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

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Abstract

For a class of polynomial kinetic systems, this work examines connections between system parameters, and uniqueness and stability of the resulting equilibria. Such systems are typically employed to describe nonlinear dynamics in chemical reaction networks, but over the last years they proved useful in modeling a wide range of nonlinear dynamic systems with applications in biology, process systems, economics or transportation problems.

In particular, a canonical representation of the set of all possible feasible equilibrium solutions is developed. The characterization is made in terms of compartmental matrices which by construction are strictly stable and define the so-called family of solutions. Feasibility is imposed by a set of constraints, which are linear in the log-transformed space of complexes, and relate to the kernel of the stoichiometric subspace. One particularly interesting representation of these constraints can be established in terms of a class of monotonous functions which turn out to be critical to conclude uniqueness of equilibrium points in a class of deficiency one networks.

One main consequence of such representation is the possibility of a simple constructive proof of the deficiency one theorem. It also allows a precise characterization of the parameter space region of complex balance solutions we refer to as the Horn set. Future directions may involve detection or design of networks having multiple equilibria, or the use of complex balance condition to provide stabilization via feedback control of open reaction systems.

Keywords: Dynamical reaction systems, mass action law, network deficiency, feasible equilibria, complex balance

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Deterministic reaction networks (also called kinetic systems), obeying a mass action law (MAL) kinetics form an important subclass of nonnegative systems which in spite of their apparent simplicity, are capable of a quite rich dynamic behavior that includes multiple equilibria conditions, oscillations or even chaos [1, 2].

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 biological systems from the level of cells up to the ecological dimension (i.e. including interaction between individuals), including among other applications studies on disease propagation dynamics, etc. Reaction networks belong to the class of nonnegative (or positive) systems the main characteristics of

1 Introduction
which is that the non-negative orthant is invariant for the dynamics. The application field of nonnegative systems extends far beyond (bio)chemistry and includes dynamical models whose state variables are naturally nonnegative or can be transformed to be nonnegative, such as certain process systems (heat exchangers, distillation columns, convection networks), economic, transportation or stochastic models. 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 that defines an additional constraint between the monomial coefficients and exponents. Still, the class of reaction network models is quite wide, and many non-chemical models can be easily transformed to kinetic form using simple transformations. Widely used examples of kinetic systems are Lotka-Volterra models into which most smooth nonlinear ODEs can be embedded, and compartmental systems. 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 by. The subsequent works by, collected in its most comprehensive form in, exploring the dynamic properties of MAL complex chemical systems, contributed to equip CRNT with a mathematical formalism that has prevail up to present.

One fundamental problem in chemical reaction network theory (CRNT) is to decide from the structure or parameters of the network, whether it can exhibit or not multiple equilibria. In answering such a question, the concept of network deficiency, a number that relates network structure with its dynamics, becomes central to characterize the network behavior.

Two essential results of CRNT are the so-called deficiency zero and deficiency one theorems, which establish conditions for networks to have just one possible equilibrium independently of parameter values (more precisely, as long as none of the reactions rate constants vanish i.e. all rate coefficients remain strictly positive). Such conditions are valid despite of the constraints imposed by the chemical species conservation which define the reaction simplex. In particular, for networks with zero deficiency, positive equilibria for any set of positive network parameters will be unique in each reaction simplex and stable. 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. Most efforts have been directed to investigate the relationships between reaction network structure and the capacities of various kinds of
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 the right hand side of the resulting dynamic system [18]. Algebraic and graph theoretical methods have been devised to check injectivity and therefore uniqueness of equilibria [18, 19]. In the same direction, extensions to cope with instabilities have been developed in [15]. 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 [16, 17].

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 those which integrate reversible as well as irreversible steps (weakly reversible networks). 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 balance 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. Having said that, it must be noted that, in agreement 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, resulting into stable equilibria [20]. As discussed in [21] and [22] irreversibility can be allowed within a reaction network, as limit cases of reversible steps under a thermodynamic consistency condition, known as the Wegscheider conditions, which necessarily assumes microreversibility.

The notion of complex balance (also known as cyclic balance or semi-detailed balance), on the other hand, generalizes the detailed balance condition to any weakly reversible network. The structure of complex balance systems has been explored in [23] and shown to be a toric variety with unique and stable equilibrium points (see also [24]). Extensions to cope with more general classes of kinetic systems have been investigated in [25, 26].

CRNT as its 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.

Reasons that hamper application are usually found within the traditionally obscure architec-
ture of their methods and proofs, and the inherent difficulties of graph theoretical methods in which the theory emerged, to properly suit applications. Some practical questions that demand attention relate to the link between dynamic behavior of a given mechanism and parameter sets (reaction rate constants), or to the design of a chemical/biochemical network with some pre-specified behaviour (e.g. bistable, oscillatory, etc).

In order to contribute to fill the gap between theory and potential applications, we adopt in this paper a geometric perspective in the line of the [27, 17, 28] to revisit the essential elements of CRNT. To that purpose the notion of ‘family of solutions’ and feasibility will be employed. Originally, both concepts have been derived in [27, 17] to study multiplicity phenomena as a function of network parameters and to describe regions in the parameter space (Horn sets) [28] complying with complex balance solutions [29].

In this contribution, feasible solutions will be characterized in terms of a class of stable Metzler matrices [30] and a set of constraints which relate to the null space associated to the stoichiometric subspace. One particularly interesting representation of these constraints will be discussed in Sections 4 and 5 and employed to conclude uniqueness for a class of positive deficiency networks. This result, we obtained by geometric methods, is equivalent to the one discussed in [31] in the context of graph theory. Such representation will constitute the basis for a constructive proof of the deficiency one theorem as well as to the characterization of the Horn set, namely that which defines in the parameter space the region of complex balance solutions.

Since as we will see, complex balance ensures stability of the equilibrium, this property can be useful to characterize stable operation regimes in open systems, where the principle of detailed balance cannot hold. This may lead to the selection or manipulation of exchange fluxes so to preserve stability of the resulting open to the environment reaction system, for instance via appropriate process optimization and/or feed-back control. Future directions may involve, in addition 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 an its algebraic counterpart will be described in Section 3. The canonical representation of the equilibrium set including feasibility conditions will be presented in Section 4. Relationships between network structure and monotonicity of feasibility conditions will be established in Section 5. This will constitute the essential result needed to conclude in Section 6 uniqueness and stability of equilibria for complex balance and some classes of deficiency 1 networks.
2 Preliminaries: Reaction Network Structure and Dynamics

Let $m$ be the number of chemical species which are transformed among themselves by a set of irreversible chemical reaction steps, and $c \in \mathbb{R}^m$ be the corresponding vector of species concentrations, defined as number of molecules (e.g. mole numbers) 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 edges.

Formally, the graph involving $n$ complexes $\{C_1, \ldots, C_n\}$ linked by irreversible reaction steps can be constructed by associating to each complex $i$ a set $I_i$ of integer elements with ordinality in $n$, and a vector $y_i$. The elements of the set $I_i$ are the indices of the complexes that are directly reachable (i.e. by one reaction step) from $C_i$ in the reaction graph. Vector $y_i \in \mathbb{R}^m$ 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 $j \in I_i$. This process results in a number $\ell$ of connected components known in CRNT as linkage classes. For each linkage class $\lambda = 1, \ldots, \ell$, we define the set $\mathcal{L}_\lambda$ as that containing as elements the indices of the complexes that belong to that linkage class. The complexes that belong to the network will be in the set

$$\mathcal{L} = \bigcup_{\lambda=1}^{\ell} \mathcal{L}_\lambda.$$  

Complexes are connected within a linkage class by sequences of irreversible reaction steps defining directed paths. Two complexes are strongly linked if they can be reached from each other by directed paths (trivially every complex is strongly linked to itself). A maximal set of strongly linked complexes defines a strong terminal linkage class if no other complex can be reached from its elements. A linkage class $\mathcal{L}_\lambda$ is said to be weakly reversible if all its complexes are strongly linked. Weakly reversible networks are those composed by weakly reversible linkage classes. Clearly, a CRN is weakly reversible if and only if all components of the reaction graph are strongly connected components.

A particular class of weakly reversible linkage class is a reversible linkage class if each reaction step is itself reversible. Therefore, reversible networks require for every $i$ and $j \in I_i$, to have that $i \in I_j$.

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1To be precise, the set $\mathcal{L}_\lambda$ will be that containing as elements $\mathcal{L}_\lambda = \{i_1, i_2, \ldots, i_{N_\lambda}\}$, with $N_\lambda = N(\mathcal{L}_\lambda)$, being $i_j$ the cardinality associated to complex $C_{i_j}$, and $N(\cdot)$ the operator which indicates the number of elements in the set.
To each linkage class $\lambda$ we associate an $n$-dimensional vector $\omega_\lambda$ which is defined as follows:

$$\omega_\lambda = \sum_{i \in L_\lambda} \varepsilon_i,$$

where $\varepsilon_i \in \mathbb{N}^n$ denotes the $i$th standard unit vector employed to represent axes on a cartesian coordinate system. Vectors $\omega_\lambda$ ($\lambda = 1, \ldots, \ell$) are orthogonal to each other since by construction, sets $L_\lambda$ are disjoint. The rate $R_{ij}$ at which a set of chemical species (reactants) representing complex $i$ is transformed into a set of products represented by complex $j$ will be assumed to be mass action, hence:

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

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 $c$ is a strictly positive vector (meaning all components strictly positive), the following alternative representation for $\psi_i(c)$ may be more convenient:

$$\ln \psi_i(c) = y_i^T \ln c,$$

where the natural logarithm operator $\ln(\cdot)$ will act on any vector element-wise. Let $\psi(c) \in \mathbb{R}^n$ be the vector containing as entries the monomials described in (2), then previous expression can be written in matrix form as:

$$\ln \psi(c) = Y^T \ln c,$$

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

### 2.1 The dynamics of reaction networks

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 of the form [11]:

$$\dot{c} = Y \cdot \kappa(\psi) \equiv Y \cdot \sum_{\lambda} A^\lambda_k(\psi),$$

with $A^\lambda_k(\psi)$ being a linear operator that accepts the following equivalent factorizations:

$$A^\lambda_k(\psi) = \sum_{i \in L_\lambda} \psi_i(c) \sum_{j \in I_i} k_{ij} \cdot (\varepsilon_j - \varepsilon_i)$$

$$\equiv \sum_{i \in L_\lambda \setminus j_\lambda} \phi_i(\psi)(\varepsilon_i - \varepsilon_{j_\lambda}),$$

$^2$Vector $\omega_\lambda$ is referred in classical CRNT as the characteristic function of linkage class $\lambda$. 

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2 Vector $\omega_\lambda$ is referred in classical CRNT as the characteristic function of linkage class $\lambda$. 

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6 Vector $\omega_\lambda$ is referred in classical CRNT as the characteristic function of linkage class $\lambda$. 

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$j_\lambda \in \mathcal{L}_\lambda$ in the above expression represents a reference complex selected from the corresponding strongly terminal linkage class and $\phi_i$ represents the net reaction rate flux around complex $i$, which is defined as:

$$
\phi_i(\psi) = \sum_{(j/i \in \mathcal{L}_j)} R_{ji} - \sum_{j \in \mathcal{L}_i} R_{ij},
$$

(7)

where the first summation at the right hand side must be understood as that extended to all $j$ that reach $i$ by a reaction step and is represented by $(j/i \in \mathcal{L}_j)$. Since vectors $\varepsilon_i$ are orthogonal, we have from (6) that $\phi_i(\psi) = \varepsilon_i^T A^\lambda_k(\psi)$ for every $i \in \mathcal{L}_\lambda$, and $\omega^T A^\lambda_k(\psi) = 0$. Therefore:

$$
\sum_{i \in \mathcal{L}_\lambda} \phi_i = \left( \sum_{i \in \mathcal{L}_\lambda} \varepsilon_i \right)^T A^\lambda_k(\psi) = 0.
$$

(8)

Fluxes $\phi_i$ as well as the operator $A_k$, are implicitly dependent on the set of reaction rate constants $k_{ij}$ of the network. By inspection of (6), it can be concluded that the image of $A_k(\psi)$ lies within the subspace $\Delta$ defined as:

$$
\Delta = \bigcup_{\lambda=1}^\ell \Delta_\lambda \text{ with } \Delta_\lambda = \text{span}\{\varepsilon_i - \varepsilon_j_\lambda \mid i \in \mathcal{L}_\lambda \setminus j_\lambda\}.
$$

(9)

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

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

This implies that $A_k(\psi) = 0$ if and only if $\phi_i = 0$ for all $i \in \mathcal{L}$. Consequently, if a positive concentration vector $c^*$ exists compatible with a zero flux condition for every complex in the network, that vector should be an equilibrium for system (5). Such equilibrium condition, known as complex balance [29], is formally defined as follows:

**Definition 2.1 (Complex Balance Equilibrium)** For a weakly reversible network, any vector $c^* \succ 0$ such that $\ln \psi^* = Y^T \ln c^*$ (Eqn [4]), makes zero every flux $\phi_i(\psi)$ in Eqn (7) is known as a complex balance equilibrium solution.

A subclass of complex balance solution, particularly meaningful from a thermodynamic point of view since it relates with microreversibility ([32, 20]) is the detailed balance condition, we define next

**Definition 2.2 (Detailed Balance Equilibrium)** If in addition, the network is reversible so that for every $i$ and $j \in \mathcal{I}_i$, we have that $i \in \mathcal{I}_j$, any vector $c^* \succ 0$ such that $R_{ij}(c^*) = R_{ji}(c^*)$ (where $R_{ij}$ is of the form [2]) is known as a detailed balance equilibrium solution.
2.2 The stoichiometric subspace

We define the stoichiometric subspace $\Sigma$ as that spanned by the union over all linkage classes $\lambda$ of the vector sets:

$$\Sigma_\lambda = \text{span}\{ y_i - y_{j_\lambda} \mid i \in L_\lambda \setminus j_\lambda \} \quad \text{and} \quad \Sigma = \bigcup_{\lambda=1}^{\ell} \Sigma_\lambda. \quad (10)$$

In what follows it will be more convenient to collect the elements from each of the sets $\{ y_i - y_{j_\lambda} \mid i \in L_\lambda \setminus j_\lambda \}$ 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. Let $s = \dim(\Sigma)$, 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:

$$\delta = n - \ell - s. \quad (11)$$

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 $S_\lambda$ so that $\delta_\lambda = N_\lambda - 1 - s_\lambda$, where $s_\lambda = \dim(\Sigma_\lambda)$. Since $s \leq \sum_\lambda s_\lambda$, it is not difficult to conclude that linkage class and network deficiencies relate as:

$$\delta \geq \sum_\lambda \delta_\lambda. \quad (12)$$

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

$$(g^r)^T = [ (g^r_1)^T \cdots (g^r_\lambda)^T \cdots (g^r_\ell)^T ].$$

Using the above description, equation $Sg^r = 0$ can be re-written for every $r = 1, \ldots, \delta$ as:

$$\sum_\lambda S_\lambda g^r_\lambda = 0 \quad \text{for} \quad r = 1, \ldots, \delta. \quad (13)$$

We will be particularly interested in solutions of system (5) on the convex region resulting from the intersection of the positive orthant in the concentration space and a linear variety associated to the stoichiometric subspace $\Sigma$ (also known in CRNT as compatibility class). Such region can be formally defined with respect to a reference concentration vector $c_0$ as:

$$\Omega(c_0) = \{ c \in \mathbb{R}^m \mid c \succeq 0, B^T(c - c_0) = 0 \}, \quad (14)$$

where $B \in \mathbb{R}^{m \times (m - s)}$ is a full rank matrix whose columns span the orthogonal complement $\Sigma^\perp$. In passing it is noted that the vector function $\sigma = B^Tc$ is constant along trajectories (5), since by combining (6) and (5) we have that:

$$\dot{c} = \sum_\lambda \sum_{i \in L_\lambda \setminus j_\lambda} \phi_i(\psi)(y_i - y_{j_\lambda}), \quad (15)$$

and the columns of $B$ are orthogonal to $S$, hence $\dot{\sigma} \equiv B^T\dot{c} = 0$. In other words, $\sigma$ is an invariant of motion for system (5). From this observation it is not difficult to conclude that any trajectory that starts in a compatibility class $\Omega(c_0)$ 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 \( M_1, \ldots, M_6 \), 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 reactions steps that take place are:

\[
\begin{align*}
A_2B + C & \rightleftharpoons AC + AB \\
AB + 2C & \rightleftharpoons AC_2B \\
AC_2B & \rightleftharpoons AC + CB
\end{align*}
\]  

(16)

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:

\[
\{C_1, C_2, C_3, C_4, C_5\} \equiv \{M_1 + M_4, M_2 + M_3, M_3 + 2M_4, M_5, M_2 + M_6\}
\]

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:

\[
\begin{align*}
\mathcal{I}_1 & = \{2\} \\
\mathcal{I}_2 & = \{1\} \\
\mathcal{I}_3 & = \{4\} \\
\mathcal{I}_4 & = \{3, 5\} \\
\mathcal{I}_5 & = \{4\}
\end{align*}
\]  

(17)

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

\[
Y = \begin{pmatrix}
1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 1 \\
0 & 1 & 1 & 0 & 0 \\
1 & 0 & 2 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 1
\end{pmatrix}
\]  

(18)

The corresponding graph representation is depicted in Figure 1. It comprises two linkage classes

\[
\begin{align*}
C_1 & \leftrightarrow C_2 \\
C_3 & \leftrightarrow C_4 \leftrightarrow C_5
\end{align*}
\]

Figure 1: Graph representation for the reaction network described by reversible steps (16).

\( \mathcal{L}_1 = \{1, 2\} \) and \( \mathcal{L}_2 = \{3, 4, 5\} \), with the corresponding vectors \( \mathbf{\omega}_\lambda \) in (1):

\[
\mathbf{\omega}_1 = \begin{pmatrix} 1 & 1 & 0 & 0 & 0 \end{pmatrix}, \quad \mathbf{\omega}_2 = \begin{pmatrix} 0 & 0 & 1 & 1 & 1 \end{pmatrix}
\]
Selecting \( j_1 = 1 \) and \( j_2 = 3 \) as reference complexes for linkage class \( \lambda = 1 \) and \( \lambda = 2 \), respectively, the net reaction fluxes around each complex, as defined in (7), become:

\[
\begin{align*}
\phi_2 &= k_{12}\psi_1 - k_{21}\psi_2 \\
\phi_4 &= k_{34}\psi_3 + k_{54}\psi_5 - (k_{43} + k_{45})\psi_4 \\
\phi_5 &= k_{45}\psi_4 - k_{54}\psi_5
\end{align*}
\] (19)

Note that by relation (8), the fluxes associated to the reference become:

\[
\begin{align*}
\phi_1 &= -\phi_2 \\
\phi_3 &= -\left(\phi_4 + \phi_5\right)
\end{align*}
\]

The image of the operator \( A_\lambda^k \) defined in (6) lies in subspace \( \Delta \) (Eqn (9)) which results from the union of the following subspaces:

\[
\begin{align*}
\Delta_1 &= \text{span}\{(\varepsilon_2 - \varepsilon_1)\} \\
\Delta_2 &= \text{span}\{(\varepsilon_4 - \varepsilon_3), (\varepsilon_5 - \varepsilon_3)\}
\end{align*}
\] (20)

Matrices \( S_\lambda \) employed in Section 2.2 to define column-wise the corresponding stoichiometric subspace (10) are of the form:

\[
S_1 = \begin{pmatrix} -1 & 1 & 1 & 0 & 1 & 0 \\ 1 & -1 & 0 & 1 & 1 & 0 \\ 1 & 1 & 0 & 1 & 2 & 1 \end{pmatrix}, \quad S_2 = \begin{pmatrix} 0 & 0 \\ 0 & 1 \\ -1 & -1 \\ -2 & -2 \\ 1 & 0 \\ 0 & 1 \end{pmatrix}
\]

The dimension of the stoichiometric subspace, i.e. the rank of matrix \( S = ( S_1 \ S_2 ) \) is \( s = 3 \), hence \( \delta = 5 - 2 - 3 = 0 \). Thus the network is zero deficiency which means that no vector \( g^r \) other than the zero vector exist such that \( Sg^r = 0 \). In other words, the kernel of \( S \) contains only the null vector.

Atoms or functional groups \( A-C \) are not modified by reactions (16). In fact, their numbers remains constant provided that reactions take place on a closed domain (i.e. no mass exchanges with the environment occur). Let \([A]_0\), \([B]_0\) and \([C]_0\) be the concentrations on a closed and homogeneous domain of \( A \), \( B \) and \( C \), respectively. Mole-number balances result into the following set of linear relations:

\[
\begin{align*}
[A]_0 &= 2[A_2B] + [AC] + [AB] + [AC_2B] \\
[B]_0 &= [A_2B] + [AB] + [AC_2B] + [CB] \\
[C]_0 &= [AC] + [C] + 2[AC_2B] + [CB]
\end{align*}
\]

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

\[
B^T(c - c_0) = 0 \quad \text{with} \quad B = \begin{pmatrix} 2 & 1 & 1 & 0 & 1 & 0 \\ 1 & 0 & 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 2 & 1 \end{pmatrix}^T
\]

where \( c \) is the vector of chemical species concentrations and \( B^Tc_0 \) the (constant) concentration of functional groups/atoms. It must be noted that the above expression is employed in (14) to
characterize the set of compatibility classes (each of them a reaction simplex). As discussed in Section 2.2, the columns of $B$ defines a basis for the orthogonal complement to the stoichiometric subspace.

**An irreversible network**

Let us consider the following set of irreversible reactions:

\[
\begin{align*}
S + I &\rightarrow 2I \\
I \rightleftharpoons R &\rightarrow S
\end{align*}
\]

This network can be interpreted as an extension of the SIR epidemic model [33] 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 disease ($R$). In this extension, individuals under recovering may evolve either to those that again susceptible to the disease or directly infected again. In the CRNT formalism it would be said that the network would comprises three species with concentrations [$S$, $I$ and $R$], and 5 complexes numbered as:

\[
\{C_1, C_2, C_3, C_4, C_5\} \equiv \{2I, S + I, S, R, I\}
\]

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

\[
Y = \begin{bmatrix}
0 & 1 & 1 & 0 & 0 \\
2 & 1 & 0 & 0 & 1 \\
0 & 0 & 0 & 1 & 0
\end{bmatrix}
\] (22)

Stoichiometric matrices $S_{\lambda}$ become:

\[
\begin{align*}
C_2 &\rightarrow C_1 \\
C_5 &\rightleftharpoons C_4 \rightarrow C_3
\end{align*}
\]

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

\[
S_1 = \begin{pmatrix}
1 \\
-1 \\
0
\end{pmatrix}, \quad S_2 = \begin{pmatrix}
-1 & -1 \\
0 & 1 \\
1 & 0
\end{pmatrix}
\]

Because both matrices are full rank, the dimension of $\Sigma_1$ and $\Sigma_2$ is $s_1 = 1$ and $s_2 = 2$, respectively. Thus $\delta_1 = N_1 - 1 - s_1 = 0$ and $\delta_2 = N_2 - 1 - s_2 = 0$. However matrix $S = (S_1 \quad S_2)$ is rank deficient since vector $S_1$ is aligned to the vector that makes the second column of $S_2$. Consequently $s = 2$, and $\delta = 5 - 2 - 2 = 1$, verifying inequality (12). A basis in the kernel of $S$, i.e. a non-zero vector $g^T$ that solves (13), results to be $g^T = (1 \quad 0 \quad 1)^T$. 
For this network, the basis that spans the orthogonal complement to the stoichiometric subspace becomes \( B = (1 1 1)^T \). A representation of a compatibility class for the reaction network considered is presented in Figure 3 with \( c = ([S], [I], [R])^T \). The reaction polyhedron \( \Omega(c_0) \) defines the region of non-negative concentrations \( (c \succeq 0) \) satisfying:

\[
[S] + [I] + [R] = B^T c_0
\]

with \( c_0 \succeq 0 \) being a constant vector.

![Figure 3: Representation of a compatibility class also known as reaction simplex or polyhedron \( \Omega(c) \).](image)

3 Linkage classes, Graphs and Compartmental Matrices

The nature and properties of equilibrium solutions in chemical reaction networks (e.g stability or not of equilibrium solutions, or the possibility of multiple equilibria) is at a large extent conditioned by the graph structure of each linkage class and the properties of some matrices associated to it which are known as compartmental matrices [34].

In this section we describe a graph which under some conditions reduces to the graph description of a linkage class. Related to that graph and its associated matrix, an auxiliary dynamic system will be constructed and its equilibrium studied in order to extract relevant properties of the corresponding compartmental matrix.

A directed graph \( G = (\mathcal{V} \cup \mathcal{E}), \mathcal{E} \) is constructed by a set of \( n + 1 \) vertices and 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 $v_i \rightarrow v_j$ 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 $V_{ji} > 0$. 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 scalars $b_i > 0$ and $a_i > 0$, respectively, which will be collected in (non-negative) vectors $a, b \in \mathbb{R}^n$. As in the description of linkage classes (Section 2) we will say that two nodes are strongly linked if they can be reached from each other by directed paths. The largest set of strongly linked nodes (not passing through the environment) in $\mathcal{L}$ from which there are not outgoing edges to other nodes will define a strong terminal set we will refer to as $\mathcal{L}_p$. Some examples of directed graphs are illustrated in Figure 4.

We will only consider graphs with one strong terminal set, and define the set of non-terminal nodes as $\mathcal{L}_q = \mathcal{L} \setminus \mathcal{L}_p$. Graphs where all nodes plus the environment constitute a strong terminal set will be referred to as weakly reversible graphs.

![Figure 4: Some typical examples of directed graphs. (a) Exchange with the environment takes place in the strong terminal set through input $a(2)$ (second coordinate of vector $a$) and output $b(1)$ (first coordinate of vector $b$). Node $Env$ represents the environment. (b) Input from the environment enters the system through a non-terminal node (coordinate $a(4)$ of vector $a$) while the output to the environment leaves from a terminal node (coordinate $b(1)$ of vector $b$).](image)

For each node $i = 1, \ldots, n$ we define a state $x_i$ and a (internal) flux:

$$\phi_i = \sum_{(j/i \in \mathcal{L}_j)} V_{ij} x_j - x_i \sum_{k \in \mathcal{L}_i} V_{ki}$$  \hspace{1cm} (23)$$

where as in Section 2 indexes that are directly reached from node $i$ are grouped in set $\mathcal{L}_i$, and $(j/i \in \mathcal{L}_j)$ refers to nodes with edges directed to $i$. Fluxes to and from the environment will be expressed by vectors $\beta = B x$ (with $B = \text{diag}(b)$) and $a$, respectively.

We consider that each state will change in time as a function of the net flux through it. Hence its dynamics by the action of fluxes can be described as:

$$\dot{x} = \sum_{i=1}^{n} \phi_i(x)(\varepsilon_i - \varepsilon_1) - B x + a$$  \hspace{1cm} (24)$$
where the states of the system are collected in vector $x \in \mathbb{R}^n$. Equation (24) can be written in the alternative form:

$$\dot{x} = Wx + a$$

(25)

where matrix $W = V - B$, and $V \in \mathbb{R}^{n \times n}$ contains as elements the coefficients in (23) and has diagonal elements of the form:

$$V_{ii} = -\sum_{j=1}^{n} V_{ji}$$

Both matrices $V$ and $W$ are compartmental and belong to the class of Metzler matrices. It is known from e.g. [35], that the eigenvalues of a compartmental matrix are either zero or they have negative real parts. Such conclusion can be also reached in a straightforward manner from the structure of compartmental matrices applying column-wise the Gershgorin disc theorem [36].

**Proposition 3.1** Consider system (25) with $a \succeq 0$ and nonnegative initial conditions $x(0) = x_0 \succeq 0$. Then $x(t) \succeq 0$ for every $t > 0$

**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 will be either aligned to the boundary or oriented to the interior of the set. Before we compute the flow let us define the set $H_k = \{x \succeq 0 \mid \varepsilon_k^T x = 0\}$ which characterizes the $k$ facet of the positive orthant. The inner product between the flow induced by (24) (equivalently (25)) on any element $x \in H_k$, and the vector orthogonal to $H_k$ takes the form:

$$\varepsilon_k^T \dot{x} = \phi_k - b_k x_k + a_k \equiv \sum_{(i/k \in \mathcal{L}_i)} V_{ki} x_i + a_k \geq 0 \quad (26)$$

where the equivalence at the right hand side holds since $x_k = 0$ in $H_k$. Thus at the $H_k$ boundary, the flow associated to the differential system will be either aligned to the boundary ($\varepsilon_k^T \dot{x} = 0$) or oriented to the interior of the set (i.e. $\varepsilon_k^T \dot{x} > 0$). Repeating the argument for all $k$ will complete the proof. 

We will now show that the dynamic system will eventually evolve to zero as the unique equilibrium solution, provided that $a = 0$ and the non-zero components of vector $b$ will coincide with nodes in the terminal set (i.e nodes that belong to $\mathcal{L}_p$).

---

3 A matrix $A \in \mathbb{R}^{n \times n}$ is compartmental if:

1. $A_{ij} \geq 0$, for $i, j = 1, \ldots, n$, $i \neq j$

2. $\sum_{i=1}^{n} A_{ij} \leq 0$, for $j = 1, \ldots, n$. 

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Figure 5: Example of a graph with \( a, b = 0 \) partitioned into a terminal set \( L_p \) and nonterminal sets \( L_{q_1}, L_{q_2} \). In this case \( L_\ell \) comprises nodes 2 and 4.

Let \( L_\ell \subset L_q \) be the set collecting those nodes in the non-terminal set that are directly linked to the terminal one (the different partitions are illustrated in Figure 5), and define \( \sigma_p = \omega_p^T x \) and \( \sigma_q = \omega_q^T x \), where:

\[
\omega_p = \sum_{i \in L_p} \varepsilon_i \quad \text{and} \quad \omega_q = \sum_{i \in L_q} \varepsilon_i.
\]  
(27)

and \( \sigma = \sigma_q + \sigma_p \). The time derivative of \( \sigma_q \) along system (24) is of the form:

\[
\dot{\sigma}_q = \omega_q^T a - \sum_{i \in L_q} b_i x_i - \sum_{j \in L_p} \sum_{i \in L_\ell} V_{ji} x_i
\]  
(28)

Note that if \( a_i = b_i = 0 \) for every \( i \in L_q \), we also have that:

\[
\dot{\sigma}_p = -\dot{\sigma}_q + \sum_{i \in L_p} (a_i - b_i x_i)
\]  
(29)

With these preliminaries we are in a position to prove the following result:

**Proposition 3.2** Consider system (25) with \( a = 0 \) and at least one positive entry, \( i \in L_p \) for vector \( b \). Then, for any \( x(0) \geq 0 \), \( x^* = 0 \) is the only equilibrium solution of (25).

**Proof:** Since \( x(0) \geq 0 \) and \( a = 0 \), by Proposition 3.1 we have that \( x(t) \geq 0 \), which implies that the state will remain in the positive orthant, and \( \sigma_p \) and \( \sigma_q \) will be larger or equal than zero so that \( \sigma = \sigma_q + \sigma_p \geq 0 \).

For \( i \in L_q \) we have from (28) that \( \dot{\sigma}_q < 0 \) as long as there exists some \( x_i > 0 \), but since \( \sigma_q \) cannot become negative, the only equilibrium state for every \( i \in L_q \) will be \( x_i^* = 0 \). In addition, because \( \dot{\sigma} = -\sum_{i \in L_p} b_i x_i \), with at least one \( b_i > 0 \) and \( \sigma \) cannot become negative, the only possible equilibrium states will correspond with \( x_i^* = 0 \) for all \( i \in L_p \). In summary, the only equilibrium equals \( x(t) = x^* \equiv 0 \), what completes the proof. \( \square \)
Proposition 3.3 Consider system (25) associated to a weakly reversible graph (i.e. $a, b \geq 0$, excluding zero vectors). Then, for any $x(0) \geq 0$, there is exactly one strictly positive equilibrium solution $x^* > 0$ for (25).

Proof: According to (24) we can describe the dynamics around each node as
\[
\dot{x}_i = \phi_i(x) - b_i x_i + a_i.
\]
Suppose that $x_i \equiv x^*_i = 0$, then we have from the above equation that:
\[
\dot{x}_i = \sum_{j \in \mathcal{L}} V_{ij} x_j + a_i.
\]
Thus the system is not at equilibrium since $\dot{x}_i > 0$, unless $x_j = 0$ for all $j \in \mathcal{L}$ and $a_i = 0$. Since there is at least one entry such that $a_i > 0$, and according to Proposition 3.1, $x^*$ must be in the positive concentration orthant, any equilibrium solution must be strictly positive, namely $x^* > 0$.

\[
\square
\]

Definition 3.1 We say that the matrix $W \in \mathbb{R}^{n \times n}$, associated to a directed graph $G = \{(V \cup v_E), \mathcal{E}\}$ is C-Metzler if its entries are of the form:
\[
W_{ij} \geq 0 \quad \text{for } i \neq j
\]
\[
W_{ii} = -(b_i + \sum_{j \neq i} W_{ji}) \quad \text{with } b_i \geq 0 \text{ and } W_{ii} < 0,
\]
provided that at least one $b_i$ associated to a terminal set (i.e. $i \in \mathcal{L}_p$) is positive.

Lemma 3.1 Any C-Metzler matrix $W$ is non-singular and stable, and its inverse $W^{-1}$ is non-positive. If the set of nodes in $\mathcal{L}$ constitute a strongly terminal set, the inverse will be strictly negative.

Proof: C-Metzler are a class of compartmental matrices. As shown elsewhere (e.g. [35], Theorem 6.4.6) their eigenvalues are either zero or they have negative real parts (i.e. purely imaginary eigenvalues or eigenvalues with positive real part are not possible). Thus it only remains to prove that no zero eigenvalue exists.

To that purpose, we have that $W$ in system (25) is C-Metzler provided that at least a positive $b_i$ exists in the terminal set. If $a = 0$, the only equilibrium solution $W x^* = 0$, according to Proposition 3.2 will be $x^* = 0$. Thus no eigenvector with zero eigenvalue exists what implies that all eigenvalues are negative and therefore $W$ is stable and invertible. This proves the first part of the statement.

In order to show that a C-Metzler matrix inverse ($W^{-1}$) is non-positive, we first note that any equilibrium solution of (25) in the positive orthant satisfies that $W x^* = -a$. Since $W$ is invertible we have that:
\[
x^* = -Na, \quad \text{with } N = W^{-1}.
\]
Let us choose \( \mathbf{a} = \varepsilon_i \), so that \( \mathbf{x}^* = -(N)_i \), where \((N)_i\) represents the \( i\)-column of \( N \) matrix. According to Proposition 3.1, \( \mathbf{x}^* \geq 0 \) for any \( \mathbf{a} \geq 0 \), so that \((N)_i \leq 0\), which means that the entries of the \( i\)-column are non-positive. Repeating the argument for \( i = 1, \ldots, n \), we conclude that all entries of \( N \) are either zero or negative. In addition, if the nodes in \( \mathcal{L} \) are strongly linked, Proposition 3.3 holds for all \( \mathbf{a} = \varepsilon_i \) with \( i \in \mathcal{L} \) and the equilibria is strictly positive so that \( N \) will be a strictly negative matrix. \( \square \)

Some general consequences on the structure of matrix \( N = W^{-1} \) can be drawn from the above result. Let us consider a graph having just one strong terminal set \( \mathcal{L}_p \) with \( p \) nodes, and \( q \) non-terminal nodes. Numbering the nodes so that the first \( p \) are in \( \mathcal{L}_p \), we can partition \( N \) as:

\[
N = \begin{bmatrix}
N_p & N_{pq} \\
\emptyset & N_q
\end{bmatrix},
\]

(31)

where sub-matrix \( N_p \in \mathbb{R}^{p \times p} \) is strictly negative, since the rows/columns correspond with nodes in the strong terminal set, while \( N_{pq} \in \mathbb{R}^{p \times q} \) and \( N_q \in \mathbb{R}^{q \times q} \) are non-positive matrices. In addition, if \( \mathbf{a}^T = (\mathbf{a}_p^T, \mathbf{0}_q^T) \), with \( \mathbf{a}_p \in \mathbb{R}^p \) and at least one element positive, and \( \mathbf{0}_q \in \mathbb{R}^q \) the zero vector, then the first \( p \) entries of the solution \( \mathbf{x}^* = -N \mathbf{a} \) will be positive, and zero the rest.

**Example:** Graph in Figure 4 depicts two different scenarios. In Figure 4a, input \( a_2 \) enters a node in the strong terminal set thus forcing the states \( x_i^* \) 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 rest (non-terminal and terminal) thus forcing the states to reach a strictly positive value.

From these observations we can conclude that if \( W \) is the C-Metzler matrix associated to this graph, the sign patterns for the first two columns \((N)_1\) and \((N)_2\) of its corresponding inverse \( N \) should be of the form \((- - 0 0)^T\) (Figure 4a). In addition we should expect for the 3rd and 4th columns (Figure 4b) a sign pattern \((- - - -)^T\). Consequently, the sign pattern of the negative inverse will be as follows:

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

(32)

\( \triangle \)

### 4 A Canonical Representation of the Equilibrium Set

Expression (15) which describes the time evolution of the concentration vector can be re-written in terms of the stoichiometric matrices discussed in Section 2.2 so that:

\[
\dot{\mathbf{c}} = \sum_{\lambda} S_{\lambda} \phi_{\lambda}(\psi_{\lambda}),
\]

(32)
where $\phi_\lambda$ is a column vector that for each linkage class collects the fluxes present in (15). $\overline{\psi}_\lambda$ represents the vector of monomials associated to the linkage class, which possibly after some re-ordering will take the form $\overline{\psi}_\lambda = (\psi_{\lambda,j}, \psi_{\lambda}^T)^T$. Element-wise, these relate to fluxes by expression (7) which in matrix form reads:

$$\overline{\phi}_\lambda(\psi_{\lambda,j}, \psi_{\lambda}) = M_k^\lambda \overline{\psi}_\lambda,$$

where $M_k^\lambda \in \mathbb{R}^{N_\lambda \times N_\lambda}$ is a compartmental matrix that includes as entries the corresponding reaction constants, and $\overline{\phi}_\lambda = (\phi_{\lambda,j}, \phi_{\lambda}^T)^T$. Note that because of (8), $M_k^\lambda$ is a column conservation matrix, which we can re-write as:

$$M_k^\lambda = \begin{pmatrix} - (1^T a_\lambda) b_\lambda^T \\ E_\lambda \end{pmatrix},$$

with $b_\lambda^T = - 1^T E_\lambda$. By construction, the first row in $M_k^\lambda$ corresponds to the reference complex $j_\lambda$ which has been chosen to be in the terminal linkage class. Vectors $a_\lambda, b_\lambda \in \mathbb{R}^{N_\lambda - 1}$ contain as elements the rate constants for reaction steps leaving and entering, respectively, the reference complex. Hence, vector $b_\lambda$ is non-zero, i.e. at least one of the off-diagonal elements of $M_k^\lambda$ corresponding to the first row must be positive, since there is at least one reaction step directed to the reference complex. The remaining rate constants are collected in matrix $E_\lambda \in \mathbb{R}^{(N_\lambda - 1) \times (N_\lambda - 1)}$.

Inspection of the representation (32) suggests that equilibrium solutions, namely those that make $\dot{c} = 0$, correspond with complex balance conditions, which require all fluxes $\phi_i$ to be zero. Alternatively, non-zero flux combinations can lead to equilibrium, if the corresponding flux vector lies in the kernel of $S$. Provided that the network has positive deficiency, such fluxes can be written as linear combinations of the basis $\{ g_r^\lambda | r = 1, \ldots, \delta \}$ as follows:

$$\phi_\lambda = \sum_r \chi_r g_r^\lambda,$$

where $\chi_r$ are scalars. That (35) leads in fact to an equilibrium solution can be easily verified by substituting it into (32) and making use of (13).

**Example:** Let us consider the network depicted in Figure 6. Its corresponding matrix $M_k^\lambda$ consists of the following sub-matrix components:

$$E_\lambda = \begin{pmatrix} -(k_{21} + k_{23}) & k_{32} & 0 & 0 \\ k_{23} & -k_{32} & 0 & 0 \\ 0 & 0 & -(k_{43} + k_{45}) & k_{54} \\ 0 & 0 & k_{45} & -k_{54} \end{pmatrix}, \quad a_\lambda = \begin{pmatrix} 0 \\ 0 \\ 0 \\ k_{15} \end{pmatrix}, \quad b_\lambda = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \quad k_{21}$$

Molecularity and stoichiometric matrices are, respectively:

$$Y = \begin{pmatrix} 1 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 1 & 2 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \end{pmatrix} \quad \text{and} \quad S = \begin{pmatrix} -1 & -1 & 1 & -1 \\ 0 & 0 & 0 & 1 \\ 1 & -1 & -1 & -1 \\ 0 & 1 & 0 & 0 \end{pmatrix}.$$
Figure 6: A one linkage class weakly reversible network consisting of 4 chemical species \( \{A, B, C, D\} \). (a) The complex graph with explicit indication of the chemical species. (b) The graph with numbered complexes, including the reference complex indicated by the square box, the graph associated to the C-Metzler matrix and the non-zero coordinates in vectors \( a_\lambda \) and \( b_\lambda \), represented in the diagram as \( a_\lambda(4) \) and \( b_\lambda(1) \), respectively.

Since \( \text{rank}(S) = 3 \), the network has deficiency \( \delta = 1 \). Thus equilibrium solutions would correspond with fluxes satisfying relation (35) where \( g_\lambda^r \) defines a one-dimensional subspace which in this case corresponds with \( g = (1 \ 0 \ 1 \ 0)^T \).

In order to compute the set of equilibrium solutions, we substitute (35) into (33) and make use of the structure of \( M_\lambda^k \) and (8) to get:

\[
E_\lambda^T \psi_\lambda + \psi_\lambda a_\lambda = \sum_r \chi_r g^r_\lambda.
\]

(39)

Since we are interested in positive equilibrium solutions, let \( \psi_{j_\lambda} > 0 \), and multiply both sides of Eqn (39) by \( 1/\psi_{j_\lambda} \), to get after some re-arrangement:

\[
E_\lambda^T f_\lambda + a_\lambda = x_\lambda G_\lambda \chi
\]

(40)

where \( x_\lambda \in \mathbb{R} \), and matrix \( G_\lambda \) and vector \( \chi \) are, respectively:

\[
G_\lambda = [g^1_\lambda \cdots g^r_\lambda \cdots g^\delta_\lambda] \quad \text{and} \quad \chi = (\chi_1, \ldots, \chi_r, \ldots, \chi_\delta)^T.
\]

The strictly positive vector \( f_\lambda \) in (40) relates to the reaction monomials by the expression:

\[
f_\lambda = \exp \left( \ln \frac{1}{\psi_{j_\lambda}} \psi_\lambda \right).
\]

(41)

Note that, provided that \( c > 0 \), \( \overline{\psi}_\lambda \) relates to species concentration by means of expressions (3) so that for each complex \( i \in L_\lambda \setminus j_\lambda \), we have that \( \ln(\psi_i/\psi_{j_\lambda}) = (y_i - y_{j_\lambda})^T \ln c \). Hence the logarithm at the right hand side of (41) can be expressed as:

\[
\ln \frac{1}{\psi_{j_\lambda}} \psi_\lambda = S_\lambda^T \ln c.
\]

(42)

Without loss of generality we can select \( \chi \in \mathbb{R}^\delta \) to be in the unit sphere (\( \| \chi \| = 1 \)), and \( x_\lambda \) in a interval \( X(\chi) \subset \mathbb{R} \), such that \( f_\lambda \) remains a strictly positive vector.
In addition, we can re-write (38) as:

$$b_\lambda^T f_\lambda = 1^T (a_\lambda - x_\lambda G_\lambda \chi).$$

(43)

**Definition 4.1 (Family of Solutions [17])** The set of positive vectors $f_\lambda$ that solve (40) for a given $\chi$ and $x_\lambda$, for every $\lambda = 1, ..., \ell$ (therefore satisfying (43)) constitutes the so-called family of solutions.

Note that because $E_\lambda$ is C-Metzler and according to Lemma 3.1, invertible, the family of solutions always exist. Such solutions implicitly depend on the rate constants of the reaction network. Since $E_\lambda$ is invertible, we can define new vectors $f_\lambda^*$ and $h_\lambda^r$ (for $r = 1, \cdots, \delta$) of the form:

$$f_\lambda^* = -(E_\lambda)^{-1} a_\lambda \quad \text{and} \quad h_\lambda^r = (E_\lambda)^{-1} g_\lambda^r, \text{ for every } \lambda \text{ and } r.$$  

(44)

In particular, since $(E_\lambda)^{-1}$ is non-positive (see Lemma 3.1), $f_\lambda^* \succeq 0$ for $a_\lambda \succeq 0$. The same Lemma leads to $f_\lambda^* \succ 0$ (a strictly positive vector), provided that the underlying graph is weakly reversible. Substituting the above relations into (40), we get the family of solutions in explicit form as:

$$f_\lambda(x_\lambda; \chi) = f_\lambda^* + x_\lambda h_\lambda(\chi) \quad \text{where} \quad h_\lambda(\chi) = \sum_{r=1}^\delta h_\lambda^r \chi^r.$$  

(45)

It must be noted that not all positive vectors defined by (45) will necessarily comply with condition (42) but only a particular subset we will refer to as the set of feasible solutions. This set will be formally characterized in the next subsection.

### 4.1 The set of feasible equilibrium solutions

Among all positive vectors $f_\lambda$ of the form (15) for every $\lambda$, we concentrate on those that are consistent with relation (12). This implies that all vectors of the form $\ln f_\lambda$ must lie in the image of $S_\lambda^T$, so that:

$$\ln f_\lambda = S_\lambda^T \xi \quad \text{for } \lambda = 1, ..., \ell,$$

(46)

for some $\xi \in \mathbb{R}^m \ (\xi \equiv \ln c)$. Let $f$ be the vector that collects as subvectors the solutions $f_\lambda$ of (10). Vector $\ln f$ must be in the range of $S^T$, but since such range is orthogonal to the kernel of $S$, the following holds:

$$(\ln f)^T g^r = 0 \quad \text{for every } r = 1, ..., \delta.$$  

Expanding these expressions by linkage classes we get the equivalent relations:

$$\sum_{\lambda} (g_\lambda^r)^T \ln f_\lambda(x_\lambda; \chi) = 0 \quad \text{for every } r = 1, ..., \delta.$$  

(47)
In order to provide a formal characterization of feasible solutions we consider a vector $k^T = (k_1^T, \ldots, k_\lambda^T, \ldots, k_\ell^T)$ which collects, by linkage class, all reaction constants of the network. Each vector $k_\lambda$ determines $M_k^\lambda$ with its corresponding matrix $E^\lambda$, and vectors $a_\lambda$ and $b_\lambda$. Given this, together with $G_\lambda$ (which is related to the stoichiometric subspace) we get $f_\lambda$ and $h^r_\lambda$ for $r = 1, \ldots, \delta$ and every $\lambda$, via relations in (44). The family of solutions is then characterized for each unit vector $\chi$ and every $\lambda$, on intervals $X_\lambda(\chi) \subset \mathbb{R}$ by functions $f_\lambda(x_\lambda; \chi) : X_\lambda(\chi) \subset \mathbb{R} \to \mathbb{R}^{(N-1)}_+$, being of the form given by expression (45).

In passing it is worth noting that for weakly reversible networks the zero is contained in all intervals $X_\lambda(\chi)$, for every vector $\chi$. This is the case since $f_\lambda^\ast > 0$ (Lemma 3.1), thus $f_\lambda(0; \chi) > 0$.

Next we introduce a class of functions we will refer to as feasibility functions, that will help to formalize feasibility of equilibrium solutions:

**Definition 4.2 (Feasibility functions)** Let $F(x; \chi', \chi) : \mathbb{R}^\delta \times \mathbb{R}^\delta \to \mathbb{R}$ be defined as:

$$F(x; \chi', \chi) = g^T(\chi') \ln f(x; \chi)$$

(48)

where $\chi, \chi' \in \mathbb{R}^\delta$ are unit vectors, $g(\chi') = G\chi'$, with $G \in \mathbb{R}^{(n-1)\times \delta}$, and $f(x; \chi) : X(\chi) \subset \mathbb{R} \to \mathbb{R}^{(N-1)}_+$ being of the form:

$$f(x; \chi) = f^\ast + xh(\chi) \quad \text{with} \quad h(\chi) = E^{-1}G\chi,$$

(49)

with $E \in \mathbb{R}^{(n-1)\times(n-1)}$ C-Metzler, and $f^\ast \geq 0$.

Based on this definition, feasibility conditions (47) can be re-written in terms of functions (48) as follows:

**Definition 4.3 (Feasibility equilibrium solutions)** For a given chemical reaction network with a parameter vector $k$, feasible equilibrium solutions are those which correspond to $\chi \in \mathbb{R}^\delta$ in the unit sphere ($\|\chi\| = 1$) and $x_\lambda \in X_\lambda(\chi)$ for $\lambda = 1, \ldots, \ell$ such that:

$$\sum_\lambda F_\lambda(x_\lambda; \epsilon_r, \chi) = 0 \quad \text{for all} \quad r = 1, \ldots, \delta.$$  

(50)

where $\epsilon_r \in \mathbb{R}^\delta$ denotes the usual unit vector.

We note that if $\chi^*$ and $x_\lambda^*$ satisfy (50) we also get that $\sum_\lambda \sum_\epsilon F_\lambda(x_\lambda^*; \epsilon_r, \chi^*) = 0$, what in turn implies the following necessary condition:

$$\sum_\lambda F_\lambda(x_\lambda^*; \chi^*) = 0, \quad \text{where} \quad F_\lambda(x_\lambda; \chi) = g_\lambda^T(\chi) \ln f_\lambda(x_\lambda; \chi).$$

(51)

As we will see in the next sections, feasibility functions $F_\lambda(x; \chi)$ will prove to be fundamental to characterize the structure of equilibrium and conclude uniqueness in some instances.

---

*whenever $\chi = \chi'$, the short form $F(x; \chi)$ will be employed.*
4.2 Example: feasibility for a one linkage class weakly reversible network

Figure 7: Example of 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 complex graph with the reference complex in the squared box.

Let us consider a weakly reversible reaction network taken from [12] and presented in Figure 7. Matrix (54) for this network takes the form:

\[
M_k = \begin{bmatrix}
-k_{12} & 0 & 0 & k_{41} \\
k_{12} & -k_{23} & 0 & 0 \\
0 & k_{23} & -k_{34} & 0 \\
0 & 0 & k_{34} & -k_{41}
\end{bmatrix}
\]  

(52)

Substituting the reaction constants given in Figure 7 leads to the following sub-matrices comprising \( M_k \):

\[
E = \begin{bmatrix}
-\beta & 0 & 0 \\
\beta & -\epsilon & 0 \\
0 & \epsilon & -\beta
\end{bmatrix}, \quad a = \begin{bmatrix}
\epsilon \\
0 \\
0
\end{bmatrix}, \quad b = \begin{bmatrix}
0 \\
0 \\
\beta
\end{bmatrix}
\]  

(53)

For this example, the stoichiometric matrix \( S \) and its kernel basis, expressed as columns of matrix \( G \) read:

\[
S = \begin{pmatrix}
-2 & -3 & -1 \\
2 & 3 & 1
\end{pmatrix}, \quad G = \begin{pmatrix}
1 & 0 & -2 \\
0 & 1 & -3
\end{pmatrix}^T
\]

In order to compute the feasibility function \( \mathbf{f}(x; \chi) \) given in Definition 4.2, we have that \( \mathbf{f}(x; \chi) : \chi(x) \subset \mathbb{R} \rightarrow \mathbb{R}^{(n-1)}_+ \) is of the form given by (49), with:

\[
\mathbf{f}^* = -E^{-1}a \equiv \begin{pmatrix}
\epsilon/\beta & 1 \\
\epsilon/\beta
\end{pmatrix}^T, \quad E^{-1} = \begin{bmatrix}
-\frac{1}{\beta} & 0 & 0 \\
-\frac{1}{\beta} & -\frac{1}{\epsilon} & 0 \\
-\frac{1}{\beta} & -\frac{1}{\epsilon} & -\frac{1}{\beta}
\end{bmatrix}
\]  

(54)

and

\[
\mathbf{h}(\chi) = E^{-1} \begin{pmatrix}
\chi_1 \\
0 \\
-2
\end{pmatrix} + \chi_2 \begin{pmatrix}
0 \\
1 \\
-3
\end{pmatrix} \equiv \chi_1 \begin{pmatrix}
-1/\beta \\
-1/\epsilon \\
1/\beta
\end{pmatrix} + \chi_2 \begin{pmatrix}
0 \\
-1/\epsilon \\
2/\beta
\end{pmatrix}
\]
When $\chi = \chi'$, function (45) reduces to $F(x; \chi) = g^T(\chi) \ln f(x; \chi)$, with $g(\chi) = G\chi$. For parameters $\beta = 2$ and $\epsilon = 1$ we have that:

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

For $\chi_1 = (1 \ 0)^T$, the entries of the vector function $f(x; \chi_1)$ will remain all positive as long as the values taken by $x$ will lie in the open interval $(-1, +1)$. Hence, its domain $X(\chi_1) \equiv (-1, +1)$.

In the same way, for $\chi_2 = (0 \ 1)^T$, $X(\chi_2) \equiv (-1/2, +1)$. Because the logarithm is defined for positive values, both domains $X(\chi_1)$ and $X(\chi_2)$ coincide also with the domains for $F(x; \chi_1)$ and $F(x; \chi_2)$. The explicit expressions become:

$$F(x; \chi_1) = \ln \frac{2(1 - x)}{(1 + x)^2} \quad \text{and} \quad F(x; \chi_2) = \ln \frac{8(1 - x)}{(1 + 2x)^3}$$

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

![Figure 8](image-url)

Figure 8: Feasibility functions $F(x; \chi)$ associated to the network presented in Figure 7 for different vectors $\chi$. (a) $\chi = (1 \ 0)^T$, (b) $\chi = (0 \ 1)^T$, (c) $\chi = (-1 \ 0)^T$, (d) $\chi = (0 \ -1)^T$.

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 $F(x; \chi)$.
matter how many linkage classes a reaction network might have, or whether the network would be weakly reversible or irreversible, and despite any particular stoichiometry their complexes may exhibit. Next section provides a formal proof of this fact which will turn out to be central to explore the nature of equilibrium solutions.

5 Monotonicity of feasibility functions

Here we study the domain and properties of feasibility functions (48) of the form \( F(x; \chi) = g^T(\chi) \ln f(x; \chi) \). In particular it will be shown that such functions are monotonous decreasing on their domain, namely in the interval \( X(\chi) \) where \( f(x; \chi) \) remains positive. In the first place, and without loss of generality let us write (49) for a given \( \chi \) in the unit sphere as:

\[
f(x) = f^* + xh.
\]  

(55)

Provided that \( f^* \succ 0 \), the values of the scalar \( x \) for which the vector function \( f(x) \) will remain strictly positive will depend on the signs of the entries in \( h \). For every of such entries \( j \) define \( p_j = h_j/f^*_j \) and introduce two index sets \( I^+ \) and \( I^- \) so that:

\[
j \in I^+, \quad \text{if } h_j > 0, \text{ thus } p_j > 0
\]

\[
j \in I^-, \quad \text{if } h_j < 0, \text{ thus } p_j < 0
\]

(56)

It is straightforward to see that \( f(x) \) will be strictly positive for every \( x \) in the open interval \( X = (L^-, L^+) \), where \( L^- = \max_{j \in I^+} \{-1/p_j\} \) and \( L^+ = \min_{j \in I^-} \{-1/p_j\} \). Note that because \( f^* \succ 0 \), the interval \( X \) includes the zero.

Let us consider a weakly reversible linkage class, and assume without loss of generality that the components of \( h \) in (55) are ordered so that:

\[
h_1 \geq \cdots \geq h_k \geq \cdots \geq h_m > 0 > h_{m+r+1} \geq \cdots \geq h_{n-1}
\]

\[
h_{m+1} = \cdots = h_{m+r} = 0
\]

(57)

Note that such order can always be induced by a suitable row and column permutation in equations \( g = Eh \) and \( Ef^* = -a \). Making use of (56), we have that \( I^+ = \{1, \cdots, m\} \), \( I^- = \{m+r+1, \cdots, n-1\} \), and the domain \( X = (L^-, L^+) \) becomes:

\[
L^- = \max_{j \in I^+} \{-f^*_j/h_j\} \quad \text{and} \quad L^+ = \min_{j \in I^-} \{-f^*_j/h_j\}
\]

(58)

Note that \( L^- = -\infty \) (respectively \( L^+ = +\infty \)) provided that \( I^+ = \emptyset \) (respectively \( I^- = \emptyset \)). Associated to \( f(x) \) we have the corresponding to function (48) for \( \chi' = \chi \), which can be written as:

\[
F(x) = g^T \ln f(x),
\]

(59)

where \( g = Eh \) and \( E \) is a C-Metzler matrix with entries of the form (30). The main result on monotonicity is now presented in the Theorem below.
**Theorem 5.1** Consider the function $F(x) : X \subset \mathbb{R} \mapsto \mathbb{R}$ defined in (59). $F(x)$ is monotonous decreasing on the domain $X$. Moreover,

$$\lim_{x \to L^+} F(x) = -\infty \quad \text{and} \quad \lim_{x \to L^-} F(x) = +\infty \quad (60)$$

**Proof:** Function (59) is well defined in the domain $X$ since $f(x)$ is strictly positive, thus the first part of the proof reduces to computing the first derivative with respect to $x \in X$ and studying its sign over the domain. We start by defining for every entry $j$ of vectors $h$ and $f^*$ a relation $p_j = h_j/f_j^*$, and re-writing $h$ as:

$$h = D(f^*)p, \quad (61)$$

where $D$ represents a diagonal matrix with elements from $f^*$ in the diagonal. Let us also re-order the $p_j$ elements so that:

$$p_1 \geq \cdots \geq p_k \geq \cdots \geq p_m > 0 > p_{m+r+1} \geq \cdots \geq p_n \geq 0$$

where the number of positive, negative an zero elements must coincide with those in (57), although not necessarily in the same order. For all nonzero $p_j$ define functions $Q_j(x) : X \mapsto \mathbb{R}$:

$$Q_j(x) = \frac{p_j}{1 + xp_j} \quad (63)$$

For every $p_j > 0$ and $x \in X$ (see relations (56)), $x > -(1/p_j)$, so that $x + (1/p_j) > 0$, thus:

$$Q_j(x) \equiv \frac{1}{x + (1/p_j)} > 0$$

Using the same argument for $p_j < 0$ we have that $Q_j(x) < 0$. In addition, for any $p_i \geq p_j$, both different from zero, we have that $Q_i(x) \geq Q_j(x)$. Consequently, from (62), for every $x \in X$ we get that:

$$Q_1(x) \geq \cdots \geq Q_k(x) \geq \cdots \geq Q_m(x) > 0 > Q_{m+r+1}(x) \geq \cdots \geq Q_n(x) > 0$$

where $m+1 = \cdots = m+r = 0$.

$$Q_{m+1}(x) = \cdots = Q_{m+r}(x) = 0 \quad (64)$$

Keeping the order established in (62) for the indexes $j$, the first derivative can be written as:

$$F'(x) = \sum_{j=1}^{n-1} \frac{g_j h_j}{f_j^*(x)}, \quad (65)$$

where $g_j$ is the $j$ coordinate of vector $g = Eh$. The derivative is well defined on $X$ since $f_j > 0$ for every $j$ and $x \in X$. Moreover, by dividing every term in the summation by $f_j^*$ and using $p_j = h_j/f_j^*$, we re-write (66) as:

$$F'(x) = \sum_{j=1}^{n-1} g_j Q_j(x), \quad (66)$$

with functions $Q_j(x)$ as in (63). A matrix $H \in \mathbb{R}^{(n-1)\times(n-1)}$ is defined as:

$$H = ED(f^*) \quad (67)$$
which by construction is C-Metzler. By means of $H$ we re-write $Ef^* = -a$ and $g = Eh$, respectively as:

$$H1 = -a \quad \text{and} \quad g = Hp$$

where (61) has been used. Because $H$ is C-Metzler, and the relations (61) and (68) hold, we are under the conditions of Lemmas A.1 and A.2 in Appendix A. In particular the right hand side of (66) has the same structure as $G(x)$ in Lemma A.2. Consequently, the first derivative is strictly negative on the domain $X$ and the result follows.

In order to show (60), we note that $f_j(x) \equiv f_j^*(1 + xp_j)$, and re-write (59) as:

$$F(x) \equiv \sum_{j=1}^{n-1} g_j \ln f_j^*(x) = \sum_{j=1}^{n-1} g_j \ln f_j^* + \sum_{j=1}^{n-1} g_j \Pi_j(x), \quad (69)$$

where $\Pi_j(x) = \ln(1 + xp_j)$. The first term on the right hand side is constant while the second term can be expanded as in (A.14) (proof of Lemma A.2) with $\Pi_j(x)$ instead of $Q_j(x)$. The expression becomes:

$$F(x) = \sum_{j=1}^{n-1} g_j \ln f_j^* + (\Pi_1 - \Pi_2)g_1 + (\Pi_2 - \Pi_3)(g_1 + g_2) + \cdots + (\Pi_k - \Pi_{k+1}) \sum_{j=1}^{k} g_j + \cdots + \Pi_m \sum_{j=1}^{m} g_j +$$

$$\cdots + \Pi_{m+r+1} \sum_{j=m+r+1}^{n} g_j + \cdots + (\Pi_\ell - \Pi_{\ell+1}) \sum_{j=\ell}^{n} g_j + \cdots + (\Pi_{n-2} - \Pi_{n-1})g_{n-1} \quad (70)$$

where $\Pi_i - \Pi_j \equiv \ln \left[ (1 + xp_i)/(1 + xp_j) \right]$. Three possible scenarios are considered depending on the signs of the $p$ entries:

1. All entries are positive or zero, so that $m + r = n$. In this case the domain $X = (-1/p_1, +\infty)$ and the following limits hold:

$$\lim_{x \to +\infty} (\Pi_k - \Pi_{k+1}) = 0$$

$$\lim_{x \to -1/p_1} (\Pi_k - \Pi_{k+1}) = \text{constant} \quad \text{if} \quad -1/p_{k+1} \leq -1/p_k < -1/p_1$$

or

$$\lim_{x \to -1/p_1} (\Pi_k - \Pi_{k+1}) = -\infty \quad \text{if} \quad -1/p_{k+1} \leq -1/p_k = -1/p_1$$

$$\lim_{x \to -1/p_1} \Pi_m = -\infty \quad \text{and} \quad \lim_{x \to +\infty} \Pi_m = +\infty$$

2. All entries are negative or zero so that $m = 0$, the domain $X = (-\infty, -1/p_{n-1})$ and the following limits hold:

$$\lim_{x \to -\infty} (\Pi_\ell - \Pi_{\ell+1}) = 0$$

$$\lim_{x \to -1/p_{n-1}} (\Pi_\ell - \Pi_{\ell+1}) = \text{constant} \quad \text{if} \quad -1/p_{n-1} < -1/p_{\ell+1} \leq -1/p_\ell$$

or

$$\lim_{x \to -1/p_{n-1}} (\Pi_\ell - \Pi_{\ell+1}) = -\infty \quad \text{if} \quad -1/p_{n-1} = -1/p_{\ell+1} \leq -1/p_\ell$$
\[
\lim_{x \to -1/p_n-1} \Pi_{r+1} = -\infty \quad \text{and} \quad \lim_{x \to -\infty} \Pi_{r+1} = +\infty
\]

3. There are both, positive, zero or negative entries so the domain becomes \( X = (-1/p_1, -1/p_{n-1}) \).

In all three scenarios, substitution of the corresponding limits and use of Lemma A.1 leads to (60).

5.1 Irreversible networks

Previous results can be extended to irreversible linkage classes, provided that a positive equilibrium solution exits. The main difference however lies in that the interval \( X \) does not contain the zero. The essential arguments behind can be found in Lemma 3.1 and the structure of inverses of C-Metzler matrices.

Consider a linkage class with \( n \) complexes to be split into a strongly terminal linkage class \( L_p \) with \( p \) complexes and a non-terminal set \( L_q \) with \( q \) complexes, so that \( L = L_p \cup L_q \). Without loss of generality, assume that complexes in the linkage class are ordered so that the associated C-Metzler matrix \( E \) will be written as:

\[
E = \begin{bmatrix}
E_p & E_{pq} \\
\emptyset & E_q
\end{bmatrix},
\]

where \( E_p \in \mathbb{R}^{p \times p}, E_q \in \mathbb{R}^{q \times q}, \) and \( E_{pq} \in \mathbb{R}^{p \times q} \). As before, feasible solutions, \( f(x) : X \subset \mathbb{R} \to \mathbb{R}^{(n-1)} \) can be written as:

\[
f(x) = f^* + xh \quad \text{with} \quad f^* \geq 0,
\]

where \( f^* = -E^{-1}a \), and \( h = E^{-1}g \). Because the reference complex belongs to \( L_p \), the coordinates of vector \( a \) that correspond to non-terminal complexes are zero, what together with the expression for the inverse of a C-Metzler matrix, and particularly with the expression (31) leads to a vector \( f^* \) with zero components at the location of non-terminal complexes. In fact we can write

\[
E^T = [f^*_p, 0^T_q],
\]

where \( f^*_p \) denotes a \( p \)-dimensional column vector of zeros. Vector \( f^*_p \), which corresponds to the terminal linkage class, is strictly positive. In addition, let \( h^T = [h^T_p, h^T_q] \), and re-write (72) as:

\[
f_p(x) = f^*_p + xh_p \\
f_q(x) = 0_q + xh_q
\]

Since \( f^*_p \) is strictly positive, there exists some domain \( X_p \) that includes the zero, for which \( f_p(x) > 0 \). Let \( X_p = X^-_p \cup X^+_p \cup \{0\} \), where \( X^-_p \) and \( X^+_p \) contain all negative and positive values, respectively. It is then straightforward to see from (73) that in order for \( f_q(x) > 0 \), \( h_q \) must have a definite sign (i.e. all components either positive or negative). If this is the case, i.e. if \( h_q > 0 \) (respectively \( h_q < 0 \)), we can always find some \( x \in X^+_p \) (respectively \( x \in X^-_p \)), so that \( f(x) > 0 \). Otherwise, no positive solution will exist.
As we will show, the feasibility function \( f_q \) is still monotonous decreasing on its domain for irreversible linkage classes, provided that a positive feasible solution exists. To show this, we first notice that because \( f_q^+ = 0 \) and \( x \in \mathbb{X} \setminus \{0\} \), the summation in (59), extended to non-terminal complexes in \( L_q \), becomes:

\[
\sum_{j \in L_q} g_j h_j = \frac{1}{x} \sum_{j \in L_q} g_j = \frac{1}{x} \mathbf{g}_q^T \mathbf{x} = \mathbf{g}_q^T \mathbf{x},
\]

where \( \mathbf{g}_q = E_q \mathbf{h}_q \). But the right hand side of the above expression is negative, since by construction positive solutions require \( \mathbf{h}_q > 0 \) (respectively \( < 0 \)) for \( x \in \mathbb{X}^+_q \) (respectively \( x \in \mathbb{X}^-_q \)). Thus \( \mathbf{g}_q^T \mathbf{x} \leq 0 \) (respectively \( \geq 0 \)). Consequently \( F'(x) < 0 \) and Theorem 6.1 applies.

**Example:** Let us consider the irreversible network represented in Figure 9. For this network matrix \( E \) and vectors \( \mathbf{a} \) and \( \mathbf{b} \) in (34) take the form:

\[
E = \begin{bmatrix}
-(k_{21} + k_{23}) & k_{32} & 0 & 0 \\
k_{23} & -k_{32} & k_{43} & 0 \\
0 & 0 & -(k_{43} + k_{45}) & k_{54} \\
0 & 0 & k_{45} & -k_{54}
\end{bmatrix}, \quad \mathbf{a} = \begin{bmatrix} 0 \\ k_{13} \\ 0 \\ 0 \end{bmatrix}, \quad \mathbf{b} = \begin{bmatrix} k_{21} \\ 0 \\ 0 \\ 0 \end{bmatrix}
\]

(74)

Molecularity and stoichiometric matrices coincide with those of the network in Figure 9 and are given in (37). Thus the network has deficiency one and \( \mathbf{g} = (1 \ 0 \ 1 \ 0)^T \). For rate constants \( k_{13} = k_{23} = k_{54} = k_{45} = 1, k_{21} = 2, k_{32} = 1.5 \) and \( k_{43} = 5 \), matrix \( E \) and its corresponding inverse are:

\[
E = \begin{bmatrix}
-3 & 3/2 & 0 & 0 \\
1 & -3/2 & 5 & 0 \\
0 & 0 & -6 & 1 \\
0 & 0 & 1 & -1
\end{bmatrix}, \quad E^{-1} = \begin{bmatrix}
1/2 & 1/2 & 1/2 & 1/2 \\
1/3 & 1 & 1 & 1 \\
0 & 0 & 1/5 & 1/5 \\
0 & 0 & 1/5 & 6/5
\end{bmatrix}
\]

For this particular set of constants, the vectors at the right hand side of (72) become:

\[
\mathbf{f}^* = \begin{bmatrix} 1/2 \\ 1/2 \\ 1/2 \\ 1/2 \end{bmatrix}, \quad \mathbf{h} = - \begin{bmatrix} 4/3 \\ 1/5 \\ 1/5 \\ 1/5 \end{bmatrix}
\]

Because the entries in \( \mathbf{h} \) corresponding to the non-terminal complexes have, all of them, a negative sign, a positive feasible solution \( \mathbf{f} \) exists. On the other hand, a related network structure with \( k_{45} = 0 \) leads to a vector:

\[
\mathbf{h} = - \begin{bmatrix}
1/2 & 1/2 & 1/2 & 1/2 \\
1/3 & 1 & 1 & 1 \\
0 & 0 & 1/5 & 1/5 \\
0 & 0 & 0 & 1
\end{bmatrix} \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}
\]

Since \( \mathbf{h} = - (1 \ 4/3 \ 1/5 \ 0)^T \), and therefore \( \mathbf{h}_q = ( -1/5 \ 0)^T \) does not have a definite sign (strictly negative or positive vector), a positive solution for \( \mathbf{f} \) does not exist. In fact at equilibrium, the fourth entry \( f_4 = 0 \).

\[ \triangle \]
Figure 9: A one linkage class irreversible network. (a) The complex graph with explicit indication of the chemical species. (b) The reference complex in a square box, graph associated to the C-Metzler matrix and non-zero entries for vectors $a_\lambda$ and $b_\lambda$ (coordinates $a_\lambda(2)$ and $b_\lambda(1)$, respectively).

6 Some network classes with unique equilibrium solutions

Chemical reaction network structure with its associated C-Metzler matrices shapes the set of feasible equilibrium solutions, that we compute via the feasibility functions given in Definition 4.2. In this section we exploit monotonicity of such functions to conclude whether or not equilibria is unique over compatibility classes.

In particular we will show that under a complex balance condition, no other equilibrium solution is compatible with the complex balance one in each compatibility class. Complex balance solutions are only possible for a given set of reaction rate constants we will refer to as the Horn set, following a previous contribution [28]. For the sake of completeness, a formal characterization of the set will be given together with some remarks on uniqueness and stability of the resulting equilibria. Finally, conditions for one particular class of non-complex balance equilibrium to be unique will be discussed. Such conditions constitute the basis for an alternative proof of the so-called deficiency one theorem [13].

Let us consider a weakly reversible network with $\ell$ linkage classes, a vector of reaction rate constants $k$ and deficiency $\delta$. According to Definition 4.1, the family of solutions in each linkage class $\lambda$ reads as in (45), for every $\chi$ in the unit circle, with:

$$h_\lambda(\chi) = (E^\lambda)^{-1}g_\lambda(\chi) \quad \text{and} \quad g_\lambda(\chi) = G_\lambda \chi$$

Since each linkage class is weakly reversible, Proposition 3.3 and Lemma 3.1 applies and $f_\lambda^* > 0$ for every $\lambda = 1, ..., \ell$. Furthermore, intervals $X_\lambda(\chi)$, which are constructed as shown in Section 5 contain the zero for every $\chi$ vector.

Vectors $f^*$ and $h$ in expression (45) are functions of the reaction rate constants. In fact, let us suppose that for a vector $k$, there exists a complex balance solution, namely a feasible $f_\lambda(0) = f_\lambda^*(k)$ for every $\lambda$. This requires $f^T = (f^T_1 \cdots f^T_\lambda \cdots f^T_\ell)$ to be in the range of
\( S^T \), and motivates the definition of the Horn set as that which collects all possible reaction rate constants that lead to complex balance solutions. Formally, the set is defined as:

\[
\mathcal{H}(k) = \{ k > 0 \mid \ln f^*(k) \in \text{Range}(S^T) \}.
\]  

(75)

**Remark 6.1** If the network is non weakly reversible, some entries in each of the vectors \( f^*_\lambda \) will be zero, thus such networks cannot accept complex balance solutions.

**Proposition 6.1 (Complex Balance Solutions)** Any weakly reversible reaction network with parameters in \( \mathcal{H}(k) \) will only accept complex balance solutions. Complex balance solutions are unique in each compatibility class, and stable.

**Proof:** We first prove that for any \( k \in \mathcal{H} \), the family of solutions \( f^*_\lambda(0; \chi) = f^*_\lambda(k) \) for every \( \lambda \) is feasible, i.e. they satisfy conditions of Definition 4.3. In that purpose we note that each term in the summation (50) becomes of the form:

\[
F^*_\lambda(0; \varepsilon_r, \chi) \equiv g^T_\lambda(\chi) \ln f^*_\lambda(k) \text{ with } g_\lambda(\chi) = \sum_{r=1}^{\delta} \chi^r g^r_\lambda
\]

By construction \( \ln f^*_\lambda \) (for every \( \lambda \)) is in the range of \( S^T_\lambda \) so it is orthogonal to the kernel of \( S_\lambda \). Hence \( (\ln f^*_\lambda)^T g^r_\lambda = 0 \) for any \( r \) and \( \lambda \), \( F^*_\lambda(0; \varepsilon_r, \chi) = 0 \) and conditions (50) and (51) hold for \( x^*_\lambda = 0 \) and every vector \( \chi \) and \( \lambda \).

In addition, by Theorem 5.1 we have that each term \( F^*_\lambda(x^*_\lambda, \chi) \) in summation (51) is monotonous decreasing in \( x^*_\lambda \), so that for each interval \( X^*_\lambda \) we have:

\[
\sum_{\lambda} F^*_\lambda(x^*_\lambda; \chi) < 0 \text{ for every } x^*_\lambda \in X^-_\lambda(\chi) \text{ and } \lambda = 1, \ldots, \ell
\]

\[
\sum_{\lambda} F^*_\lambda(x^*_\lambda; \chi) > 0 \text{ for every } x^*_\lambda \in X^+_\lambda(\chi) \text{ and } \lambda = 1, \ldots, \ell
\]

where \( X^-_\lambda \) and \( X^+_\lambda \) are the negative and positive subintervals, respectively, so that \( X^*_\lambda = X^-_\lambda \cup \{0\} \cup X^+_\lambda \). Since this holds for every \( \chi \), no feasible solutions other than the complex balance can be expected.

In order to prove uniqueness in each compatibility class, we note that by using (41) we can write the complex balance solution as \( \ln f^* = S^T \ln c \). Suppose that \( c_1 \) and \( c_2 \) are two concentration vectors that are compatible with the same \( f^* \) so that \( S^T(\ln c_1 - \ln c_2) = 0 \). By Proposition 6.1 both solutions cannot belong to the same compatibility class which proves uniqueness. Finally, stability of complex balance solutions follows from Proposition B.2 in Appendix B. □

The above result can be considered an alternative version of the one given by [29] on the existence of complex balance solutions for weakly reversible reactions. In passing we remark that zero deficiency reaction networks, if weakly reversible, will only accept a family of solutions satisfying...
\[ \mathbf{f}^* = S^T \ln \mathbf{c} \]. Since \( \delta = 0 \), the subspace defined by the columns of \( S^T \) (\( \text{Range}(S^T) \)) will span all the complex space what in turn implies that any vector \( \mathbf{k} \) will be an element of the Horn set \( \mathcal{H}(\mathbf{k}) \). In addition, it is straightforward to conclude from the arguments in the proof we just presented that any solution will be unique (one per compatibility class) and stable. If the network is irreversible positive solutions are not expected to be found. Such conclusions have been presented in the form of a theorem known in CRNT as the zero deficiency theorem \[12\].

**Example: The Horn set for a weakly reversible reaction** Let us consider the example presented in Section 4.2 of a deficiency \( \delta = 2 \) network. The corresponding graph structure, including stoichiometry and the set of possible parameters is depicted in Figure 7. For this 2-parameter network, and following expression (75) the Horn set is obtained by finding those \( (\epsilon, \beta) \) so that \( \ln \mathbf{f}^* \) is orthogonal to \( \mathbf{g}^1 \) and \( \mathbf{g}^2 \). This is equivalent to \( \ln \mathbf{f}^* \) lying in \( \text{Range}(S^T) \), which can be written as:

\[
\begin{pmatrix} 1 & 0 & -2 \\ 0 & 1 & -3 \end{pmatrix} \ln \begin{pmatrix} \frac{\epsilon}{\beta} \\ 1 \end{pmatrix} = 0.
\]

(76)

The above condition holds for parameters on the Horn set described as \( \alpha = \beta \). Then, by construction \( \ln \mathbf{f}(0; \chi) = 0 \) for every \( \chi \), so that \( \mathbf{F}(0; \chi) = 0 \). Since \( \mathbf{F}(\mathbf{x}; \chi) \) is monotonous decreasing, only complex balance solutions exist for parameters in the Horn set. \( \triangle \)

**Remark 6.2** If the network is compatible with thermodynamics, meaning reversible with a detailed balance solution (note that this implicitly requires the system to be closed), any allowed reaction constant for the network must be in \( \mathcal{H}(\mathbf{k}) \). In this way, the definition of the Horn set can be considered as an alternative statement of the Wegscheider conditions (see \[22\] for a classical statement of the conditions)

Next we present a result that can be interpreted as an alternative proof of the deficiency one theorem originally proposed by \[13\] and recently by \[31\], both employing diverse graph theoretical formalisms. The conditions behind are simple and can be phrased as follows:

In order for the theorem to hold, a basis in the kernel of \( S \) must have at most one vector \( \mathbf{g}^r \) per lineage class. In addition, the only possible nonzero coordinates for each of those vectors must be at the location of the complexes that correspond to the linkage class the vector is associated to. Formally, this last condition can be expressed as:

\[
(\mathbf{g}^i)^T \omega_j = \delta_{ij}
\]

where \( \omega_j \) are the characteristic functions of a linkage class \( \Pi \), and \( \delta_{ij} \) the Kronecker delta. The structure of the vectors is illustrated in Figure 10 for a network consisting of 3 linkage classes, with the grey areas representing the non-zero vector coordinates.

As sketched in the same figure, such particular structure for the \( \mathbf{g}^r \) vectors makes the corresponding feasibility conditions (Definition \[43\]) to be decoupled along linkage classes thus leading
to one particular $x^*_\lambda$ solution per linkage class.

Figure 10: The underlying condition behind the deficiency one theorem requires vectors $g^\lambda_r$ in the basis of the kernel of $S$ to be as depicted, 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.

**Proposition 6.2** (*Deficiency One Theorem*) Let us consider a weakly reversible reaction network with $\ell$ linkage classes such that $\delta = \sum_\lambda \delta_\lambda$, where $\delta_\lambda$ is either 0 or 1. Then there will be a unique equilibrium in each compatibility class.

**Proof:** From the assumptions, in order for each linkage class to have at most deficiency one $\delta \leq \ell$, otherwise there will exists at least one linkage class with more than one vector $g^\lambda_r \neq 0$. Since each linkage class $\lambda$ will contribute to the network deficiency with one vector $g^\gamma$ at most, we will have that $g^\lambda_r \neq 0$ and $g^k_r = 0$ for every $k \neq \lambda$ (i.e. the remaining $\ell - 1$ sub-vectors will be zero) and $r \leq \min(\delta, \ell) \leq \ell$. For this particular set of vectors, equation (49) for any $\chi$ in the unit circle becomes $f_\lambda(x; \chi) = f^\lambda_r + x_\lambda h_\lambda$ with $h_\lambda = (E^\lambda)^{-1}g^\lambda_r$, and $r \leq \min(\delta, \ell)$. On the other hand, condition (50) reduces to just one term in each summation, so that:

$$F_\lambda(x_\lambda) = 0 \text{ for } \lambda = 1, \ldots, \min(\delta, \ell) \text{ with } F_\lambda(x_\lambda) = (g^\lambda_r)^T \ln f_\lambda(x_\lambda)$$

According to Theorem 5.1 each function $F_\lambda(x_\lambda)$ is monotonous decreasing and because of (60), it becomes zero at a point $\tilde{x}_\lambda \in X_\lambda$. Moreover, there exists a unique feasible solution $f_\lambda(\tilde{x}_\lambda)$ for each linkage class $\lambda$. Combining the solution for each linkage class and using Eqn (46), we get that $S^T \xi = \ln \tilde{f}$, with $\xi \equiv \ln c$. Uniqueness then follows by applying Proposition B.1.

As a final remark, we note that this result allows us to conclude uniqueness (although not stability) of equilibria for networks with deficiency other than zero under a quite particular condition that we can express as follows:

The number of linkage classes in the network cannot exceed the deficiency of the network,
otherwise we would find at least two $g^* \neq 0$ associated to the same linkage class, what would preclude decoupling of the feasibility conditions (4.3) along linkage classes.

### 6.1 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:

$$
\begin{align*}
2A \rightleftharpoons B & \quad B \rightleftharpoons 2C & \quad 2C \rightleftharpoons D \\
B \rightleftharpoons A + C & \quad 2C \rightleftharpoons A + C \\
C + E \rightleftharpoons 2G & \\
A + D \rightleftharpoons E & \quad E \rightleftharpoons F & \quad A + D \rightleftharpoons F
\end{align*}
$$

(77)

This particular reaction network comprises $n = 10$ complexes and $\ell = 3$ linkage classes we represent in graph form in Figure 11 with explicit indication of the species (Figure 11a) as well as in terms of numbered complexes (Figure 11b).

![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](image)

Complexes are grouped by linkage class in the sets $L_1 = \{1, 2, 3, 4, 5\}$, $L_2 = \{6, 7, 8\}$ and $L_3 = \{9, 10\}$. The stoichiometry associated to the complexes is given column-wise by the following molecularity matrix (Section 2.1):

$$
Y = \begin{pmatrix}
2 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 2 & 0 & 1 & 0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 2 & 0 & 0
\end{pmatrix}
$$

(78)

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

\[
S_1 = \begin{pmatrix}
-2 & -2 & -2 & -1 \\
1 & 0 & 0 & 0 \\
0 & 2 & 0 & 1 \\
0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
\end{pmatrix}, \quad S_2 = \begin{pmatrix}
-1 & -1 \\
0 & 0 \\
0 & 0 \\
1 & 0 \\
0 & 1 \\
0 & 0 \\
-2 \\
\end{pmatrix}, \quad S_3 = \begin{pmatrix}
0 \\
0 \\
1 \\
0 \\
0 \\
0 \\
-2 \\
\end{pmatrix}.
\]

Net reaction fluxes take the form:

\[
\phi_2 = k_{1,2} \psi_1 + k_{3,2} \psi_3 + k_{5,2} \psi_5 - (k_{2,1} + k_{2,3} + k_{2,5}) \psi_2 \\
\phi_3 = k_{2,3} \psi_2 + k_{4,3} \psi_4 + k_{5,3} \psi_5 - (k_{3,2} + k_{3,4} + k_{3,5}) \psi_3 \\
\phi_4 = k_{3,4} \psi_3 - k_{4,3} \psi_4 \\
\phi_5 = k_{2,5} \psi_2 + k_{3,5} \psi_3 - (k_{5,2} + k_{5,3}) \psi_5 \\
\phi_7 = k_{6,7} \psi_6 + k_{7,8} \psi_8 - (k_{7,6} + k_{7,8}) \psi_7 \\
\phi_8 = k_{6,8} \psi_6 + k_{7,8} \psi_7 - (k_{8,6} + k_{8,7}) \psi_8 \\
\phi_{10} = k_{9,10} \psi_9 - k_{10,9} \psi_{10}
\]

The remaining fluxes \( \phi_1, \phi_6 \) and \( \phi_9 \), associated to the reference complexes, are obtained by means of relation (S).

The dimension of the stoichiometric subspace, which coincides with the rank of matrix \( S = [ S_1 \ S_2 \ S_3 ] \), is \( s = 6 \), and renders a network deficiency \( \delta = 10 - 3 - 6 = 1 \). Hence the kernel of \( S \) is one dimensional with a basis \( g^1 = ( 0 \ -1/2 \ 0 \ 1 \ 0 \ 0 \ 0 )^T \). As shown in Section 2.2 we identify the following three sub-vectors in \( g^1 \) that solve (13):

\[
g_1^1 = (0 \ -1/2 \ 0 \ 1)^T \\
g_2^1 = (0 \ 0)^T \\
g_3^1 = (0)^T
\]

The canonical representation of the equilibrium set will be expressed in terms of matrices \( M_k^\lambda \) that appear in Eqn (33). From the expressions (79) for the fluxes we have that:

\[
M_k^1 = \begin{bmatrix}
-k_{1,2} & 0 & 0 & 0 \\
k_{1,2} & -k_{2,1} & -k_{2,3} & +k_{2,5} \\
0 & k_{2,3} & -k_{3,2} & +k_{3,4} & +k_{3,5} \\
0 & 0 & k_{3,4} & -k_{4,3} & 0 \\
0 & 0 & k_{3,5} & 0 & -(k_{5,2} + k_{5,3}) \\
\end{bmatrix}
\]

\[
M_k^2 = \begin{bmatrix}
-(k_{6,7} + k_{6,8}) & k_{7,6} \\
k_{6,7} & -(k_{7,6} + k_{7,8}) \\
k_{6,8} & k_{7,8} & -(k_{8,6} + k_{8,7})
\end{bmatrix}, \quad M_k^3 = \begin{bmatrix}
-k_{9,10} & k_{9,10} & -k_{10,9} \\
k_{9,10} & -k_{10,9} \\
0 & 0 & (k_{5,2} + k_{5,3})
\end{bmatrix}
\]

Comparing each matrix with the structure given in [34] we get for each linkage class:

\[
E^1 = \begin{bmatrix}
-(k_{2,1} + k_{2,3} + k_{2,5}) & k_{3,2} & 0 & k_{5,2} \\
k_{2,3} & -(k_{3,2} + k_{3,4} + k_{3,5}) & k_{4,3} & k_{5,3} \\
0 & k_{3,4} & -k_{4,3} & 0 \\
k_{2,5} & k_{3,5} & 0 & -(k_{5,2} + k_{5,3})
\end{bmatrix}
\]
\[ E^2 = \begin{bmatrix} -(k_{7,6} + k_{7,8}) & k_{8,7} \\ k_{7,8} & -(k_{8,6} + k_{8,7}) \end{bmatrix}, \quad E^3 = \begin{bmatrix} -k_{10,9} \end{bmatrix} \]  

\[ a_1 = \begin{bmatrix} k_{1,2} & 0 & 0 & 0 \end{bmatrix}^T, \quad a_2 = \begin{bmatrix} k_{6,7} & k_{6,8} \end{bmatrix}^T, \quad a_3 = \begin{bmatrix} k_{9,10} \end{bmatrix}^T \]  

Equations (15) to describe the family of solutions read as follows:

\[ f_1(x_1) = f_1^* + x_1 h_1 \]
\[ f_2(x_2) = f_2^* \]
\[ f_3(x_3) = f_3^* \]

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

\[ f_1^* = (1.0000, 30.1818, 75.4545, 2.1091)^T, \quad f_2^* = (0.2000, 0.8571)^T \]
\[ h_1 = (-0.2500, -7.5455, -18.8636, -1.0273)^T, \quad f_3^* = (0.2500) \]

As it can be seen in Figure 12 (a), function \( F_1^1(x_1) = (g_1^1)^T \ln f_1(x_1) \) is monotonous decreasing, with one solution (intersection with the x-axis) at \( x_1^* = -6.69 \) so that Proposition 6.2 applies. Another example is represented in Figure 12 (b) 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 \( X_1 = (L_1^-, L_1^+) \), with \( L_1^- = -0.6154 \) and \( L_1^+ = +0.3636 \). Vector \( h_1 \) for this parameter set becomes \( h_1 = (-0.0500, 0.1857, 0.1857, -0.0786)^T. \) For this case the function crosses the x-axis at \( x_1^* = -0.5854 \).

Figure 12: Function \( F_1^1(x) = (g_1^2)^T \ln f_1(x) \) corresponding to linkage class 1. Note that for the other linkage classes the functions are zero since vectors \( g_1^2 \) and \( g_1^3 \) are identically zero. In (a) the function is represented for the set of rate constants in Table 1. In (b) the function is represented for all rate constants in (a) but \( k_{2,1} = k_{5,2} = 10.0 \)
In order to compute all possible equilibrium solutions in the concentration space we make use of \( \mathbf{f}^T = [ f_1^T(x_1^*) \ f_2^T \ f_3^T ] \), where the first vector \( f_1^T(x_1^*) \) for \( x_1^* = -6.69 \) and \( x_1^* = -0.5854 \) takes, respectively the values:

\[
\begin{align*}
f_1(x_1^*) &= ( 2.6725 \ 80.6609 \ 201.6523 \ 8.9815 )^T \\
f_1(x_1^*) &= ( 0.2293 \ 0.0056 \ 0.0056 \ 0.0746 )^T
\end{align*}
\]

The set of equilibrium concentrations is then computed by solving \( \ln \mathbf{f} = S^T \ln \mathbf{c} \). 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 any compatibility class defined in \([14]\) with \( B = ( 1/2 \ 1 \ 1/2 \ 1 \ 3/2 \ 3/2 \ 1 )^T \) in just one point per reaction simplex.

7 Conclusions

In this paper a canonical representation of the set of feasible equilibrium solutions for weakly reversible reaction networks is given. The characterization is made in terms of a class of stable Metzler matrices which are employed to define the family of solutions. Feasibility is imposed by a set of constraints, that relate to the kernel of the stoichiometric subspace. A particularly interesting class of monotonous functions can be linked to such constraints which turn out to be critical to conclude uniqueness in a class of deficiency one networks. They are in fact central for a constructive proof of the deficiency one theorem as well as to the characterization of the set which defines in the parameter space, the region of complex balance solutions (Horn set). Future directions may involve detection or design of networks having multiple equilibria.

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A Two Lemmas required to prove monotonicity

The following results relate directly to the properties of C-Metzler matrices.

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

$$H 1 = -a,$$  \hspace{1cm} (A.1)

with $a \succeq 0$. Let $p \neq 0$ be a vector with components satisfying:

$$p_1 \geq \cdots \geq p_k \geq \cdots \geq p_m > 0 > p_{m+r+1} \geq \cdots \geq p_n$$

with $p_{m+1} = \cdots = p_{m+r} = 0$ \hspace{1cm} (A.2)

and

$$g = Hp$$ \hspace{1cm} (A.3)

Then:

$$\sum_{j=1}^{k} g_j \leq 0 \text{ for every } 1 \leq k \leq m$$ \hspace{1cm} (A.4)

and

$$\sum_{j=\ell}^{n} g_j \geq 0 \text{ for every } m + r + 1 \leq \ell \leq n$$ \hspace{1cm} (A.5)

Moreover:

$$\sum_{j=1}^{m} g_j < 0 \text{ and } \sum_{j=m+r+1}^{n} g_j > 0$$ \hspace{1cm} (A.6)

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

$$H(p - p_k 1) = g + p_k a$$ \hspace{1cm} (A.7)

Summing the first $k$ elements and reordering terms results in:

$$\sum_{j=1}^{k} g_j = \sum_{i=1}^{k-1} \left( (p_i - p_k) \sum_{j=1}^{k} H_{ji} \right) + \sum_{i=1}^{k} \sum_{j=k+1}^{n} H_{ij}(p_j - p_k) + (-p_k) \sum_{j=1}^{k} a_j$$ \hspace{1cm} (A.8)

The first term at the RHS is non-positive since by construction $p_i - p_k \geq 0$ for $i = 1, \cdots, k - 1$, and $H$ is C-Metzler. In addition, for any sub-matrix containing the first $k$ rows and $k$ columns of $H$ is also C-Metzler and for any $0 < k < n$ we have that:

$$\sum_{j=1}^{k} H_{ji} \leq 0 \text{ for } i = 1, \cdots, k$$

The second and third terms respectively are also non-positive: since $H_{ij} \geq 0$ for every $i \neq j$ and $p_j - p_k \leq 0$ for $j = k + 1, \cdots, n$, and because $a$ is a nonnegative vector. Thus, relation (A.4) follows.
In a similar way we prove (A.5). Substituting $p_\ell < 0$ for $p_k$ in (A.7), we get:

$$H(p - p_\ell 1) = g + p_\ell a.$$  \hfill (A.9)

Summing the elements of $g$ from $\ell$ to $n$ gives

$$\sum_{j=\ell}^{n} g_j = \sum_{i=\ell+1}^{n} \left((p_i - p_\ell) \sum_{j=\ell}^{n} H_{ji}\right) + \sum_{i=\ell}^{n} \sum_{j=1}^{\ell-1} H_{ij}(p_j - p_\ell) + (-p_\ell) \sum_{j=\ell}^{n} a_j \hfill (A.10)$$

The first term on the RHS of (A.10) is non-negative, since $(p_i - p_\ell) \leq 0$ for $i = \ell + 1, \ldots, n$. Because of the C-Metzler property of $H$ we have that:

$$\sum_{j=\ell}^{n} H_{ji} \leq 0, \text{ for any } i = \ell + 1, \ldots, n$$

The second term in (A.9) is again 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 trivially non-negative due to the negativity of $p_\ell$ and the non-negativity of $a$.

In order to prove inequalities (A.6) we note that $H$, which is invertible, must satisfy (A.1). This requires $a$ to be non-zero, otherwise $1$ would be in the kernel of $H$ what would lead to a contradiction. Let us express $H$ as:

$$H = \begin{bmatrix} H_{11} & H_{12} \\ H_{21} & H_{22} \end{bmatrix} \hfill (A.11)$$

where $H_{11} \in \mathbb{R}^{m \times m}$ and $H_{22} \in \mathbb{R}^{(n-m) \times (n-m)}$ have strictly negative diagonal elements, and $H_{12} \in \mathbb{R}^{m \times (n-m)}$ are $H_{21} \in \mathbb{R}^{(n-m) \times m}$ are non-negative (their elements are either positive or zero).

Suppose that the first $m$ coordinates of the vector $a$ are zero, then in order for $H$ to be C-Metzler and satisfy (A.1), $H_{12}$ must have at least one positive entry. We show this by noting that:

$$H_{11}1_m + H_{12}1_{n-m} = 0.$$ 

If $H_{12} = 0$ that would imply $H_{11}1_m = 0$. In other words, $H_{11}$ would be singular, since $1_m$ would be an eigenvector with zero eigenvalue.

On the other hand, because $H$ is C-Metzler all its eigenvalues are negative, and the matrix lower block diagonal, since $H_{12} = 0$. But this implies that none of the eigenvalues of $H_{11}$ and $H_{22}$ can be zero, what is in contradiction with $H_{12} = 0$. Therefore, at least one entry of $H_{12}$ must be positive, and this makes the second term on the right hand side of (A.8) for $k = m$, strictly positive, i.e.:

$$\sum_{j=1}^{m} g_j < 0$$
The same argument extended to the negative case will prove that

\[ \sum_{j=m+r+1}^{n} g_j > 0. \]

\[ \square \]

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

\[ G(x) = \sum_{i=1}^{n} g_i Q_i(x) \]  
(A.12)

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

\[ Q_1(x) \geq \cdots \geq Q_k(x) \geq \cdots \geq Q_m(x) > 0 > Q_{m+r+1}(x) \geq \cdots \geq Q_n(x) \]  
(A.13)

Then \( G(x) < 0 \) for every \( x \in X \).

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

\[ G(x) = (Q_1 - Q_2)g_1 + (Q_2 - Q_3)(g_1 + g_2) + \cdots + (Q_k - Q_{k+1}) \sum_{j=1}^{k} g_j + \cdots + Q_m \sum_{j=1}^{m} g_j + \cdots + Q_{m+r+1} \sum_{j=m+r+1}^{n} g_j + \cdots + (Q_{\ell} - Q_{\ell-1}) \sum_{j=\ell}^{n} g_j + \cdots + (Q_n - Q_{n-1})g_n \]  
(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 \( x \in X \), what implies that \( (Q_k - Q_{k+1}) \geq 0 \) for every \( k = 1, \ldots, m-1 \) and \( (Q_{\ell} - Q_{\ell-1}) \leq 0 \) for every \( \ell = m+r+1, \ldots, n \). Thus from Lemma A.1 we have that:

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

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

**B Some convenient results on uniqueness and stability**

**Lemma B.1** ([37]) Let \( V(x) : X \rightarrow \mathbb{R} \), with \( X \subseteq \mathbb{R}^n \) its domain, a convex function with continuous derivatives on \( X \), and \( \nu(x) : X \rightarrow \mathbb{R}^n \) be the gradient of \( V(x) \). Then the following inequalities hold for every \( x \in X \):
(i) $\nu^T(x_1)(x - x_1) \leq V(x) - V(x_1)$ for any $x_1 \in X$.

(ii) $[\nu(x_2) - \nu(x_1)]^T(x_2 - x_1) \geq 0$ for any $x_1, x_2 \in X$.

*inequalities are strict whenever $x \neq x_1$ or $x_1 \neq x_2$ in (i) and (ii), respectively.*

**Proof:** In order to prove the first part choose any $x_1 \in X$ 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:

$$H(x; x_1) = V(x_1) + \nu^T(x_1)(x - x_1), \text{ and } B_1(x; x_1) = V(x) - H(x; x_1)$$

By construction the function is strictly positive, i.e. it is positive for all $x \in X$ other than $x_1$, so the result (i) follows in a straightforward manner since:

$$B_1(x; x_1) \equiv V(x) - V(x_1) - \nu^T(x_1)(x - x_1) \geq 0, \text{ so that } V(x) - V(x_1) \geq \nu^T(x_1)(x - x_1)$$

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 $x_2 \in X$:

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

where the inequality holds for any $x \in X$. In particular it holds for $x = x_1$, thus:

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

which implies that $B_1(x_2; x_1) \leq [\nu(x_2) - \nu(x_1)]^T(x_2 - x_1)$, and the assertion is in this way proved. \(\square\)

**Proposition B.1** The set $U(c_0) = \{c \in \mathbb{R}^m \mid c, c_0 \succeq 0, \ S^T(\ln c - \ln c_0) = 0\}$, contains just one element in each compatibility class.

**Proof:** Suppose that there are two elements $U(c_0)$ that belong to the same compatibility class. Because $c^*, c^{**} \in U(c_0)$ we have that $S^T (\ln c^* - \ln c^{**}) = 0$. This implies that $(\ln c^* - \ln c^{**})$ is orthogonal to the stoichiometric subspace $\Sigma$. On the other hand, since $c^*$ and $c^{**}$ are assumed to be in the same compatibility class, $c^* - c^{**}$ belong to the stoichiometric subspace $\Sigma$. Then we have that:

$$(\ln c^* - \ln c^{**})^T (c^* - c^{**}) = 0 \quad (B.1)$$
But according to Lemma B.1, condition (ii) with a convex function candidate \( V(c) = c^T (\ln c - 1) \), for equality (B.1) to be satisfied \( c^* = c^{**} \). Consequently there is only one element in each compatibility class.

\[ \square \]

**Proposition B.2** Complex balance solutions are locally asymptotically stable.

**Proof:** First of all, let us make use of (6) to write the right hand side of (5) as a summation over \( \lambda \) of functions:

\[
\mathcal{R}^\lambda(c) = \sum_{i \in \mathcal{L}_\lambda} \psi_i(c) \sum_{j \in \mathcal{I}_i} k_{ij} \cdot (y_j - y_i) \quad (B.2)
\]

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

\[
\mathcal{R}^\lambda(c) = \sum_{i \in \mathcal{L}_\lambda} e^{z_i} \sum_{j \in \mathcal{I}_i} \psi_i c_{kj} \cdot (z_j - z_i) \quad (B.3)
\]

where \( z_i = y_i^T \phi \). An upper bound for (B.3) can be established from Lemma B.1 with \( V(z) = e^z : \mathbb{R} \to \mathbb{R} \) so that:

\[
e^{z_i}(z_j - z_i) \leq e^{z_j} - e^{z_i} \quad (B.5)
\]

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:

\[
e^{z_j} - e^{z_i} = (\epsilon_j - \epsilon_i)^T \sum_{k=1}^n \epsilon_k e^{z_k} \quad (B.6)
\]

Combining (B.6) with (B.5) and substituting the resulting expression in (B.3) we get:

\[
\mathcal{R}^\lambda(c) \leq \left( \sum_{i=1}^n e^{z_i} e_i^T \right) \left[ \sum_{i \in \mathcal{L}_\lambda} \psi_i \sum_{j \in \mathcal{I}_i} k_{ij} \cdot (\epsilon_j - \epsilon_i) \right] \equiv \sum_{i=1}^n e^{z_i} e_i^T A^\lambda_k(\psi^*) \quad (B.7)
\]

Where we recall once again that the equality holds if and only if \( z_i = z_j \) for every \( i, j \in \mathcal{L}_\lambda \). A Lyapunov function candidate is constructed as in the proof of Lemma B.1:

\[
B(c; c^*) = V(c) - V(c^*) - \nu^T(c^*)(c - c^*) \geq 0
\]

where the convex function \( V(c) \) is of the form:

\[
V(c) = \sum_{i=1}^m c_i (\ln c_i - 1)
\]
Computing the derivative of $B$ along (5) we get:

$$
\dot{B} = \sum_{\lambda=1}^{\ell} \pi^{R^\lambda} \leq \left( \sum_{i=1}^{n} e_i e_i^T \right) \sum_{\lambda=1}^{\ell} A_k^\lambda (\psi^*) = 0 \quad \text{(B.8)}
$$

The result then follows since $B_1(c; e^*) \geq 0$ and $\dot{B}_1(c; e^*) \leq 0$ \hfill □