entries so the interval becomes $\mathbb{X} = (-1/p_1, -1/p_{N-1})$. In the limit as $x^+ \to -1/p_1$ all terms in (82) are constant (see limits (A.21) in Proposition A.2) except the first term associated to $F^+(x)$. Concerning this term, we have that $\sum_{i=1}^{s} g_i < 0$ (i.e. strictly negative according to Proposition A.1) so by using (A.19) of Proposition A.2, we get:

$$\lim_{x^+ \to L^-} F(x) = \lim_{x^+ \to -(\frac{1}{p_1})} (\Pi_1(x) - \Pi_{s+1}(x)) \sum_{i=1}^{s} g_i = +\infty.$$

In the limit as $x^- \to -1/p_{N-1}$, all terms in (82) are constant, but the last one associated to $F^-(x)$. Again, using Propositions A.1 and A.2, we have that:

$$\lim_{x^- \to L^+} F(x) = \lim_{x^- \to -(\frac{1}{p_{N-1}})} (\Pi_{N-1}(x) - \Pi_{t-1}(x)) \sum_{i=t}^{N-1} g_i = -\infty.$$

3. All entries are positive or zero, so that $m + r = N - 1$. In this case, the interval $\mathbb{X} = (-1/p_1, +\infty)$, and (82) reduces to:

$$F(x) = \sum_{i=1}^{N-1} g_i \ln f_i^* + F^+(x).$$

As in the previous case, $\lim_{x^+ \to L^-} F(x) = +\infty$. On the other hand, in the limit as $x \to +\infty$, by Proposition A.2, all terms but the last one in $F^+(x)$ are constant. Because $\sum_{i=1}^{m} g_i < 0$ (Lemma A.1), and $\lim_{x \to +\infty} \Pi_m(x) = +\infty$, we have that:

$$\lim_{x \to +\infty} F(x) = \lim_{x \to +\infty} \Pi_m(x) \sum_{i=1}^{m} g_i = -\infty.$$

4. All entries are negative or zero so that $m = 0$, the interval $\mathbb{X} = (-\infty, -1/p_{N-1})$ and (82) reduces to:

$$F(x) = \sum_{i=1}^{N-1} g_i \ln f_i^* + F^-(x).$$

As in case 2, $\lim_{x^- \to L^+} F(x) = -\infty$. On the other hand, in the limit as $x \to -\infty$, by Proposition A.2, all terms but the first one in $F^-(x)$ are constant, and because $\sum_{i=m+r+1}^{N-1} g_i > 0$ (Lemma A.1) and $\lim_{x \to -\infty} \Pi_{m+r+1} = +\infty$, we have that:

$$\lim_{x \to -\infty} F(x) = \lim_{x \to -\infty} \Pi_{m+r+1}(x) \sum_{i=m+r+1}^{N-1} g_i = +\infty.$$

$\square$

6 Some network classes with unique equilibrium solutions

Chemical reaction network structure, with its associated C-Metzler matrices, influences the set of feasible equilibrium solutions that we compute by applying conditions in Lemma 4.2 and are related to the feasibility functions given in Definition 4.3. In this section, we exploit monotonicity of these functions to explore existence and uniqueness of equilibria within positive stoichiometric compatibility classes for weakly reversible reaction networks.

Monotonicity will be used to identify sub-sets within the space of possible reaction rate coefficients leading to complex balancing and in line with the classical works in [35, 34, 22], to conclude existence and uniqueness of equilibria within positive stoichiometric compatibility classes.

The monotonicity argument will also be employed to show existence and uniqueness of equilibrium solutions for a class of positive deficiency networks. This might support the construction of an alternative proof of the well-known deficiency one theorem [24, 8] for weakly reversible reaction networks.

6.1 Zero flux conditions and complex balanced equilibrium

Here we examine the equilibrium solutions $\mathbf{c}^*$ for the dynamic system (36), that result from all fluxes in the network to be zero, namely $\phi_\lambda(\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda) = 0$ for every $\lambda = 1, \ldots, \ell$. In exploring such a case (we will refer to as the zero flux condition), we first note that $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{0}; \boldsymbol{\chi})$ (i.e. the family of solutions (Definition 4.1) evaluated at $\mathbf{x} = 0$) corresponds to a zero flux condition. This can be shown by substituting $x_\lambda = 0$ for every $\lambda = 1, \ldots, \ell$ in (52), and and using the fact that $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{0}; \boldsymbol{\chi})$ implies that $\mathbf{f}_\lambda(0; \boldsymbol{\chi}) = \mathbf{f}_\lambda^*$, so that Eqn (52) becomes:

$$\phi_\lambda(\psi_{j_\lambda}, 0; \boldsymbol{\chi}) = \psi_{j_\lambda}(\mathbf{a}_\lambda + E_\lambda \mathbf{f}_\lambda^*) = 0,$$

where the zero flux condition follows since $\mathbf{f}_\lambda^* = -E_\lambda^{-1} \mathbf{a}_\lambda$ for every $\lambda = 1, \ldots, \ell$. Let us denote $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{0}; \boldsymbol{\chi})$ by $\mathbf{f}_{\boldsymbol{\eta}}^*$, which by construction is of the form:

$$(\mathbf{f}_{\boldsymbol{\eta}}^*)^T = \begin{bmatrix} (\mathbf{f}_1^*)^T & \cdots & (\mathbf{f}_\lambda^*)^T & \cdots & (\mathbf{f}_\ell^*)^T \end{bmatrix}. \tag{85}$$

If the network is irreversible, it follows from Proposition 4.3 that the domain $\mathbb{D}_{\eta}(\boldsymbol{\chi})$, is either empty for some $\boldsymbol{\chi} \in \mathbb{U}$, or if not, it does not contain the zero. Hence, $\mathbf{f}_{\eta}^*$ cannot be a strictly positive vector, what in turns results in some species concentrations (associated to the zero entries of $\mathbf{f}_{\eta}^*$) to be zero. Since there is no strictly positive equilibrium vector $\mathbf{c}^*$ complying with a zero flux condition, irreversible networks do not accept complex balanced equilibrium, according to Definition 2.1.

On the other hand, if the network is weakly reversible, Proposition 4.3 asserts that for every $\boldsymbol{\chi} \in \mathbf{U}$, there exists a domain $\mathbb{D}_{\eta}(\boldsymbol{\chi})$, which contains the zero, such that $\mathbf{f}_{\eta}(\mathbf{x}; \boldsymbol{\chi})$ is strictly positive, and consequently $\mathbf{f}_{\eta}^* > 0$. If in addition, $\mathbf{f}_{\eta}^*$ belongs to the set of feasible solutions (Definition 4.2), there exist strictly positive vectors $\mathbf{c} = \exp(\boldsymbol{\xi})$, such that $\ln \mathbf{f}_{\eta}^* = S^T \boldsymbol{\xi}$, which are equilibrium solutions of system (36). According to Definition 2.1, those equilibria are complex balanced.

We recall from Eqns (41), (49) and (51) that $\mathbf{f}_{\eta}^*$ depends on the reaction rate coefficients through E_{λ} and a_{λ} for $\lambda = 1, \ldots, \ell$, which in the last instance determine feasibility, in the sense of Definition 4.2. For convenience, we collect the set of reaction rate coefficients of the network into a vector $\boldsymbol{k} \in \mathbb{R}_{>0}^{\rho}$, where ρ denotes the number of irreversible reaction steps in the network, and introduce the so-called *Horn set* [1], that is formally defined as:

$$\mathcal{H} = \{\boldsymbol{k} \in \mathbb{R}_{>0}^{\rho} \mid \ln \mathbf{f}_{\eta}^* \in \text{Im}(S^T)\}. \tag{86}$$

Note that the set is only meaningful for $\mathbf{f}_{\eta}^* > 0$, which as discussed above requires the network to be weakly reversible. The result we present next shows that the set $\mathcal{H}$ contains all possible reaction rate coefficients leading to complex balanced equilibrium solutions.

Proposition 6.1 *Any chemical reaction network with $\boldsymbol{k} \in \mathcal{H}$ will only accept complex balanced equilibrium solutions.*

Proof: For any $\boldsymbol{k} \in \mathcal{H}$, $\mathbf{f}_{\eta}^*$ is an element of the set of feasible solutions (Definition 4.2), since there exist vectors $\boldsymbol{\xi} \in \mathbb{R}^m$ such that:

$$\ln \mathbf{f}_{\eta}^* = S^T \boldsymbol{\xi}, \tag{87}$$

and as discussed above, the corresponding strictly positive vectors $\mathbf{c} = \exp(\boldsymbol{\xi})$ must be complex balanced equilibrium solutions satisfying:

$$\ln \mathbf{f}_{\eta}^* = S^T \ln \mathbf{c}. \tag{88}$$

In fact, as we will prove next, these are the only possible equilibrium solutions. First, we note that by Proposition 4.4, for any $\boldsymbol{\chi} \in \mathbf{U}$ we have that:

$$\sum_{\lambda} \text{F}_{\lambda}(0; \boldsymbol{\chi}) = 0. \tag{89}$$

Suppose that for a $\boldsymbol{k} \in \mathcal{H}$ there exists a non-zero flux condition that lead to an equilibrium solution. This implies that there exists at least one $\boldsymbol{\chi}^* \in \mathbf{U}$ and $\mathbf{x}^* \in \mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}^*)$ with $\mathbf{x}^* \neq \mathbf{0}$ such that $\mathbf{f}_{\boldsymbol{\eta}}(\mathbf{x}^*; \boldsymbol{\chi}^*)$ is feasible, and therefore relation (66) applies, so that:

$$\sum_\lambda \mathrm{F}_\lambda(x_\lambda^*; \boldsymbol{\chi}^*) = 0, \tag{90}$$

Since the network is weakly reversible, by Proposition 4.3 we have that the domain $\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}^*) = \mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi}^*) \cap \mathbb{D}_0$ is non-empty, contains the zero, and can be partitioned as:

$$\mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}^*) = \mathbb{D}_{\boldsymbol{\eta}}^-(\boldsymbol{\chi}^*) \cup \{\mathbf{0}\} \cup \mathbb{D}_{\boldsymbol{\eta}}^+(\boldsymbol{\chi}^*),$$

with $\mathbb{D}_{\boldsymbol{\eta}}^-(\boldsymbol{\chi}^*) = \mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi}^*) \cap \mathbb{R}_{<0}^\ell$ and $\mathbb{D}_{\boldsymbol{\eta}}^+(\boldsymbol{\chi}^*) = \mathbb{X}_{\boldsymbol{\eta}}(\boldsymbol{\chi}^*) \cap \mathbb{R}_{>0}^\ell$. Since $\mathbf{x}^* \in \mathbb{D}_{\boldsymbol{\eta}}(\boldsymbol{\chi}^*)$ and $\mathbf{x}^* \neq \mathbf{0}$, then it either belongs to $\mathbb{D}_{\boldsymbol{\eta}}^-(\boldsymbol{\chi}^*)$ or to $\mathbb{D}_{\boldsymbol{\eta}}^+(\boldsymbol{\chi}^*)$.

Suppose that $\mathbf{x}^* \in \mathbb{D}_{\boldsymbol{\eta}}^-(\boldsymbol{\chi}^*)$, then we have that $x_\lambda^* < 0$ for every $\lambda = 1, \cdots, \ell$. By Theorem 5.1, every function $\mathrm{F}_\lambda(x_\lambda; \boldsymbol{\chi}^*)$ in (66) is monotonous decreasing. Thus, for every λ, the following strict inequalities hold:

$$\mathrm{F}_\lambda(0; \boldsymbol{\chi}^*) < \mathrm{F}_\lambda(x_\lambda^*; \boldsymbol{\chi}^*).$$

The summation over λ results in:

$$\sum_\lambda \mathrm{F}_\lambda(0; \boldsymbol{\chi}^*) < \sum_\lambda \mathrm{F}_\lambda(x_\lambda^*; \boldsymbol{\chi}^*) = 0,$$

what is in contradiction with expression (89). A similar argument for $\mathbf{x}^* \in \mathbb{D}_{\boldsymbol{\eta}}^+(\boldsymbol{\chi}^*)$ leads to:

$$\sum_\lambda \mathrm{F}_\lambda(0; \boldsymbol{\chi}^*) > \sum_\lambda \mathrm{F}_\lambda(x_\lambda^*; \boldsymbol{\chi}^*) = 0,$$

which again is in contradiction with (89). This proves that for any $\boldsymbol{k} \in \mathcal{H}$, the set of feasible solutions contains just one element $\mathbf{f}_{\boldsymbol{\eta}}^*$, which corresponds to complex balanced equilibrium solutions. $\qquad \square$

Proposition 6.2 *For each $\boldsymbol{k} \in \mathcal{H}$, there exists exactly one complex balanced equilibrium in each positive stoichiometric compatibility class, and this equilibrium is locally asymptotically stable within the corresponding stoichiometric compatibility class. Furthermore, if the reaction network consists of one linkage class, then the asymptotic stability of the equilibrium point corresponding to any $k \in \mathcal{H}$ within its stoichiometric compatibility class is global.*

Proof: As discussed above, for a given $\boldsymbol{k} \in \mathcal{H}$, the set of feasible solutions contains just one element $\mathbf{f}_{\boldsymbol{\eta}}^*$. Let $\mathbf{c}_0 \in \mathbb{R}_{>0}^m$ be one (complex balanced) equilibrium point so that according to (88) we have that $\ln \mathbf{f}_{\boldsymbol{\eta}}^* = S^T \ln \mathbf{c}_0$. Then, any (complex balanced) equilibrium satisfies:

$$S^T(\ln \mathbf{c} - \ln \mathbf{c}_0) = 0, \tag{91}$$

which coincides with the set $\mathcal{U}(\mathbf{c}_0)$ defined as (B.1) in Proposition B.1. From this proposition, it follows that the set contains exactly one element in each positive stoichiometric compatibility class.

That each equilibrium is locally asymptotically stable follows from a standard result presented in [22] (Lecture 5, Proposition 5.3) and summarized in Appendix B (Proposition B.2). The global stability of the complex balanced equilibria in the single linkage class case is proved in [3]. $\qquad\qquad\square$

Remark 6.1 *For weakly reversible deficiency zero reaction networks, $\mathrm{Im}(S^T)$ spans $\mathbb{R}^{n-\ell}$, what in turn implies that any vector of reaction rate coefficients $\boldsymbol{k} \in \mathbb{R}^{\rho}_{>0}$ will be an element of the Horn set (86). Thus, from Propositions 6.1 and 6.2, it follows that any equilibrium solution will be unique (one in each positive stoichiometric compatibility class) and locally asymptotically stable. If the network is irreversible, positive equilibrium does not exist. Such conclusions have been formally stated in the so-called Deficiency Zero Theorem. [23]. Additionally, we remark here that according to recent results, the stability of any complex balanced equilibrium point is most probably global [14].*

Remark 6.2 *If the reaction network is elementary and compatible with thermodynamics (this implying detailed balancing), any allowed reaction constant for the network must be in $\mathcal{H}$. In this way, the definition of the Horn set could be considered as an alternative statement of the Wegscheider conditions (see [28] for a classical statement of the conditions).*

Example: The Horn set for a weakly reversible reaction

Let us consider the example discussed in Subsection 4.3 of a one linkage class network of deficiency $\delta = 2$. The corresponding graph structure, stoichiometry, and the set of possible parameters is depicted in Figure 7. For this 2-parameter network, the Horn set (86) is obtained by finding those (ϵ, β) that make $\ln \mathbf{f}^*$ orthogonal to $\mathbf{g}^1$ and $\mathbf{g}^2$. Note that this implies that $\ln \mathbf{f}^*$ lies in $\mathrm{Range}(S^T)$. The conditions can be written as:

$$\begin{bmatrix} 1 & 0 & -2 \\ 0 & 1 & -3 \end{bmatrix} \ln \begin{pmatrix} \epsilon/\beta \\ 1 \\ \epsilon/\beta \end{pmatrix} = 0. \tag{92}$$

This results in a set with parameters satisfying $\alpha = \beta$, that lead to complex balanced solutions. By construction, $\ln \mathbf{f}(0; \boldsymbol{\chi}) = \mathbf{0}$ for every $\boldsymbol{\chi}$, and therefore $\mathrm{F}(0; \boldsymbol{\chi}) = 0$. Since $\mathrm{F}(x; \boldsymbol{\chi})$ is monotonous decreasing, only complex balanced solutions exist for parameters in the Horn set.

6.2 The Deficiency One Theorem revisited

Next, we present a result that might be a basis for an alternative proof of the deficiency one theorem for weakly reversible reaction networks. The theorem was originally proposed by [24] and recently discussed by [8], employing in both cases a graph theoretical formalism. The argument we propose builds on the following observations: On the one hand, the existence of a basis in the kernel of S that has at most one vector $\mathbf{g}^r$ per linkage class. On the other hand, a particular orthogonal structure for such basis.

The structure is such that for each element of the basis, the only possible nonzero coordinates must be at the location of the complexes that correspond to the linkage class the vector is associated to. Orthogonality on a normalized basis is formally expressed as:

$$(\mathbf{g}^i)^T \mathbf{g}^j = \delta_{ij}, \tag{93}$$

where δ_{ij} denotes the Kronecker delta. The structure of the vectors is illustrated in Figure 9, for a network consisting of 3 linkage classes, with the grey areas representing the non-zero vector coordinates. As sketched in the same figure, that particular structure of the $\mathbf{g}^r$ vectors decouples the corresponding feasibility conditions (Lemma 4.2) along linkage classes, so to have one feasibility function per linkage class. As we will see, monotonicity of such functions (Theorem 5.1) will ensure uniqueness.
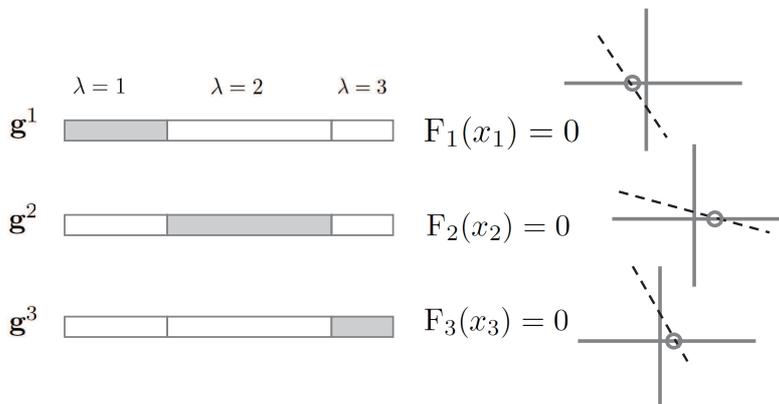

Figure 9: Vectors $\mathbf{g}^r$ form a basis of the kernel of S where the grey areas indicate the only possible non-zero coordinates. This structure decouples feasibility conditions (at most one per linkage class). Monotonicity of $F_\lambda(x_\lambda)$, schematically represented as discontinuous lines at the right of the figure, then leads to just one solution per linkage class.

Theorem 6.1 *Let us consider a weakly reversible reaction network with ℓ linkage classes such that $\delta = \sum_\lambda \delta_\lambda$, where δ_λ is either 0 or 1. Then, there will be a unique equilibrium in each positive stoichiometric compatibility class.*

Proof: Let t be the number of linkage classes having deficiency 1. Since for each linkage class, δ_λ can be either zero or 1, then $t \leq \ell$. Assume, without loss of generality, that the deficiencies of linkage classes $\lambda = 1, \ldots, t$ are 1, whereas for the remaining $\lambda = t+1, \ldots, \ell$, linkage deficiencies are $\delta_\lambda = 0$.

For the first t linkage classes, let the non-zero vectors $\mathbf{p}^\lambda \in \mathbb{R}^{N_\lambda - 1}$ (for $\lambda = 1, \ldots, t$) be the basis associated to the kernel of S_λ so that $S_\lambda \mathbf{p}^\lambda = 0$. From the assumption, we have that:

$$\delta = \sum_\lambda \delta_\lambda = t,$$

and a basis $\{\mathbf{g}^\lambda \mid \lambda = 1, \ldots, t\}$ for the kernel of S satisfying (93) under proper normalization can be constructed as:

$$
\begin{array}{c}
(\mathbf{g}^1)^T = [\,(\mathbf{p}^1)^T \quad \cdots \quad (\mathbf{0}_\lambda)^T \quad \cdots \quad (\mathbf{0}_t)^T \quad \cdots \quad (\mathbf{0}_\ell)^T\,] \\
\vdots \qquad \vdots \qquad \vdots \qquad \vdots \qquad \vdots \\
(\mathbf{g}^\lambda)^T = [\,(\mathbf{0}_1)^T \quad \cdots \quad (\mathbf{p}^\lambda)^T \quad \cdots \quad (\mathbf{0}_t)^T \quad \cdots \quad (\mathbf{0}_\ell)^T\,] \\
\vdots \qquad \vdots \qquad \vdots \qquad \vdots \qquad \vdots \\
(\mathbf{g}^t)^T = [\,(\mathbf{0}_1)^T \quad \cdots \quad (\mathbf{0}_1)^T \quad \cdots \quad (\mathbf{p}^t)^T \quad \cdots \quad (\mathbf{0}_\ell)^T\,]
\end{array}
\tag{94}
$$

where $\mathbf{0}_\lambda \in \mathbb{R}^{N_\lambda - 1}$ for $\lambda = 1, \ldots, \ell$ are zero vectors. Note that under the assumptions of the theorem, for any equivalent basis $\{\widehat{\mathbf{g}}^\lambda \mid \lambda = 1, \ldots, t\}$ of the kernel of S, the sub-vectors $\widehat{\mathbf{g}}_\lambda^\lambda$ in (15) must satisfy that $S_\lambda \widehat{\mathbf{g}}_\lambda^\lambda = 0$ for $\lambda = 1, \ldots, t$. This is so since each element $\widehat{\mathbf{g}}^\lambda$ of the basis can be expressed as a linear combination of (94), what in addition implies that the vectors $\widehat{\mathbf{g}}_\lambda^\lambda$ and $\mathbf{p}^\lambda$ are parallel. Equivalently, there exists a non-zero scalar μ_λ such that $\widehat{\mathbf{g}}_\lambda^\lambda = \mu_\lambda \mathbf{p}^\lambda$.

Using the basis $\{\mathbf{g}^\lambda \mid \lambda = 1, \ldots, t\}$, conditions (64) in Lemma 4.2 can be written as:

$$(\mathbf{g}^\lambda)^T \ln \mathbf{f}_\eta(\mathbf{x}; \boldsymbol{\chi}) = 0, \quad \text{for} \quad \lambda = 1, \cdots, t. \tag{95}$$

Taking into account the structure of the basis components (94), conditions in (95) reduce to:

$$
\begin{array}{ccc}
(\mathbf{p}^1)^T & \ln & (\mathbf{f}_1^* + z_1 E_1^{-1} \mathbf{p}^1) = & 0 \\
& \vdots & & \vdots \\
(\mathbf{p}^\lambda)^T & \ln & (\mathbf{f}_\lambda^* + z_\lambda E_\lambda^{-1} \mathbf{p}^\lambda) = & 0 \\
& \vdots & & \vdots \\
(\mathbf{p}^t)^T & \ln & (\mathbf{f}_t^* + z_t E_t^{-1} \mathbf{p}^t) = & 0
\end{array}
\tag{96}
$$

where $z_\lambda = x_\lambda \chi_\lambda$ for $\lambda = 1, \ldots, t$. The left hand side of each of the expressions in (96), that we denote as $\mathrm{F}_\lambda(z_\lambda)$ for $(\lambda = 1, \ldots, t)$, is of the form (71) (Section 5). According to Theorem 5.1, each of those functions is monotonous decreasing and because of (72), it becomes zero at a point $z_\lambda^* \in \mathbb{X}_\lambda$. Therefore, the set of feasible solutions contains just one element:

$$\mathbf{f}_\eta^T(z_1^*, \ldots, z_t^*) = [\; \mathbf{f}_1^T(z_1^*) \quad \cdots \quad \mathbf{f}_\lambda^T(z_\lambda^*) \quad \cdots \quad \mathbf{f}_t^T(z_t^*) \quad (\mathbf{f}_{t+1}^*)^T \quad \cdots \quad (\mathbf{f}_\ell^*)^T \;], \tag{97}$$

with $\mathbf{f}_\lambda(z_\lambda^*) = \mathbf{f}_\lambda^* + z_\lambda^* \mathbf{h}_\lambda$ for $\lambda = 1, \cdots, t$.

Similarly to the proof of Proposition 6.2, let $\mathbf{c}_0 \in \mathbb{R}^m_{>0}$ be one equilibrium point so that according to (88), $\mathbf{f}^T_{\boldsymbol{\eta}}(z^*_1, \ldots, z^*_t) = S^T \ln \mathbf{c}_0$. Then, any equilibrium satisfies:
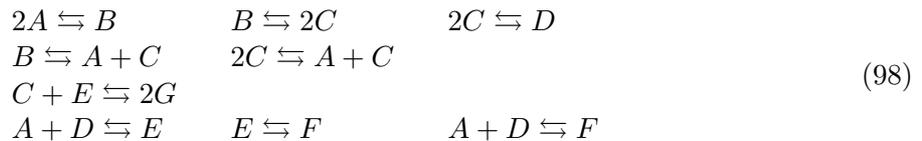
$$S^T (\ln \mathbf{c} - \ln \mathbf{c}_0) = 0,$$

which coincides with the set (B.1). Finally, from Proposition B.1, it follows that the set contains exactly one element in each positive stoichiometric compatibility class. $\qquad\square$

As a final remark, we note that this result allows us to conclude uniqueness of equilibria in each positive stoichiometric compatibility class (although not stability), for networks with deficiency other than zero, provided that feasibility conditions in Lemma 4.2 can be decoupled along linkage classes, as discussed above.

6.3 A complex network satisfying the deficiency one theorem

Let us consider a reaction network involving $m = 7$ chemical species, we label with capital letters from A to G. The (reversible) reaction steps that take place are:

$$
\begin{array}{lll}
2A \leftrightharpoons B & B \leftrightharpoons 2C & 2C \leftrightharpoons D \\
B \leftrightharpoons A + C & 2C \leftrightharpoons A + C & \\
C + E \leftrightharpoons 2G & & \\
A + D \leftrightharpoons E & E \leftrightharpoons F & A + D \leftrightharpoons F
\end{array}
\tag{98}
$$

This particular reaction network comprises $n = 10$ complexes and $\ell = 3$ linkage classes, we represent in graph form in Figure 10, with explicit indication of the species (Figure 10a) as well as in terms of numbered complexes (Figure 10b).
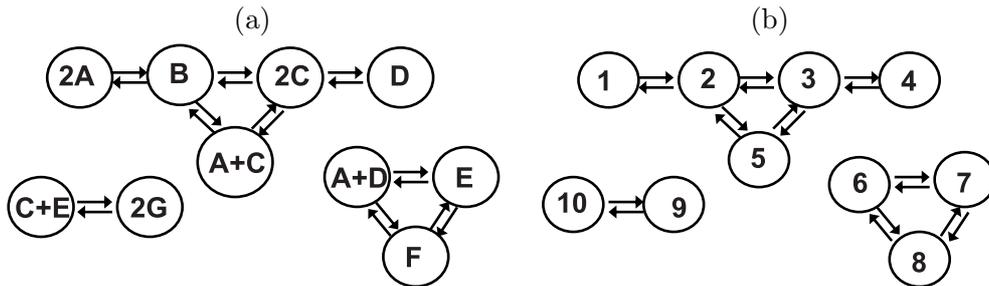

Figure 10: Graph representation for the reaction network. (a) The species that are part of each complex are explicitly indicated. (b) The same graph described in terms of numbered complexes.

Complexes are grouped by linkage class in the sets $\mathcal{L}_1 = \{1, 2, 3, 4, 5\}$, $\mathcal{L}_2 = \{6, 7, 8\}$ and $\mathcal{L}_3 = \{9, 10\}$. The stoichiometry associated to the complexes is given (column-wise) in the

following molecularity matrix (Section 2.1):

$$Y = \begin{bmatrix} 2 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 2 & 0 & 1 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 2 & 0 \end{bmatrix}. \tag{99}$$

Choosing $j_1 = 1$, $j_2 = 6$ and $j_3 = 9$, as the reference complexes, matrices S_λ, at the right of expression (36), become:

$$S_1 = \begin{bmatrix} -2 & -2 & -2 & -1 \\ 1 & 0 & 0 & 0 \\ 0 & 2 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad S_2 = \begin{bmatrix} -1 & -1 \\ 0 & 0 \\ 0 & 0 \\ -1 & -1 \\ 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix}, \quad S_3 = \begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ -2 \end{bmatrix}.$$

Net reaction fluxes take the form:

$$\begin{aligned} \phi_2(\boldsymbol{\psi}) &= k_{1,2}\psi_1 + k_{3,2}\psi_3 + k_{5,2}\psi_5 - (k_{2,1} + k_{2,3} + k_{2,5})\psi_2 \\ \phi_3(\boldsymbol{\psi}) &= k_{2,3}\psi_2 + k_{4,3}\psi_4 + k_{5,3}\psi_5 - (k_{3,2} + k_{3,4} + k_{3,5})\psi_3 \\ \phi_4(\boldsymbol{\psi}) &= k_{3,4}\psi_3 - k_{4,3}\psi_4 \\ \phi_5(\boldsymbol{\psi}) &= k_{2,5}\psi_2 + k_{3,5}\psi_3 - (k_{5,2} + k_{5,3})\psi_5 \\ \phi_7(\boldsymbol{\psi}) &= k_{6,7}\psi_6 + k_{8,7}\psi_8 - (k_{7,6} + k_{7,8})\psi_7 \\ \phi_8(\boldsymbol{\psi}) &= k_{6,8}\psi_6 + k_{7,8}\psi_7 - (k_{8,6} + k_{8,7})\psi_8 \\ \phi_{10}(\boldsymbol{\psi}) &= k_{9,10}\psi_9 - k_{10,9}\psi_{10} \end{aligned} \tag{100}$$

The remaining fluxes $\phi_1(\boldsymbol{\psi})$, $\phi_6(\boldsymbol{\psi})$ and $\phi_9(\boldsymbol{\psi})$, associated to the reference complexes, are obtained by means of relation (8).

The dimension of the stoichiometric subspace, which coincides with the rank of matrix $S = \begin{bmatrix} S_1 & S_2 & S_3 \end{bmatrix}$, is $s = 6$, and renders a network deficiency $\delta = 10 - 3 - 6 = 1$. Hence, the kernel of S is one dimensional with a basis $\mathbf{g}^1 = \begin{pmatrix} 0 & -1/2 & 0 & 1 & 0 & 0 & 0 \end{pmatrix}^T$. As shown in Section 2.2, we identify the following three sub-vectors in $\mathbf{g}^1$ that solve (16):

$$\begin{aligned} g_1^1 &= \begin{pmatrix} 0 & -1/2 & 0 & 1 \end{pmatrix}^T, \\ g_2^1 &= \begin{pmatrix} 0 & 0 \end{pmatrix}^T, \\ g_3^1 &= (0)^T. \end{aligned}$$

The canonical representation of the equilibrium set will be expressed in terms of matrices M_λ that appear in Eqn (37). From the expressions (100) for the fluxes, we have that:

$$M_1 = \begin{bmatrix} -k_{1,2} & k_{2,1} & 0 & 0 & 0 \\ k_{1,2} & -(k_{2,1} + k_{2,3} + k_{2,5}) & k_{3,2} & 0 & k_{5,2} \\ 0 & k_{2,3} & -(k_{3,2} + k_{3,4} + k_{3,5}) & k_{4,3} & k_{5,3} \\ 0 & 0 & k_{3,4} & -k_{4,3} & 0 \\ 0 & k_{2,5} & k_{3,5} & 0 & -(k_{5,2} + k_{5,3}) \end{bmatrix} \tag{101}$$

$$M_2 = \begin{bmatrix} -(k_{6,7} + k_{6,8}) & k_{7,6} & k_{8,6} \\ k_{6,7} & -(k_{7,6} + k_{7,8}) & k_{8,7} \\ k_{6,8} & k_{7,8} & -(k_{8,6} + k_{8,7}) \end{bmatrix}, \quad M_3 = \begin{bmatrix} -k_{9,10} & k_{10,9} \\ k_{9,10} & -k_{10,9} \end{bmatrix}. \quad (102)$$

Comparing each matrix with the structure given in (41), we get for each linkage class:

$$E_1 = \begin{bmatrix} -(k_{2,1} + k_{2,3} + k_{2,5}) & k_{3,2} & 0 & k_{5,2} \\ k_{2,3} & -(k_{3,2} + k_{3,4} + k_{3,5}) & k_{4,3} & k_{5,3} \\ 0 & k_{3,4} & -k_{4,3} & 0 \\ k_{2,5} & k_{3,5} & 0 & -(k_{5,2} + k_{5,3}) \end{bmatrix} \quad (103)$$

$$E_2 = \begin{bmatrix} -(k_{7,6} + k_{7,8}) & k_{8,7} \\ k_{7,8} & -(k_{8,6} + k_{8,7}) \end{bmatrix}, \quad E_3 = \begin{bmatrix} -k_{10,9} \end{bmatrix} \quad (104)$$

$$\begin{array}{lll} a_1 = \begin{bmatrix} k_{1,2} & 0 & 0 & 0 \end{bmatrix}^T & a_2 = \begin{bmatrix} k_{6,7} & k_{6,8} \end{bmatrix}^T & a_3 = \begin{bmatrix} k_{9,10} \end{bmatrix}^T \\ b_1 = \begin{bmatrix} k_{2,1} & 0 & 0 & 0 \end{bmatrix}^T & b_2 = \begin{bmatrix} k_{7,6} & k_{8,6} \end{bmatrix}^T & b_3 = \begin{bmatrix} k_{10,9} \end{bmatrix}^T \end{array} \quad (105)$$

Expressions of the form (51), which describe the family of solutions, become as follows:

$$\begin{aligned} \mathbf{f}_1(x_1) &= \mathbf{f}_1^* + x_1 \mathbf{h}_1 \\ \mathbf{f}_2(x_2) &= \mathbf{f}_2^* \\ \mathbf{f}_3(x_3) &= \mathbf{f}_3^* \end{aligned} \quad (106)$$

where vectors at the right hand side, for the parameters given in Table 1, become:

$$\begin{array}{ll} \mathbf{f}_1^* = (1.0000 \quad 30.1818 \quad 75.4545 \quad 2.1091)^T, & \mathbf{f}_2^* = (0.2000 \quad 0.8571)^T \\ \mathbf{h}_1 = (-0.2500 \quad -7.5455 \quad -18.8636 \quad -1.0273)^T & \mathbf{f}_3^* = (0.2500) \end{array} \quad (107)$$

As it can be seen in Figure 11a, function $F_1(x_1) = (g_1^1)^T \ln f_1(x_1)$ is monotonous decreasing,

Table 1: Reaction rate coefficients for the network

$k_{1,2} = 2.0$	$k_{2,1} = 2.0$	$k_{2,3} = 16.0$	$k_{3,2} = 0.5$	$k_{3,4} = 2.5$	$k_{4,3} = 1.0$
$k_{2,5} = 1.2$	$k_{5,2} = 1.0$	$k_{3,5} = 0.1$	$k_{5,3} = 1.0$	$k_{6,7} = 1.0$	$k_{7,6} = 1.0$
$k_{7,8} = 10.0$	$k_{8,7} = 1.4$	$k_{8,6} = 2.1$	$k_{6,8} = 1.0$	$k_{9,10} = 1.0$	$k_{10,9} = 4.0$

with one solution (intersection with the x-axis) at $x_1^* = -6.69$ as asserted by Theorem 6.1. Another example is represented in Figure 11b, for a network with reaction rates as in Table 1, except for constants $k_{2,1}$ and $k_{5,2}$ which now take the value 10. The domain of the function is now constrained to the interval $\mathbb{X}_1 = (L_1^-, L_1^+)$, with $L_1^- = -0.6154$ and $L_1^+ = +0.3636$. Vector $\mathbf{h}_1$ for this parameter set becomes $\mathbf{h}_1 = (-0.0500 \quad 0.1857 \quad 0.1857 \quad -0.0786)^T$. For this case the function crosses the x-axis at $x_1^* = -0.5854$.

In order to compute all possible equilibrium solutions in the concentration space, we make use of $\mathbf{f}_\eta^T(\mathbf{x}^*) = \begin{bmatrix} \mathbf{f}_1^T(x_1^*) & \mathbf{f}_2^{*T} & \mathbf{f}_3^{*T} \end{bmatrix}$, where $\mathbf{f}_1^T(x_1^*)$ for $x_1^* = -6.69$ and $x_1^* = -0.5854$ takes, respectively, the values:

$$\begin{aligned} \mathbf{f}_1(x_1^*) &= (2.6725 \quad 80.6609 \quad 201.6523 \quad 8.9815)^T, \\ \mathbf{f}_1(x_1^*) &= (0.2293 \quad 0.0056 \quad 0.0056 \quad 0.0746)^T. \end{aligned}$$
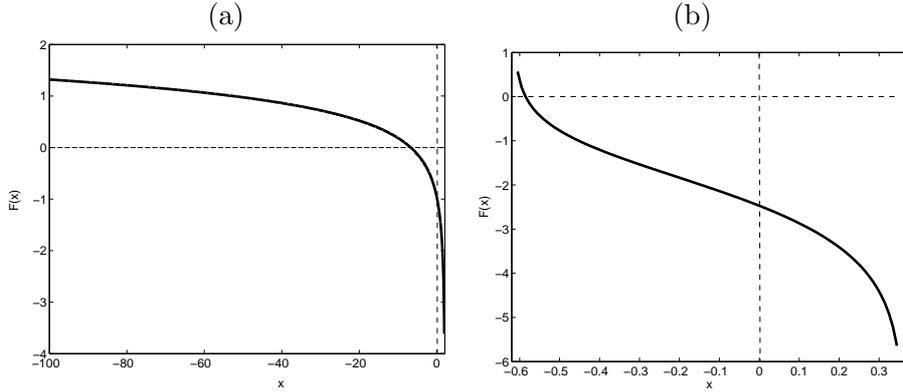
41

Figure 11: Function $F_1(x) = (g_1^1)^T \ln f_1(x)$ corresponding to linkage class 1. Note that for the other linkage classes the functions are zero since vectors g_2^1 and g_3^1 are identically zero. In (a) the function is represented for the set of rate coefficients in Table 1. In (b) the function is represented for two modified rate constants, $k_{2,1} = k_{5,2} = 10.0$.

The set of equilibrium concentrations is then computed by solving $\ln \mathbf{f_\eta} = S^T \ln \mathbf{c}$. In particular, for this network we can express the first 6 chemical species in terms of species G, what leads to a straight line in the $\ln \mathbf{c}$-space, which intersects the interior of any positive stoichiometric compatibility class defined in (17) (with $B = \begin{pmatrix} 1/2 & 1 & 1/2 & 1 & 3/2 & 3/2 & 1 \end{pmatrix}^T$) in just one point.

7 Conclusions

This contribution concentrates on the study of feasibility conditions to identify admissible equilibria for weakly reversible mass action law (MAL) systems. To that purpose, a flux-based form of the model equations describing the time evolution of the species concentration has been exploited, in combination with results from the theory of linear compartmental systems to develop a canonical representation of the equilibrium set. Ingredients of such representation include the so-called family of solutions, with the corresponding positivity conditions, and the feasibility functions employed to characterize the set of feasible (equilibrium) solutions.

One main result of this contribution is that the introduced feasibility functions are monotonously decreasing on their domain. This allows us to establish connections with classical results in CRNT related to the existence and uniqueness of equilibria within positive stoichiometric compatibility classes. In particular, we employ monotonicity to identify regions in the set of possible reaction rate coefficients leading to complex balancing, and to conclude uniqueness of equilibria for a class of positive deficiency networks. It is our hope that the proposed results might support the understanding of the deficiency one theorem from a different point of view, with the possibility of an alternative proof.

A number of examples of different complexity are employed to illustrate the notions presented and their relations. As the examples show, all components used for the characterization of equilibria, in particular the family of solutions and the feasibility functions, can be computed efficiently in an algorithmic way, even for large kinetic models. Future work will be focused on the constructive application of these functions for the computational search or design of networks with unique equilibria.

Acknowledgements

References

[1] A. A. Alonso and G. Szederkenyi. On the geometry of equilibrium solutions in kinetic systems obeying the mass action law. *In Proc. of International Symposium on Advanced Control of Chemical Processes -ADCHEM 2012, Singapore*, 2012.

[2] A. A. Alonso and B. E. Ydstie. Stabilization of distributed systems using irreversible thermodynamics. *Automatica*, 37:1739–1755, 2001.

[3] D.F. Anderson. A proof of the global attractor conjecture in the single linkage class case. *SIAM J. Appl. Math.*, 71:1487–1508, 2011.

[4] R. Aris. Prolegomena to the rational analysis of systems of chemical reactions. *Arch. Rational Mech. Anal.*, 19(2):81–99, 1965.

[5] R. Aris. Prolegomena to the rational analysis of systems of chemical reactions ii. some addenda. *Arch. Rational Mech. Anal.*, 27(5):356–364, 1968.

[6] K. J. Arrow. A "dynamic" proof of the Frobenius-Perron theorem for metzler matrices. Technical Report 542, The Economic Series, Institute for Mathematical Studies and Social Sciences. Technical Report N0, 1989.

[7] A. Berman and R.J. Plemmons. *Nonnegative Matrices in the Mathematical Sciences.* SIAM, Philadelphia, 1994.

[8] B. Boros. Notes on the deficiency-one theorem: multiple linkage classes. *Math. Biosci.*, 235:110–122, 2012.

[9] V. Chellaboina, S.P. Bhat, W.M. Haddad and D.S. Bernstein. Modeling and analysis of mass-action kinetics – nonnegativity, realizability, reducibility, and semistability. *IEEE Control Syst. Mag.*, 29:60–78, 2009.

[10] B. L. Clarke. Theorems on chemical network stability. *J. Chem. Phys.*, 62:773–775, 1975.

[11] B. L. Clarke. *Stability of Complex Reaction Networks*, volume XLIII of *Advances in Chemical Physics*. Wiley, 1980.

[12] C. Conradi and D. Flockerzi. Multistationarity in mass action networks with applications to ERK activation. *J. Math. Biol.*, 65:107–156, 2012.

[13] C. Conradi, D. Flockerzi, J. Raisch and J. Stelling. Subnetwork analysis reveals dynamic features of complex (bio)chemical networks. *Proc. Natl. Acad. Sci. U.S.A.*, 104:19175–19180, 2007.

[14] G. Craciun. Toric differential inclusions and a proof of the global attractor conjecture. *arXiv:1501.02860 [math.DS]*, 2015.

[15] G. Craciun, A. Dickenstein, A. Shiu and B. Sturmfels. Toric dynamical systems. *J. of Symb. Comput.*, 44:1551–1565, 2009.

[16] 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.

[17] 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.

[18] G. Craciun and C. Pantea. Identifiability of chemical reaction networks. *J. Math. Chem.*, 44:244–259, 2008.

[19] P. Érdi and J. Tóth. *Mathematical Models of Chemical Reactions. Theory and Applications of Deterministic and Stochastic Models*. Manchester University Press, Manchester, 1989.

[20] L. Farina and S. Rinaldi. *Positive Linear Systems – Theory and Applications*. Wiley, 2000.

[21] M. Feinberg. Complex balancing in general kinetic systems. *Arch. Rational Mech. Anal.*, 49:187–194, 1972.

[22] M. Feinberg. Lectures of chemical reaction networks. Technical report, University of Wisconsin, 1979.

[23] M. Feinberg. Chemical reaction network structure and the stability of complex isothermal reactors. *Chem. Eng. Sci.*, 42:2229–2268, 1987.

[24] M. Feinberg. The existence and uniqueness of steady states for a class of chemical reaction networks. *Arch. Rational Mech. Anal.*, 132:311–370, 1995.

[25] M. Feinberg and F. Horn. Chemical mechanism structure and the coincidence of the stoichiometric and kinetic subspaces. *Arch. Rational Mech. Anal.*, 66:83–97, 1977.

[26] D. Fife. Which linear compartmental systems contain traps? *Math. Biosci.*, 14:311–315, 1972.

[27] G.H. Golub and C.F. Van Loan. *Matrix Computations, 3rd Ed.* Johns Hopkins University Press, Baltimore, 1996.

[28] A.N. Gorban, E.M. Mirkes and G.S. Yablonsky. Thermodynamics in the limit of irreversible reactions. *Physica A*, 392:1318–1335, 2013.

[29] A.N. Gorban and M. Shahzad. The Michaelis-Menten-Stueckelberg Theorem. *Entropy*, 13:966–1019, 2011.

[30] A.N. Gorban and G.S. Yablonsky. Extended detailed balance for systems with irreversible reactions. *Chem. Eng. Sci.*, 63:5388–5399, 2011.

[31] W. M. Haddad, V. Chellaboina and Q. Hui. *Nonnegative and Compartmental Dynamical Systems.* Princeton University Press, 2010.

[32] K. M. Hangos. Engineering model reduction and entropy-based Lyapunov functions in chemical reaction kinetics. *Entropy*, 12(4):772–797, 2010.

[33] B. Hernández-Bermejo, V. Fairén and L. Brenig. Algebraic recasting of nonlinear ODEs into universal formats. *J. Phys. A, Math. Gen.*, 31:2415–2430, 1998.

[34] F. Horn. Necessary and sufficient conditions for complex balancing in chemical kinetics. *Arch. Rational Mech. Anal.*, 49:172–186, 1972.

[35] F. Horn and R. Jackson. General mass action kinetics. *Arch. Rational Mech. Anal.*, 47:81–116, 1972.

[36] M. D. Johnston, D. Siegel and G. Szederkenyi. Computing weakly reversible linearly conjugate chemical reaction networks with minimal deficiency. *Math. Biosci.*, 241:88–98, 2013.

[37] N.G. Van Kampen. *Stochastic Processes in Physics and Chemistry.* Elsevier, 2nd Ed., 1981.

[38] W.O. Kermack and A.G. McKendrick. A contribution to the mathematical theory of epidemics. *Proceedings of the Royal Society A: Mathematical, Physical and Engineering Sciences*, 115(772):700–721, 1927.

[39] H. K. Khalil. *Nonlinear Systems.* Prentice-Hall, 1996.

[40] F.J. Krambeck. The mathematical structure of chemical kinetics in homogeneous single-phase systems. *Arch. Rational Mech. Anal.*, 38(5):317–347, 1970.

[41] G. Liptak, G. Sederkenyi and K.M. Hangos. Kinetic feedback design for polynomial systems. *J. Process Control*, 41:56–66, 2016.

[42] M. Mincheva and G. Cracium. Multigraph conditions for multistability, oscillations and pattern formation in biochemical reaction networks. *Proc. IEEE*, 96(8):1281–1291, 2008.

[43] S. Muller and G. Regensburger. Generalized mass action systems: complex balancing equilibria and sign vectors of the stoichiometric and kinetic-order subspaces. *SIAM J. Appl. Math.*, 72:1926–1947, 2012.

[44] I. Otero-Muras, J.R. Banga and A.A. Alonso. Exploring multiplicity conditions in enzymatic reaction networks. *Biotechnol. Prog.*, 25(3):619–631, 2009.

[45] I. Otero-Muras, J.R. Banga and A.A. Alonso. Characterizing multistationarity regimes in biochemical reaction networks. *PLoS ONE*, 7(7):e39194, 2012.

[46] M. Perez-Millan, A. Dickenstein, A. Shiu and C. Conradi. Chemical reaction systems with toric steady states. *Bull. Math. Biol.*, 74:1027–1065, 2012.

[47] R. J. Plemmons. M-Matrix Characterizations. I – Nonsingular M-Matrices. *Linear Algebra Appl.*, 18:175–188, 1977.

[48] N. Samardzija, L. D. Greller and E. Wassermann. Nonlinear chemical kinetic schemes derived from mechanical and electrical dynamical systems. *J. Chem. Phys.*, 90 (4):2296–2304, 1989.

[49] N. Z. Shapiro and L. S. Shapley. Mass action laws and the gibbs free energy function. *Journal of the Society for Industrial and Applied Mathematics*, 13(2):353–375, 1965.

[50] G. Szederknyi and K. M. Hangos. Finding complex balanced and detailed balanced realizations of chemical reaction networks. *Journal of Mathematical Chemistry*, 49:1163–1179, 2011.

[51] A. Van der Schaft, S. Rao and B. Jayawardhana. On the mathematical structure of balanced chemical reaction networks governed by mass action kinetics. *SIAM J. Appl. Math.*, 73(2):953–973, 2013.

[52] A. I. Volpert. Differential equations on graphs. *Math. USSR Sbornik*, 17:571–582, 1972.

[53] Y. B. Zeldovich. *Selected Works of Yakov Borisovich Zeldovich, Volume I: Chemical Physics and Hydrodynanics*, chapter Proof of the Uniqueness of the Solution of the Equations of the Law of Mass Action, pages 144–147. Princeton University Press, 2014.

A   Some results required to prove Theorem 5.1

Lemma A.1 *Let $H \in \mathbb{R}^{n \times n}$ be C-Metzler and such that:*

$$H\mathbf{1}_n = -\mathbf{a}, \tag{A.1}$$

with $\mathbf{a} \geq 0$. Let $\mathbf{p} \in \mathbb{R}^n$ (with $\mathbf{p} \neq 0$) be a vector with m positive, r zero and $n - m - r$ negative components satisfying:

$$p_1 \geq \cdots \geq p_k \geq \cdots \geq p_m > 0 > p_{m+r+1} \geq \cdots \geq p_\ell \geq \cdots \geq p_n, \tag{A.2}$$
$$p_{m+1} = \cdots = p_{m+r} = 0,$$

and

$$\mathbf{g} = H\mathbf{p}. \tag{A.3}$$

Then:

$$\sum_{i=1}^{k} g_i \leq 0 \quad \text{for every} \quad 1 \leq k \leq m, \tag{A.4}$$

and

$$\sum_{i=\ell}^{n} g_i \geq 0 \quad \text{for every} \quad m + r + 1 \leq \ell \leq n. \tag{A.5}$$

Moreover:

$$\sum_{i=1}^{m} g_i < 0 \quad \text{and} \quad \sum_{i=m+r+1}^{n} g_i > 0. \tag{A.6}$$

Proof: Multiplying both sides of (A.1) by the scalar $p_k > 0$ and subtracting the result from (A.3), we get:

$$H(\mathbf{p} - p_k \mathbf{1}_n) = \mathbf{g} + p_k \mathbf{a}. \tag{A.7}$$

Summing the first k elements and reordering terms results in:

$$\sum_{i=1}^{k} g_i = \sum_{j=1}^{k-1} \left(\sum_{i=1}^{k} H_{ij} \right) (p_j - p_k) + \sum_{j=k+1}^{n} \left(\sum_{i=1}^{k} H_{ij} \right) (p_j - p_k) + (-p_k) \sum_{i=1}^{k} a_i. \tag{A.8}$$

Since H is C-Metzler, according to Definition 3.1, for every $j = 1, \ldots, k$, with $k = 1, \ldots, n$, we have that:

$$\sum_{i=1}^{k} H_{ij} = -b_j - \sum_{i=k+1}^{n} H_{ij} \leq 0.$$

The first term at the right hand side of (A.8) is non-positive since, by construction, $p_j - p_k \geq 0$ for $j = 1, \ldots, k-1$, and the above summations are non-positive. The second term is non-positive since for every $j = k+1, \ldots, n$ and $i \neq j$, $H_{ij} \geq 0$ and $p_j - p_k \leq 0$. Thus, relation (A.4) follows, since $\mathbf{a}$ is a nonnegative vector and p_k is positive for $k = 1, \ldots, m$, so the third term at the right hand side of (A.8) is also non-positive.

In a similar way we prove (A.5). Substituting $p_\ell < 0$ for p_k in (A.7), we get:

$$H(\mathbf{p} - p_\ell \mathbf{1}_n) = \mathbf{g} + p_\ell \mathbf{a}. \tag{A.9}$$

Summing the elements of $\mathbf{g}$ from $\ell = m + r + 1, \ldots, n$ gives:

$$\sum_{i=\ell}^{n} g_i = \sum_{j=\ell+1}^{n} \left(\sum_{i=\ell}^{n} H_{ij} \right) (p_j - p_\ell) + \sum_{j=1}^{\ell-1} \left(\sum_{i=\ell}^{n} H_{ij} \right) (p_j - p_\ell) + (-p_\ell) \sum_{i=\ell}^{n} a_i. \tag{A.10}$$

Because H is C-Metzler, we have that:

$$\sum_{i=\ell}^{n} H_{ij} \leq 0, \text{ for any } j = \ell, \ldots, n.$$

Thus, the first term at the right hand side of of (A.10) is non-negative, since $(p_j - p_\ell) \leq 0$ for $j = \ell + 1, \ldots, n$. The second term in the expression is also non-negative, since the off-diagonal elements of H are non-negative and $(p_j - p_\ell) \geq 0$ for $j = 1, \ldots, \ell - 1$. Finally, the last term in (A.10) is non-negative due to the negativity of p_ℓ and the non-negativity of $\mathbf{a}$.

Strict inequalities (A.6) can be proven in a straightforward manner from expressions (A.8) and (A.10), if the non-zero components of vector $\mathbf{a} \geq 0$ are within the first m and last $n - m - r$ entries. This would be the case, since the last terms at the right hand side in both equations would be strictly negative (with $k = m$), and positive (with $\ell = m + r + 1$), respectively.

If the non-zero components are not within the first m, nor within the last $n - m - r$ entries, the strict inequalities still hold. In order to prove this point, we express H as:

$$H = \left[\begin{array}{c|c} H_{11} & H_{12} \\ \hline H_{21} & H_{22} \end{array} \right], \tag{A.11}$$

where $H_{11} \in \mathbb{R}^{m \times m}$. Let the first m components of vector $\mathbf{a}$ to be zero. Then, $H_{12} \in \mathbb{R}^{m \times (n-m)}$ in (A.11) must necessarily have at least one positive element (any non-zero element must be positive because H is C-Metzler). Suppose, on the contrary, that H_{12} is a zero matrix. Then, by using (A.1) we have that:

$$H_{11} \mathbf{1}_m = 0,$$

which means that H_{11}, and consequently H, are not invertible, contradicting the fact that H is C-Metzler and therefore, non-singular. Since at least one entry of H_{12} is positive, the second term at the right hand side of (A.8) for $k = m$ must be strictly negative.

A similar line of arguments can be employed if the last $n - m - r$ components of $\mathbf{a}$ are zero, with matrix $H_{22} \in \mathbb{R}^{(n-m-r) \times (n-m-r)}$ and $H_{21} \in \mathbb{R}^{(n-m-r) \times (m+r)}$, instead of H_{11} and H_{12}. Now, we suppose that H_{21} is a zero matrix, what combined with (A.1) leads to:

$$H_{22} \mathbf{1}_{n-m-r} = 0.$$

Thus H_{22}, and consequently H, are not invertible, what is in contradiction with the fact that H is C-Metzler and therefore, non-singular. Since at least one entry of H_{21} must be positive, the second term at the right hand side of (A.10), for $\ell = n - m - r$, must be strictly positive, completing the proof. $\square$

Lemma A.2 *Let $\mathbb{X} \subset \mathbb{R}$ and consider the function $G(x) : \mathbb{X} \mapsto \mathbb{R}$ defined as:*

$$G(x) = \sum_{i=1}^{n} g_i Q_i(x), \tag{A.12}$$

where g_i are the coordinates of the vector $\boldsymbol{g} = H\boldsymbol{p}$, with H and $\boldsymbol{p}$ as in Lemma A.1. For every $i = 1, \ldots, n$ and $x \in \mathbb{X}$, let also have that:

$$Q_1(x) \geq \cdots \geq Q_k(x) \geq \cdots \geq Q_m(x) > 0 > Q_{m+r+1}(x) \geq \cdots \geq Q_\ell(x) \geq \cdots \geq Q_n(x),$$
$$Q_{m+1}(x) = \cdots = Q_{m+r}(x) = 0. \tag{A.13}$$

Then, $G(x) < 0$ for every $x \in \mathbb{X}$.

Proof: First, we note that (A.12) can be re-written as:

$$G(x) = (Q_1(x) - Q_2(x))g_1 + (Q_2(x) - Q_3(x))(g_1 + g_2) + \cdots + (Q_k(x) - Q_{k+1}(x)) \sum_{i=1}^{k} g_i + \cdots + Q_m(x) \sum_{i=1}^{m} g_i +$$

$$Q_{m+r+1}(x) \sum_{i=m+r+1}^{n} g_i + \cdots + (Q_\ell(x) - Q_{\ell-1}(x)) \sum_{i=\ell}^{n} g_i + \cdots + (Q_n(x) - Q_{n-1}(x))g_n, \quad \text{(A.14)}$$

where implicitly, each Q_i is assumed to be a function of x. From (A.13), we have that $Q_i(x) - Q_j(x) \geq 0$ for every $Q_i(x) \geq Q_j(x)$ and $x \in \mathbb{X}$, what implies that $(Q_k(x) - Q_{k+1}(x)) \geq 0$ for every $k = 1, \ldots, m-1$, and $(Q_\ell(x) - Q_{\ell-1}(x)) \leq 0$ for every $\ell = m + r + 1, \ldots, n$. Thus, from Lemma A.1, we have that:

$$G(x) \leq Q_m(x) \sum_{j=1}^{m} g_j + Q_{m+r+1}(x) \sum_{j=m+r+1}^{n} g_j.$$

The signs $Q_m(x) > 0$, $Q_{m+r+1}(x) < 0$ as well as inequalities (A.6), from Lemma A.1, make the right hand side of the above expression strictly negative, what completes the proof. $\square$

Proposition A.1 *Under the conditions of Lemma A.1, let the m positive and the $n - m - r$ negative components of $\boldsymbol{p} \in \mathbb{R}^n$ satisfy:*

$$p_1 \geq \cdots \geq p_{s-1} \geq p_s > p_{s+1} \geq \cdots \geq p_m > 0, \tag{A.15}$$

$$0 > p_{m+r+1} \geq \cdots \geq p_{t-1} > p_t \geq p_{t+1} \geq \cdots \geq p_n. \tag{A.16}$$

Then:

$$\sum_{i=1}^{s} g_i < 0 \quad \text{and} \quad \sum_{i=t}^{n} g_i > 0, \tag{A.17}$$

for some $s = 1, \ldots, m-1$ and $t = m + r + 2, \ldots, n$.

Proof: The line of arguments is similar to that employed in Lemma A.1 to prove (A.6). If the non-zero components of vector $\mathbf{a} \geq 0$ are within the first s and the last $n - t + 1$ entries, it is straightforward to prove strict inequalities from expressions (A.8) and (A.10), for the last terms at the right hand side in both equations (with $k = s$ and $\ell = t$) are strictly negative, and positive, respectively.

If, on the other hand, the first s and the last $n - t + 1$ entries of $\mathbf{a} \geq 0$ are zero, then matrix H, which can be expressed as in (A.11) with $H_{11} \in \mathbb{R}^{s \times s}$, must have for $H_{12} \in \mathbb{R}^{s \times (n-s)}$ at least one positive element. Otherwise, from (A.1), we would have that:

$$H_{11}\mathbf{1}_s = 0,$$

what contradicts the hypothesis that H is C-Metzler and therefore, non-singular. Since at least one entry of H_{12} must be positive, and because of (A.15), $p_j - p_s > 0$ (for $j = s+1, \ldots, n$) the second term at the right hand side of (A.8), for $k = s$, is strictly negative, what proves the first inequality in (A.17).

In order to prove the second inequality, we make use of a similar argument with $H_{22} \in \mathbb{R}^{(n-t+1) \times (n-t+1)}$ in (A.11), to show that $H_{21} \in \mathbb{R}^{(n-t+1) \times (m+r)}$ must have at least one positive entry. From (A.16), we also have that $p_j - p_t > 0$ (for $j = 1, \ldots, t-1$) so the second term at the right hand side of (A.10), for $\ell = t$, must be strictly positive. This proves the second inequality in (A.17). $\qquad \square$

Proposition A.2 *Let us consider the following set of ordered parameters $p_1 > p_k \geq p_{k+1} > 0 > p_{\ell-1} \geq p_\ell > p_n$, and functions $\Pi_j : \mathbb{R} \to \mathbb{R}$ of the form $\Pi_j(x) = \ln(1 + xp_j)$, with p_j being a given parameter within the ordered set. Then, we have that:*

$$\lim_{x^+ \to -(\frac{1}{p_1})} \Pi_1(x) = \lim_{x^- \to -(\frac{1}{p_n})} \Pi_n(x) = -\infty, \qquad (A.18)$$

$$\lim_{x^+ \to -(\frac{1}{p_1})} (\Pi_1(x) - \Pi_k(x)) = \lim_{x^- \to -(\frac{1}{p_n})} (\Pi_n(x) - \Pi_\ell(x)) = -\infty, \qquad (A.19)$$

$$\lim_{x^+ \to -(\frac{1}{p_1})} (\Pi_k(x) - \Pi_{k+1}(x)) = C_1, \qquad \lim_{x^- \to -(\frac{1}{p_n})} (\Pi_{\ell-1}(x) - \Pi_\ell(x)) = C_2, \qquad (A.20)$$

$$\lim_{x \to +\infty} (\Pi_k(x) - \Pi_{k+1}(x)) = C_3, \qquad \lim_{x \to -\infty} (\Pi_{\ell-1}(x) - \Pi_\ell(x)) = C_4, \qquad (A.21)$$

where C_1, C_2, C_3 and C_4 are constants.

Proof: The limits in (A.18) follow since Π_1 increases and Π_n decreases monotonically in their respective domains $(-1/p_1, +\infty)$, $(-\infty, -1/p_n)$. In order to prove (A.19), we have that:

$$\lim_{x^+ \to -(\frac{1}{p_1})} \Pi_k(x) = \Pi_k(-1/p_1), \text{ and } \lim_{x^- \to -(\frac{1}{p_n})} \Pi_\ell(x) = \Pi_\ell(-1/p_n),$$

which are (negative) constants, because $p_1 > p_k$ and $p_\ell > p_n$. Using (A.18), we then get (A.19).

In order to compute the limits in (A.20), we have that:

$$0 < 1 - \frac{p_k}{p_1} \le 1 - \frac{p_{k+1}}{p_1}. \text{ Thus, } \lim_{x^+ \to -(\frac{1}{p_1})} (\Pi_k(x) - \Pi_{k+1}(x)) = \ln \frac{1 - (p_k/p_1)}{1 - (p_{k+1}/p_1)} \le 0.$$

Similarly:

$$0 < 1 - \frac{p_\ell}{p_n} \le 1 - \frac{p_{\ell-1}}{p_n}. \text{ Thus, } \lim_{x^- \to -(\frac{1}{p_n})} (\Pi_{\ell-1}(x) - \Pi_\ell(x)) = \ln \frac{1 - (p_{\ell-1}/p_n)}{1 - (p_\ell/p_n)} \ge 0.$$

In proving (A.21), we have that:

$$\lim_{x \to +\infty} (\Pi_k(x) - \Pi_{k+1}(x)) = \ln \lim_{x \to +\infty} \frac{1 + xp_k}{1 + xp_{k+1}}, \text{ and } \lim_{x \to -\infty} (\Pi_{\ell-1}(x) - \Pi_\ell(x)) = \ln \lim_{x \to -\infty} \frac{1 + xp_{\ell-1}}{1 + xp_\ell}.$$

Thus, by the theorem of l'Hopital, we have that:

$$\lim_{x \to +\infty} (\Pi_k(x) - \Pi_{k+1}(x)) = \ln \frac{p_k}{p_{k+1}} \ge 0, \text{ and } \lim_{x \to -\infty} (\Pi_{\ell-1}(x) - \Pi_\ell(x)) = \ln \frac{p_{\ell-1}}{p_\ell} \le 0.$$

$\square$

B Some convenient results on uniqueness and stability

For the sake of completeness, here we summarize in the form of propositions, two fundamental results from CRNT on uniqueness and stability. The complete set of arguments can be found in [22].

Lemma B.1 (see also [2]) *Let $V(x) : \mathbb{X} \to \mathbb{R}$, with $\mathbb{X} \subseteq \mathbb{R}^n$ its domain, a convex function with continuous derivatives in $\mathbb{X}$, and $\nu(x) : \mathbb{X} \to \mathbb{R}^n$ be the gradient of $V(x)$. Then, the following inequalities hold for every $x \in \mathbb{X}$:*

(i) $\nu^T(x_1)(x - x_1) \le V(x) - V(x_1)$, *for any $x_1 \in \mathbb{X}$.*

(ii) $[\nu(x_2) - \nu(x_1)]^T (x_2 - x_1) \ge 0$, *for any $x_1, x_2 \in \mathbb{X}$.*

Inequalities are strict whenever $x \ne x_1$ or $x_1 \ne x_2$ in (i) and (ii), respectively.

Proof: In order to prove the first part, choose any $x_1 \in \mathbb{X}$ and construct a function $B_1(x; x_1)$ as the difference between $V(x)$ and its supporting hyperplane at x_1. The supporting hyperplane is of the form $H(x; x_1) = V(x_1) + \nu^T(x_1)(x - x_1)$, and $B_1(x; x_1) = V(x) - H(x; x_1)$. By construction, the function is strictly positive, i.e. it is positive for all $x \in \mathbb{X}$ other than x_1, and result (i) follows in a straightforward manner, since $B_1(x; x_1) = V(x) - V(x_1) - \nu^T(x_1)(x - x_1) \ge 0$, what implies that $V(x) - V(x_1) \ge \nu^T(x_1)(x - x_1)$.

To prove the second part, we note that $B_1(x; x_1)$ is itself a convex function since $\nabla_x B_1 = \nu(x) - \nu(x_1)$, so its Hessian coincides with that of the convex function $V(x)$. By using the same supporting hyperplane argument, we construct the following strictly positive definite function around some $x_2 \in \mathbb{X}$:

$$B_2(x; x_1, x_2) = B_1(x; x_1) - B_1(x_2; x_1) - [\nu(x_2) - \nu(x_1)]^T (x - x_2) \geq 0,$$

where the inequality holds for any $x \in \mathbb{X}$. In particular, it holds for $x = x_1$, and therefore:

$$B_1(x_2; x_1) + [\nu(x_2) - \nu(x_1)]^T (x_1 - x_2) \leq 0,$$

which implies that $B_1(x_2; x_1) \leq [\nu(x_2) - \nu(x_1)]^T (x_2 - x_1)$, and proves (ii). $\qquad\square$

Proposition B.1 (Corollary 4.14 [22]) *Let $\mathbf{c}_0 \in \mathbb{R}_{>0}^m$ be a fixed reference. The set*

$$\mathcal{U}(\mathbf{c}_0) = \{\mathbf{c} \in \mathbb{R}_{>0}^m \mid S^{\mathrm{T}}(\ln \mathbf{c} - \ln \mathbf{c}_0) = 0\}, \tag{B.1}$$

contains exactly one element in each positive stoichiometric compatibility class.

Proof: In proving uniqueness, suppose that there are two elements: $\mathbf{c}^*, \mathbf{c}^{**} \in \mathcal{U}(\mathbf{c}_0)$, that belong to the same stoichiometric compatibility class. Then, we have that $S^T(\ln \mathbf{c}^* - \ln \mathbf{c}^{**}) = 0$, what implies that $(\ln \mathbf{c}^* - \ln \mathbf{c}^{**})$ is orthogonal to the stoichiometric subspace Ξ. Because $\mathbf{c}^*$ and $\mathbf{c}^{**}$ are assumed to be in the same compatibility class, the vector $\mathbf{c}^* - \mathbf{c}^{**}$ must belong to the stoichiometric subspace Ξ, and the following relation hold:

$$(\ln \mathbf{c}^* - \ln \mathbf{c}^{**})^T (\mathbf{c}^* - \mathbf{c}^{**}) = 0. \tag{B.2}$$

Using the convex function $V(\mathbf{c}) = \mathbf{c}^T(\ln \mathbf{c} - \mathbf{1})$, with gradient $\nu(\mathbf{c}) = \ln \mathbf{c}$, and applying Lemma B.1 (condition (ii)), it follows that equality (B.2) holds if and only if $\mathbf{c}^* = \mathbf{c}^{**}$, what proves that the set $\mathcal{U}(\mathbf{c}_0)$ can have at most one element in each positive stoichiometric compatibility class.

As pointed out in [22], the question of existence (i.e. that each (positive) stoichiometric compatibility class in fact meets $\mathcal{U}(\mathbf{c}_0)$) is somewhat more difficult to answer than uniqueness. The complete argument can be found in [22] (Proposition 4.13). $\qquad\square$

Proposition B.2 (see also [22]) *Complex balanced equilibria are locally asymptotically stable in all positive stoichiometric compatibility classes.*

Proof: First of all, let us make use of Eqn (5) to write the right hand side of system (4) as a summation over λ, of functions:

$$\mathcal{R}^\lambda(\mathbf{c}) \equiv \sum_{i \in \mathcal{L}_\lambda} \psi_i(\mathbf{c}) \sum_{j \in \mathcal{I}_i} k_{ij} \cdot (\boldsymbol{y}_j - \boldsymbol{y}_i). \tag{B.3}$$

Select some positive reference $\mathbf{c}^* > 0$ (its associated vector $\boldsymbol{\psi}^*$ is strictly positive) and re-write the previous expression in the equivalent form:

$$\mathcal{R}^\lambda(\overline{\nu}) = \sum_{i\in\mathcal{L}_\lambda} \mathrm{e}^{\boldsymbol{y}_i^T \overline{\nu}} \sum_{j\in\mathcal{I}_i} \psi_i^* k_{ij} \cdot (\boldsymbol{y}_j - \boldsymbol{y}_i), \tag{B.4}$$

where $\overline{\nu} = \ln\mathbf{c} - \ln\mathbf{c}^*$. The inner product between $\overline{\nu}$ and $\mathcal{R}^\lambda(\mathbf{c})$ (B.4) results into the following scalar function:

$$\overline{\nu}^T \mathcal{R}^\lambda(\overline{\nu}) = \sum_{i\in\mathcal{L}_\lambda} \mathrm{e}^{z_i(\overline{\nu})} \sum_{j\in\mathcal{I}_i} \psi_i^* k_{ij} \cdot (z_j(\overline{\nu}) - z_i(\overline{\nu})), \tag{B.5}$$

where $z_i(\overline{\nu}) = \boldsymbol{y}_i^T \overline{\nu}$. In order to get an upper bound for (B.5), we make use of Lemma B.1 (condition (i)), with the convex function $V(z) = \mathrm{e}^z$, to obtain:

$$\mathrm{e}^{z_i}(z_j - z_i) \leq \mathrm{e}^{z_j} - \mathrm{e}^{z_i}. \tag{B.6}$$

For any scalars z_i and z_j. Strict convexity of $V(z)$ ensures that the equality holds only if $z_i = z_j$. We also have that:

$$\mathrm{e}^{z_j} - \mathrm{e}^{z_i} = (\boldsymbol{\varepsilon}_j - \boldsymbol{\varepsilon}_i)^T \sum_{k=1}^n \boldsymbol{\varepsilon}_k \mathrm{e}^{z_k}. \tag{B.7}$$

Combining (B.7) with (B.6), and substituting the resulting expression in (B.5), we get:

$$\overline{\nu}^T \mathcal{R}^\lambda(\overline{\nu}) \leq \left(\sum_{i=1}^n \mathrm{e}^{z_i(\overline{\nu})} \boldsymbol{\varepsilon}_i^T \right) \left[\sum_{i\in\mathcal{L}_\lambda} \psi_i^* \sum_{j\in\mathcal{I}_i} k_{ij} \cdot (\boldsymbol{\varepsilon}_j - \boldsymbol{\varepsilon}_i) \right] = \tag{B.8}$$

$$\left(\sum_{i=1}^n \mathrm{e}^{z_i(\overline{\nu})} \boldsymbol{\varepsilon}_i^T \right) A_k^\lambda(\boldsymbol{\psi}^*).$$

If the reference corresponds with a complex balanced equilibrium, then for every $\lambda = 1, \ldots, \ell$, $A_k^\lambda(\boldsymbol{\psi}^*) = 0$ and so is the right hand side of (B.8). Note that inequality is strict, in the sense that it holds whenever $z_i \neq z_j$, for every $i, j \in \mathcal{L}_\lambda$.

Local asymptotic stability is proved by the standard Lyapunov stability method (see for instance [39]) with the following Lyapunov function candidate, constructed as in the proof of Lemma B.1:

$$B(\mathbf{c}; \mathbf{c}^*) = V(\mathbf{c}) - V(\mathbf{c}^*) - \nu^T(\mathbf{c}^*)(\mathbf{c} - \mathbf{c}^*) \geq 0,$$

with $V(\mathbf{c})$, being a convex function of the form:

$$V(\mathbf{c}) = \sum_{i=1}^m c_i(\ln c_i - 1).$$

Computing the derivative of B along (4), and using (B.8), we get:

$$\dot{B} = \sum_{\lambda=1}^\ell \overline{\nu}^T \mathcal{R}^\lambda(\overline{\nu}) \leq \left(\sum_{i=1}^n \mathrm{e}^{z_i(\overline{\nu})} \boldsymbol{\varepsilon}_i^T \right) \sum_{\lambda=1}^\ell A_k^\lambda(\boldsymbol{\psi}^*) = 0. \tag{B.9}$$

The result then follows, since $B(\mathbf{c}; \mathbf{c}^*) \geq 0$ and $\dot{B}(\mathbf{c}; \mathbf{c}^*) \leq 0$, with equality only if $\mathbf{c} = \mathbf{c}^*$. $\qquad \square$