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Characterizing feasible equilibrium solutions for Mass Action Law (MAL) kinetic systems

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***Abstract*—A canonical representation of the set of feasible equilibrium solutions for MAL reaction networks is given in terms of a class of strictly stable Metzler matrices which define the so-called family of solutions. Main consequences of such representation are a simple characterization of uniqueness of complex balance solutions as well as a short proof of the deficiency one theorem. Future directions may involve detection or design of networks having multiple equilibria.**

***Index Terms*—reaction networks, weak reversibility, mass action law, complex balance, uniqueness of equilibrium solutions**

I. Introduction

The theory of chemical reaction networks was developed in the 70's by Horn, Jackson and Feinberg ([12], [8]) to understand the dynamics of general chemical kinetics with reactions that take place in well stirred media, and rates obeying the so-called mass action law (MAL). In spite of the their apparent simplicity, such systems may exhibit (usually when open to mass exchange with the environment) a quite rich dynamic behavior including multiple equilibria, oscillations or even chaos [7], [5].

One of the main problems in chemical reaction network theory (CRNT) is whether a given network can exhibit or not multiple equilibria on a given set of reaction polyhedrons (also known as reaction simplex) which constrain the dynamic evolution of the system. In answering such 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 the theory are the so-called deficiency zero and deficiency one theorems [9], [10] which establish conditions for networks to have just one possible equilibria in each reaction simplex independently of parameter values (more precisely, as long as none of the reactions vanish i.e. all rate coefficients remain strictly positive). In particular, for weakly reversible networks with zero deficiency, positive equilibria for any set of positive network parameters will be stable, what suggests network robustness with respect to parameter variability.

CRNT has received renewed interest over the last years because of its potential to explore complex behavior and function in biological systems (see for instance [6] or [14]). Unfortunately, many of the methods and results that compose the theory remain unexploited due mainly to the usually obscure architecture of its arguments and proofs.

In this paper we will adopt a geometric perspective to revisit the essential ingredients required to prove both deficiency theorems for weakly reversible networks. To that purpose the notion of 'family of solutions' and feasibility will be employed. Originally, both concepts have been derived in [13], [14] to study multiplicity phenomena as a function of network parameters and to describe regions in the parameter space (Horn sets) [1] complying with complex balance solutions [11].

Feasible solutions are described in terms of a class of stable Metzler matrices [2] and a set of constraints which relate to the kernel of the stoichiometric subspace. One particularly interesting representation of these constraints will be discussed in Section 4 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 [4] in the context of graph theory.

Main consequences of this representation are discussed in Section 5. As we will show, they will pave the way 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. Future directions may involve detection or design of networks having multiple equilibria.

The paper is organized as follows: Section II provides a formal description of chemical reaction networks. The set of possible equilibrium solutions is characterized in Section II-B by the so-called set of feasible solutions, establishing connections with reaction rate constants and the kernel of the stoichiometric subspace. Section IV discusses some properties of feasible solutions which will be employed in Section V to explain uniqueness of complex balance and some classes of equilibrium solutions for

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deficiency one networks. The paper concludes in Section VI with an outline of some consequences of the results and future directions to be explored.

II. Preliminaries: Reaction Network Structure and Dynamics

Let m be the number of chemical species participating in a given set of r irreversible chemical reaction steps transforming a given set of reactants into reaction products, and let $\mathbf{c} \in \mathbb{R}^m$ be the corresponding vector of species concentrations (defined as number of molecules, e.g. mole numbers per unit of volume). Each set of species in a reaction step is referred to as a reaction complex or simply a *complex*. Complexes and reaction steps describe a graph where complexes correspond to nodes and reaction steps to edges.

Formally, the graph of a reaction network with n complexes $\{\mathcal{C}_1, \ldots, \mathcal{C}_n\}$ and r reactions steps can be constructed by associating to each complex i a set $\mathcal{I}_i$ of integer elements with ordinality in n, and a vector $\boldsymbol{y}_i$. The set $\mathcal{I}_i$ collects as elements the indexes of those complexes reached from complex i. Vector $\boldsymbol{y}_i \in \mathbb{R}^m$ has as entries the (positive) stoichiometric coefficients of the molecular species that participate in complex i.

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

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

Complexes within a linkage class are connected 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). The largest 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.

To each linkage class λ we associate a n-dimensional vector $\boldsymbol{\omega}_\lambda$ which is defined as follows:[2]

$$\boldsymbol{\omega}_\lambda = \sum_{i \in \mathcal{L}_\lambda} \boldsymbol{\varepsilon}_i. \tag{1}$$

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

[2]Vector $\boldsymbol{\omega}_\lambda$ is referred in classical CRNT as the *characteristic function* of linkage class λ.

where $\boldsymbol{\varepsilon}_i \in \mathbb{N}^n$ denotes the ith standard unit vector used to represent axes on a cartesian coordinate system. Vectors $\boldsymbol{\omega}_\lambda$ $(\lambda = 1, ..., \ell)$ are orthogonal to each other since by construction, sets $\mathcal{L}_\lambda$ are disjoint. For reasons that will become clear later on, we will select for each linkage class $\mathcal{L}_\lambda$ an arbitrary complex from the corresponding terminal linkage class as a reference complex j_λ.

The rate R_{ij} at which a set of chemical species (reactants) associated to complex i is transformed into a set of products associated to complex j will be assumed to be mass action, hence:

$$R_{ij} = k_{ij}\psi_i(\mathbf{c}), \quad \text{with} \quad \psi_i(\mathbf{c}) = \prod_{j=1}^{m} c_j^{y_{ji}} \equiv \mathbf{c}^{\boldsymbol{y}_i}, \tag{2}$$

where $k_{ij} > 0$ is the corresponding reaction rate constant. Whenever $\mathbf{c}$ is a strictly positive vector (meaning all components strictly positive), the following alternative representation for $\psi_i(c)$ may be more convenient:

$$\ln \psi_i(\mathbf{c}) = \boldsymbol{y}_i^{\mathrm{T}} \ln \mathbf{c}, \tag{3}$$

where the natural logarithm operator $\ln(\cdot)$ will act on any vector element-wise.

A. The dynamics of reaction networks

The time evolution of species concentrations on a well-mixed reaction medium can be described by a set of ordinary differential equations of the form [8]

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

where $Y \in \mathbb{R}^{m \times n}$ is the so-called *molecularity matrix* which collects as columns the stoichiometric vectors $\boldsymbol{y}_i$ associated to the complexes of the network. $\boldsymbol{\psi}(\mathbf{c}) \in \mathbb{R}^n$ is a vector containing as entries the scalar function monomials described in (2), and $A_k^\lambda(\boldsymbol{\psi})$ is a linear operator that accepts the following equivalent factorizations:

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

where as mentioned in the previous section j_λ is the reference complex for linkage class $\mathcal{L}_\lambda$ and ϕ_i represents the net reaction rate flux around complex i, which is expressed as:

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

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. Since vectors $\boldsymbol{\varepsilon}_i$ are orthogonal, we have that $\phi_i(\boldsymbol{\psi}) = \boldsymbol{\varepsilon}_i^{\mathrm{T}} A_k^\lambda(\boldsymbol{\psi})$ for every $i \in \mathcal{L}_\lambda$, and $\boldsymbol{\omega}_\lambda^T A_k^\lambda(\boldsymbol{\psi}) = 0$. Therefore:

$$\sum_{i \in \mathcal{L}_\lambda} \phi_i = \left(\sum_{i \in \mathcal{L}_\lambda} \boldsymbol{\varepsilon}_i \right)^T A_k^\lambda(\boldsymbol{\psi}) = 0 \tag{7}$$

Fluxes ϕ_i as well as the operator A_k, are implicitly dependent on the set of reaction rate constants of the network k_{ij}. By inspection of (5), it can be concluded that the image of $A_k(\boldsymbol{\psi})$ lies within the subspace Δ defined as:

$$\Delta = \bigcup_{\lambda=1}^{\ell} \Delta_\lambda \quad \text{with} \quad \Delta_\lambda = \text{span}\{\boldsymbol{\varepsilon}_i - \boldsymbol{\varepsilon}_{j_\lambda} \mid i \in \mathcal{L}_\lambda \setminus j_\lambda\} \ . \tag{8}$$

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

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

Moreover $A_k(\boldsymbol{\psi}) = 0$ if and only if $\phi_i = 0$ for all $i \in \mathcal{L}$. Such a zero flux condition for every complex in the network is known in CRNT as *complex balance* [11].

B. The stoichiometric subspace

We define the stoichiometric subspace Σ as that spanned by the union over all linkage classes λ of the vector sets:

$$\Sigma_\lambda = \text{span}\{\boldsymbol{y}_i - \boldsymbol{y}_{j_\lambda} \mid i \in \mathcal{L}_\lambda \setminus j_\lambda\} \quad \text{and} \quad \Sigma = \bigcup_{\lambda=1}^{\ell} \Sigma_\lambda \ . \tag{9}$$

In the following it will be more convenient to collect the elements from each of the sets $\{\boldsymbol{y}_i - \boldsymbol{y}_{j_\lambda} \mid i \in \mathcal{L}_\lambda \setminus j_\lambda\}$ 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 $s = \dim(\Sigma)$, i.e. the rank of S, then it follows from the rank-nullity theorem that the dimension of the kernel (null space) of S will be:

$$\delta = n - \ell - s. \tag{10}$$

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 which is nothing but the dimension of the kernel of S_λ and is computed as $\delta_\lambda = N_\lambda - 1 - s_\lambda$, where $s_\lambda = \dim(\Sigma_\lambda)$. The following inequality relates network and linkage class deficiencies:

$$\delta \geq \sum_\lambda \delta_\lambda$$

Let $\{g^r \mid r = 1, \ldots, \delta\}$ be a basis for the kernel of S, so that $Sg^r = 0$ for every $r = 1, \ldots, \delta$. We can rewrite this equation for every r as:

$$\sum_\lambda S_\lambda g_\lambda^r = 0 \quad \text{for} \quad r = 1, \ldots, \delta, \tag{11}$$

where $g_\lambda^r \in \mathbb{R}^{N_\lambda - 1}$ are sub-vectors of g^r. We will be particularly interested in solutions of system (4) 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 Σ (also known in CRNT as *compatibility class*). Such region is formally defined with respect to a reference concentration vector $\mathbf{c}_0$ as:

$$\Omega(\mathbf{c}_0) = \{\mathbf{c} \in \mathbb{R}^m | \mathbf{c} \succeq 0, B^{\mathrm{T}}(\mathbf{c} - \mathbf{c}_0) = 0\}, \tag{12}$$

where $B \in \mathbb{R}^{(m\times m-s)}$ is a full rank matrix whose columns span the orthogonal complement $\Sigma^\perp$.

III. A canonical representation of the equilibrium set

Combining (5) into (4), the expression reads:

$$\dot{\mathbf{c}} = \sum_\lambda \sum_{i\in\mathcal{L}_\lambda\setminus j_\lambda} \phi_i(\boldsymbol{\psi})(y_i - y_{j_\lambda}). \tag{13}$$

Eqn (13) can be re-written in terms of the stoichiometric matrices discussed above, so that:

$$\dot{\mathbf{c}} = \sum_\lambda S_\lambda \boldsymbol{\phi}_\lambda(\overline{\boldsymbol{\psi}}_\lambda), \tag{14}$$

where $\boldsymbol{\phi}_\lambda$ is a column vector that for each linkage class collects the fluxes present in expression (13). $\overline{\boldsymbol{\psi}}_\lambda$ represents the vector of monomials associated to the linkage class, which possibly after some re-ordering will take the form $\overline{\boldsymbol{\psi}}_\lambda = (\psi_{j_\lambda}, \boldsymbol{\psi}_\lambda^T)^T$. Element-wise, these are related by expressions of the form (6) which in matrix form can be expressed as:

$$\overline{\boldsymbol{\phi}}_\lambda(\boldsymbol{\psi}) = M_k^\lambda \overline{\boldsymbol{\psi}}_\lambda, \tag{15}$$

where $M_k^\lambda \in \mathbb{R}^{N_\lambda\times N_\lambda}$ is the matrix that includes as entries the corresponding reaction constants, and $\overline{\boldsymbol{\phi}}_\lambda = (\phi_{j_\lambda}, \boldsymbol{\phi}_\lambda^T)^T$. Note that because of (7) M_k^λ is a column conservation matrix, we can re-write as:

$$M_k^\lambda = \left[\begin{array}{c|c} -(1^T a_\lambda) & b_\lambda^T \\ \hline a_\lambda & E^\lambda \end{array}\right], \tag{16}$$

with $b_\lambda^T = -1^T E^\lambda$. By construction, the first row in M_k^λ corresponds with the reference complex j_λ 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_λ is non-zero, i.e. at least one of the off-diagonal elements corresponding to the first row must be positive, because there is at least one reaction step directed to the reference complex. The remaining rate constants are collected in matrix $E^\lambda \in \mathbb{R}^{(N_\lambda-1)\times(N_\lambda-1)}$.

By comparing (4) with the equivalent representations (13) or (14), it is easy to see that equilibrium solutions (i.e. those that make $\dot{\mathbf{c}} = 0$) correspond either to complex balance conditions which require all fluxes ϕ_i to be zero, or to non-zero flux combinations, provided that the network has positive deficiency. Non-zero flux vectors that comply with equilibrium lie in the span of the set $\{g_\lambda^r \mid r = 1, \ldots, \delta\}$ that contains as elements the vector that solve (11). Therefore, fluxes can be written as:

$$\boldsymbol{\phi}_\lambda = \sum_r \alpha_r g_\lambda^r, \tag{17}$$

where α_r are scalars. That (17) leads in fact to an equilibrium solution can be easily verified by substituting it into (14) and making use of (11).

In order to compute the set of equilibrium solutions, we substitute (17) into (15) and make use of the structure of M_k^λ (16) and (7) to get:

$$b_\lambda^T \boldsymbol{\psi}_\lambda \quad - \quad \psi_{j_\lambda}(1^T a_\lambda) = -\sum_r \alpha_r (1^T g_\lambda^r) \qquad (18)$$

$$E^\lambda \boldsymbol{\psi}_\lambda \quad + \quad \psi_{j_\lambda} a_\lambda = \sum_r \alpha_r g_\lambda^r. \qquad (19)$$

Since we are interested in positive equilibrium solutions or equilibrium solutions, let $\psi_{j_\lambda} > 0$, and re-write Eqn (19) as:

$$E^\lambda \mathrm{f}_\lambda + a_\lambda = \mathrm{G}_\lambda \boldsymbol{x}_\lambda \qquad (20)$$

where f_λ is a vector function of the form:

$$\mathrm{f}_\lambda = \exp\left(\ln \frac{1}{\psi_{j_\lambda}} \boldsymbol{\psi}_\lambda\right). \qquad (21)$$

and matrix G_λ and vector $\boldsymbol{x}_\lambda$ are, respectively:

$$\mathrm{G}_\lambda = [g_\lambda^1 \cdots g_\lambda^r \cdots g_\lambda^\delta] \text{ and } \boldsymbol{x}_\lambda = \frac{1}{\psi_{j_\lambda}} (\alpha_1, \ldots, \alpha_\delta)^T$$

Note that, provided that $\mathbf{c} \succ 0$, $\overline{\boldsymbol{\psi}}_\lambda$ relates to species concentration by means of (3) so that for each complex $i \in \mathcal{L}_\lambda \setminus j_\lambda$ in linkage class λ, we have that $\ln(\psi_i/\psi_{j_\lambda}) = (\boldsymbol{y}_i - \boldsymbol{y}_{j_\lambda})^T \ln \mathbf{c}$. Hence the logarithm at the right hand side of (21) can be expressed as:

$$\ln \frac{1}{\psi_{j_\lambda}} \boldsymbol{\psi}_\lambda = S_\lambda^T \ln \mathbf{c}. \qquad (22)$$

Similarly, we can re-write (18) as:

$$b_\lambda^T \mathrm{f}_\lambda = 1^T (a_\lambda - \mathrm{G}_\lambda \boldsymbol{x}_\lambda). \qquad (23)$$

The set of positive vectors f_λ that solve (20) for given $\boldsymbol{x}_\lambda$ and $\lambda = 1, ..., \ell$ (and therefore satisfies (23)) constitutes the so-called family of solutions in [14]. Note however that not all the elements of this set will comply with condition (22) but only a particular subset we will refer to as the set of feasible solutions. This set will be formally characterized next.

Among all positive vectors f_λ that solve (20) for $\lambda = 1, ..., \ell$ we concentrate on those that are consistent with relation (3) (or equivalently, with (22)) and impose on vectors $\ln \mathrm{f}_\lambda$ the condition that they must lie in the range of S_λ^T, so that there exists some $\ln \mathbf{c} \in \mathbb{R}^m$ such that:

$$\ln \mathrm{f}_\lambda = S_\lambda^T \ln \mathbf{c} \quad \text{for} \quad \lambda = 1, ..., \ell. \qquad (24)$$

Let f be the vector which collect as sub-vectors the solutions f_λ of (20). Vector $\ln \mathrm{f}$ must be in the range of S^T, but since the range is orthogonal to the kernel of S we must have that:

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

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

$$\sum_\lambda (g_\lambda^r)^T \ln \mathrm{f}_\lambda(\boldsymbol{x}_\lambda) = 0 \quad \text{for every} \quad r = 1, ..., \delta, \qquad (25)$$

Then, the set of feasible solutions can be characterized as follows:

Definition III.1. The set of positive vectors $\mathrm{f}_\lambda(\boldsymbol{x}_\lambda)$ that for given $\boldsymbol{x}_\lambda$ and every λ satisfy:

$$E^\lambda \mathrm{f}_\lambda(\boldsymbol{x}_\lambda) = -a_\lambda + \mathrm{G}_\lambda \boldsymbol{x}_\lambda \quad \text{and} \quad \sum_\lambda \mathrm{G}_\lambda^T \ln \mathrm{f}_\lambda(\boldsymbol{x}_\lambda) = 0 \qquad (26)$$

determine equilibrium solutions in the positive orthant of the concentration space. Equations in (26) define the set of feasible solutions.

Note that feasible complex balance solutions are those which satisfy (26) with $\boldsymbol{x}_\lambda = 0$ for all λ.

IV. Properties of feasible solutions

Here we will elaborate on some observations made about Eqns (26) that will bring insight on the domain and main characteristics of feasible solutions. One way or another, most interesting properties of feasible solutions derive from the structure of matrices E^λ associated to (16) and therefore to the operator A_k^λ. From (5), it follows that entries of matrices E^λ are of the form:

$$\begin{aligned} &E_{ij}^\lambda \geq 0 && \text{for } i \neq j \\ &E_{ii}^\lambda = -(b_i + \textstyle\sum_{j \neq i} E_{ij}^\lambda) && \text{with } b_i \geq 0 \text{ and } E_{ii}^\lambda < 0 \end{aligned} . \qquad (27)$$

In this way, they are a class of Metzler matrices [2], and therefore called E-Metzler. It can be shown elsewhere (e.g. [3]) that such matrices are non-singular and strictly stable.

A. Alternative representations of the family of solutions

With some abuse of notation, let us re-write (26) for a given linkage class λ with $\delta = 1$ as follows:

$$E\mathrm{f}(\boldsymbol{x}) = -a + xg, \qquad (28)$$

where $a \in \mathbb{R}^{n-1}$ is a vector of nonnegative elements and x a scalar. Vector $g \in \mathbb{R}^{n-1}$ lies in the the kernel of S_λ. Matrix $E \in \mathbb{R}^{(n-1)\times(n-1)}$ is E-Metzler as described above. Because E is invertible we can define new vectors f^* and h as:

$$E\mathrm{f}^* = -a \quad \text{and} \quad Eh = g.$$

In particular $\mathrm{f}^* \succeq 0$ since $a \succeq 0$ and E is Metzler stable [2]. Moreover, if the underlying network is weakly reversible $\mathrm{f}^* \succ 0$, i.e. a strictly positive vector. By substituting these relations into (28), we express $\mathrm{f}(x)$ as:

$$\mathrm{f}(x) = \mathrm{f}^* + xh. \qquad (29)$$

If $\mathrm{f}^* \succ 0$, the values of x for which $\mathrm{f}(x)$ will remain strictly positive will depend on the signs of the entries of $(h)_j$.

In this way, for every j let $(p)_j = (h)_j/(\mathrm{f}^*)_j$ and define two index sets $\mathcal{I}^+$ and $\mathcal{I}^-$ so that:

$$\begin{array}{ll}\text{for any} \quad j\in\mathcal{I}^+, & (h)_j > 0, \quad (\text{thus} \quad (p)_j > 0)\\ \text{for any} \quad j\in\mathcal{I}^-, & (h)_j < 0, \quad (\text{thus} \quad (p)_j < 0)\end{array} \tag{30}$$

If $(h)_j = 0$, $(p)_j = 0$. Let $L^- = \max_{j\in\mathcal{I}^+}\{-1/(p)_j\}$ and $L^+ = \min_{j\in\mathcal{I}^-}\{-1/(p)_j\}$. Then it is straightforward to see that $\mathrm{f}(x)$ will be strictly positive for every x in the open interval $\mathbb{X} = (L^-, L^+)$, so that

$$\mathrm{f}(x) : \mathbb{X} \subset \mathbb{R} \mapsto (\mathbb{R}^+)^{n-1}.$$

Note that whenever $\mathrm{f}^* \succ 0$, i.e a strictly positive vector, $0 \in \mathbb{X}$.

B. Monotonicity in feasible solutions

The result to be discussed in this section will show that the entries of vector $\mathrm{G}_\lambda^T \ln \mathrm{f}_\lambda(x)$ in the summation of (26) are in fact functions of a scalar x, monotonous decreasing in its argument. To that purpose let us consider (29), and assume without loss of generality that the components of h are ordered so that:

$$\begin{array}{l}(h)_1 \geq \cdots \geq (h)_k \geq \cdots \geq (h)_m > 0\\ (h)_{m+1} = \cdots = (h)_{m+r} = 0\\ 0 > (h)_{m+r+1} \geq \cdots \geq (h)_\ell \geq \cdots \geq (h)_{n-1}\end{array} \tag{31}$$

Note that such order can always be induced by a suitable permutation of rows in systems $g = Eh$ and $E\mathrm{f}^* = -a$. Following the discussion in section IV-A, we have that $\mathcal{I}^+ = \{1, \cdots, m\}$ and $\mathcal{I}^- = \{m+r+1, \cdots, n-1\}$, and the domain $\mathbb{X} = (L^-, L^+)$ becomes:

$$L^- = \max_{j\in\mathcal{I}^+}\{-(\mathrm{f}^*)_j/(h)_j\}$$

$$L^+ = \min_{j\in\mathcal{I}^-}\{-(\mathrm{f}^*)_j/(h)_j\} \tag{32}$$

It should be noted that $L^- \equiv -\infty$ (respectively $L^+ \equiv +\infty$) provided that $\mathcal{I}^+ = \emptyset$ (respectively, $\mathcal{I}^- = \emptyset$). Associated to $\mathrm{f}(x)$ we construct a scalar function:

$$\mathrm{F}(x) = g^T \ln \mathrm{f}(x), \tag{33}$$

where $g = Eh$ and E is E-Metzler with entries of the form (27).

Lemma IV.1. Consider the function $\mathrm{F}(x) : \mathbb{X} \subset \mathbb{R} \mapsto \mathbb{R}$ defined in (33). $\mathrm{F}(x)$ is monotonous decreasing on the domain $\mathbb{X}$. Moreover,

$$\lim_{x\to L^+} F(x) = -\infty \quad \text{and} \quad \lim_{x\to L^-} F(x) = +\infty \tag{34}$$

Proof: First, let us define for every entry j of vectors h and f^* a relation $p_j = (h)_j/(\mathrm{f}^*)_j$ and re-write h as:

$$h = \mathcal{D}(\mathrm{f}^*)p, \tag{35}$$

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

$$\begin{array}{l}p_1 \geq \cdots \geq p_k \geq \cdots \geq p_m > 0\\ p_{m+1} = \cdots = p_{m+r} = 0\\ 0 > p_{m+r+1} \geq \cdots \geq p_\ell \geq \cdots \geq p_{n-1}\end{array} \tag{36}$$

where the number of positive, negative an zero elements coincide with those in (31), although not necessary in the same order. For all nonzero p_j elements define functions $Q_j(x) : \mathbb{X} \mapsto \mathbb{R}$:

$$Q_j(x) = \frac{p_j}{1 + xp_j} \tag{37}$$

For every $p_j > 0$ (resp. $p_j < 0$) and $x \in \mathbb{X}$, $Q_j(x) > 0$ (resp. $Q_j(x) < 0$). In addition, for any $p_i \geq p_j$, we have that $Q_i(x) \geq Q_j(x)$. Hence, from (36) we also have for every $x \in \mathbb{X}$ that:

$$\begin{array}{l}Q_1(x) \geq \cdots \geq Q_k(x) \geq \cdots \geq Q_m(x) > 0\\ Q_{m+1}(x) = \cdots = Q_{m+r}(x) = 0\\ 0 > Q_{m+r+1}(x) \geq \cdots \geq Q_\ell(x) \geq \cdots \geq Q_{n-1}(x)\end{array} \tag{38}$$

Function (33) is well defined in the domain $\mathbb{X}$ since $\mathrm{f}(x)$ is strictly positive, thus the first part of the proof reduces to computing the first derivative and studying its sign over the domain. The first derivative can be written as:

$$\mathrm{F}'(x) = \sum_{j=1}^{n-1} \frac{(g)_j (h)_j}{(\mathrm{f})_j(x)}, \tag{39}$$

where $(g)_j$ are the j entries of vector $g = Eh$. Eqn (39) can be re-written in terms of functions $Q_j(x)$ as:

$$\mathrm{F}'(x) = \sum_{j=1}^{n-1} g_j Q_j(x) \tag{40}$$

We define the matrix $H = E\mathcal{D}(\mathrm{f}^*)$ which by construction is E-Metzler, and re-write $E\mathrm{f}^* = -a$ and $g = Eh$ as $H\mathbf{1} = -a$ and $g = Hp$. Because H is E-Metzler, and satisfies conditions in Lemma A.2, with Eqn (40) instead of $G(x)$, the first derivative is strictly negative on the domain $\mathbb{X}$.

In order to show (34), we note that $(\mathrm{f})_j(x) \equiv (\mathrm{f}^*)_j(1 + xp_j)$, and re-write (33) as:

$$\mathrm{F}(x) \equiv \sum_{j=1}^{n-1}(g)_j \ln(\mathrm{f})_j(x) = \sum_{j=1}^{n-1}(g)_j \ln(\mathrm{f}^*)_j + \sum_{j=1}^{n-1}(g)_j \Pi_j(x), \tag{41}$$

where $\Pi_j(x) = \ln(1 + xp_j)$. The first term on the right hand side is constant while the second term can be expressed as:

$$\sum_{j=1}^{n-1}(g)_j\Pi_j(x) = \cdots (\Pi_k - \Pi_{k+1}) \sum_{j=1}^{k} g_j + \cdots$$

$$+\Pi_m \sum_{j=1}^{m} g_j + \Pi_{m+r+1} \sum_{j=m+r+1}^{n} g_j + \cdots$$

$$+(\Pi_{\ell+1} - \Pi_\ell) \sum_{j=\ell}^{n} g_j + \cdots + (\Pi_{n-2} - \Pi_{n-1}) g_{n-1} \tag{42}$$

where $\Pi_i - \Pi_j \equiv \ln\left[(1 + xp_i)/(1 + xp_j)\right]$. Taking the limits $x \to L^-$ and $x \to L^+$ and using Lemma A.1 leads to (34) ☐

V. Uniqueness of some classes of equilibrium solutions

The formal description of the set of feasible solutions expressed in Eqns (26) will serve to characterize some classes of unique equilibrium sets. Uniqueness must be understood in the sense that there will be room for one equilibrium solution in each compatibility class only. In keeping with that intention, let us first write $\boldsymbol{x}_\lambda = x\boldsymbol{\chi}$ with x a scalar and $\boldsymbol{\chi} \in \mathbb{R}^\delta$ an arbitrary vector in the unit sphere ($\|\boldsymbol{\chi}\| = 1$). Any feasible solution for this particular $\boldsymbol{x}_\lambda$ reduces to find some $x \in \mathbb{R}$ such that $\mathrm{f}_\lambda(x;\boldsymbol{\chi}) = \mathrm{f}^*_\lambda + x\mathcal{H}_\lambda\boldsymbol{\chi}$ (where $E^\lambda\mathcal{H}_\lambda = \mathrm{G}_\lambda$) is positive and

$$\sum_\lambda \mathrm{G}_\lambda^T \ln \mathrm{f}_\lambda(x;\boldsymbol{\chi}) = 0. \tag{43}$$

Pre-multiplying Eqn (43) by χ, and using $g_\lambda = G_\lambda\chi$ and $h_\lambda = \mathcal{H}_\lambda\chi$ (note that $g_\lambda = E^\lambda h_\lambda$), we get:

$$\sum_\lambda \mathrm{F}_\lambda(x;\chi) = 0, \tag{44}$$

where each term in the above summation is of the form $\mathrm{F}_\lambda(x) = g_\lambda^T \ln \mathrm{f}_\lambda(x;\boldsymbol{\chi})$ and satisfies the conditions of Lemma IV.1. Suppose that the reaction network accepts a complex balance solution. This implies that (for every $\boldsymbol{\chi}$):

$$\sum_\lambda \mathrm{F}_\lambda(0;\chi) = 0, \tag{45}$$

Since by Lemma IV.1, each $\mathrm{F}_\lambda(x;\chi)$ is monotonous decreasing in each argument, no feasible solutions other than the complex balance can be expected (see also [11]).

Next we present a result that can be interpreted as an alternative statement of the deficiency one theorem originally proposed by [10] and recently by [4].

Proposition V.1. Let us have a weakly reversible reaction network such that $\delta = \sum_\lambda \delta_\lambda$, where δ_λ is either 0 or 1. Then there will be a unique equilibrium in each compatibility class.

Proof: By the assumptions, each linkage class λ will contribute to the network deficiency with one vector g^r at most, such that: $g^r_\lambda \neq 0$ and $g^r_k = 0$ for every $k \neq \lambda$ (i.e. the remaining $\ell - 1$ sub-vectors will be zero). For this case, any feasible solution (26) reduces to:

$$\begin{aligned} E^\lambda \mathrm{f}_\lambda(\boldsymbol{x}_\lambda) &= -a_\lambda + x_\lambda g^r_\lambda \\ \mathrm{F}_\lambda(x_\lambda) &= 0 \quad \text{for} \quad \lambda = 1, \ldots, \ell \end{aligned}$$

with $x_\lambda \in \mathbb{X}_\lambda$, and $\mathrm{F}_\lambda(x_\lambda) = (g^r_\lambda)^T \ln \mathrm{f}_\lambda(x_\lambda)$. According to Lemma IV.1, each function $\mathrm{F}_\lambda(x_\lambda)$ is monotonous decreasing and because of (34), it becomes zero at some point $\bar{x}_\lambda \in \mathbb{X}_\lambda$. Since E^λ is invertible, there exists a unique vector $\mathrm{f}_\lambda(\bar{x}_\lambda)$ for each linkage class λ. Using Eqn 24, we also have that:

$$S_\lambda^T \ln \mathbf{c} = \ln \mathrm{f}_\lambda(\bar{x}_\lambda). \tag{46}$$

In order to prove uniqueness, we assume that there exists two equilibrium solutions in the concentration space $\mathbf{c}^*$ and $\mathbf{c}^{**}$ for the same compatibility class. Then for each λ we have from the above relation that:

$$S_\lambda^T(\ln \mathbf{c}^* - \ln \mathbf{c}^{**}) = 0$$

which implies that $(\ln \mathbf{c}^* - \ln \mathbf{c}^{**})$ must be orthogonal to Σ. Since $\mathbf{c}^*$ and $\mathbf{c}^{**}$ are assumed to be in the same compatibility class, $\mathbf{c}^* - \mathbf{c}^{**}$ must be in Σ and the following equality would hold:

$$(\ln \mathbf{c}^* - \ln \mathbf{c}^{**})^T(\mathbf{c}^* - \mathbf{c}^{**}) = 0 \tag{47}$$

But according to Lemma A.3, condition (ii) with a convex function candidate $V(\mathbf{c}) = \mathbf{c}^T(\ln \mathbf{c} - \mathbf{1})$, for equality (47) to be satisfied $\mathbf{c}^* = \mathbf{c}^{**}$. In other words the equilibrium must be unique. □

VI. 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 of equilibria 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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Appendix

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

$$H\mathbf{1} = -a, \tag{48}$$

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

$$\begin{array}{l} p_1 \geq \cdots \geq p_k \geq \cdots \geq p_m > 0 \\ p_{m+1} = \cdots = p_{m+r} = 0 \\ 0 > p_{m+r+1} \geq \cdots \geq p_\ell \geq \cdots \geq p_n \end{array} \tag{49}$$

and

$$g = Hp \tag{50}$$

Then:

$$\sum_{j=1}^{k} g_j \leq 0 \quad \text{for every} \quad 1 \leq k \leq m \tag{51}$$

and

$$\sum_{j=\ell}^{n} g_j \geq 0 \quad \text{for every} \quad m+r+1 \leq \ell \leq n \tag{52}$$

In particular:

$$\sum_{j=1}^{m} g_j < 0 \quad \text{and} \quad \sum_{j=m+r+1}^{n} g_j > 0 \tag{53}$$

Proof: Multiplying both sides of (48) by the scalar $p_k > 0$ and subtracting the result from (50) we get:

$$H(p - p_k\mathbf{1}) = g + p_k a \tag{54}$$

Summing the first k elements and reordering terms results in:

$$\sum_{j=1}^{k} g_j = \sum_{i=1}^{k-1}\left((p_i - p_k)\sum_{j=1}^{k} H_{ji}\right) + \cdots$$
$$+ \sum_{i=1}^{k}\sum_{j=k+1}^{n} H_{ij}(p_j - p_k) + (-p_k)\sum_{j=1}^{k} a_j \tag{55}$$

The first term on the right is non-positive since by construction $p_i - p_k \geq 0$ for $i = 1, \cdots, k-1$, and H is E-Metzler and therefore any submatrix containing the first (or last) k rows and k columns of H is also E-Metzler for any $0 < k < n$, i.e.

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

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 (51) follows.

The proof for (52) goes very similarly. Let us substitute $p_\ell < 0$ for p_k in (54). Then we get:

$$H(p - p_\ell\mathbf{1}) = g + p_\ell a. \tag{56}$$

Summing the elements of g from ℓ to n gives

$$\sum_{j=\ell}^{n} g_j = \sum_{i=\ell+1}^{n}\left((p_i - p_\ell)\sum_{j=\ell}^{n} H_{ji}\right) + \cdots$$
$$\cdots + \sum_{i=\ell}^{n}\sum_{j=1}^{\ell-1} H_{ij}(p_j - p_\ell) + (-p_\ell)\sum_{j=\ell}^{n} a_j \tag{57}$$

The first term on the right hand side of (56) is non-negative, since $(p_i - p_\ell) \leq 0$ for $i = \ell+1, \ldots, n$ and due to the E-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 (56) 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 (56) is trivially non-negative due to the negativity of p_ℓ and the non-negativity of a.

We prove (53) by first noting that H must satisfy (48) and is invertible, thus a cannot be a zero vector, otherwise $\mathbf{1}$ would be in the kernel of H which is a contradiction.

If $r = 0$ it follows that either $\sum_{j=1}^{m} a_j$ or $\sum_{j=m+1}^{n} a_j$ (or both) are strictly positive, thus contributing with a negative (respectively positive) term to (55) (respectively, to (57)).

A similar conclusion can be reached for $r \neq 0$ provided that some non-negative a-entries are in locations between 1 and m or between $m+r+1$ and n.

It remains to prove that this is also the case provided that all non-negative entries of a are in $\{a_{m+1}, \ldots, a_{m+r}\}$. Let express H as:

$$H = \left[\begin{array}{c|c} H_{11} & H_{12} \\ \hline H_{21} & H_{22} \end{array}\right], \tag{58}$$

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). By assumption, the first m entries of a are zero so that:

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

First, let us assume that $H_{12} = 0$. This would imply that $H_{11}\mathbf{1}_m = 0$, but then H_{11} has a zero eigenvalue which is not compatible with the assumption that H is invertible, since H is a lower block-triangular matrix, the eigenvalues of which are given by the union of the eigenvalues of H_{11} and H_{22}. Therefore, at least one entry of H_{12} must be positive, and this makes the second term on the right hand side of (55) for $k = m$, strictly positive, i.e.:

$$\sum_{j=1}^{m} g_j < 0.$$

The same argument extended to the negative will prove that

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

□

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

$$G(x) = \sum_{i=1}^{n} g_i Q_i(x) \tag{59}$$

where g_i are elements of a vector $g = Hp$ with H and p as in lemma A.1. Let also for every $i = 1, \cdots, n$ and $x \in \mathbb{X}$, $Q_i(x)$ satisfy:

$$\begin{array}{l} Q_1(x) \geq \cdots \geq Q_k(x) \geq \cdots \geq Q_m(x) > 0 \\ Q_{m+1}(x) = \cdots = Q_{m+r}(x) = 0 \\ 0 > Q_{m+r+1}(x) \geq \cdots \geq Q_\ell(x) \geq \cdots \geq Q_n(x). \end{array} \tag{60}$$

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

Proof: First we note that (59) can be re-written as:

$$\begin{aligned} G(x) = {} & (Q_1 - Q_2)g_1 + (Q_2 - Q_3)(g_1 + g_2) + \cdots \\ & +(Q_k - Q_{k+1}) \sum_{j=1}^{k} g_j + \cdots + Q_m \sum_{j=1}^{m} g_j + \cdots \\ & +Q_{m+r+1} \sum_{j=m+r+1}^{n} g_j + \cdots + (Q_{\ell+1} - Q_\ell) \sum_{j=\ell}^{n} g_j + \cdots \\ & +(Q_n - Q_{n-1})g_n \end{aligned} \tag{61}$$

and the result follows by using Lemma A.1 and the order relation. □

Lemma A.3. Let $V(x) : \mathbb{X} \to \mathbb{R}$, with $\mathbb{X} \subseteq \mathbb{R}^n$ its domain, a convex function with continuous derivatives on $\mathbb{X}$, and $\nu(x) : \mathbb{X} \to \mathbb{R}^n$ be the gradient of $V(x)$. Then the following inequalities hold for every $x \in \mathbb{X}$:

(i) $\nu^T(x_1)(x - x_1) \leq V(x) - V(x_1)$ for any $x_1 \in \mathbb{X}$.
(ii) $[\nu(x_2) - \nu(x_1)]^T (x_2 - x_1) \geq 0$ for any $x_1, x_2 \in \mathbb{X}$.

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 $x_1 \in \mathbb{X}$ and construct a function $B_1(x; x_1)$ as the difference between $V(x)$ and its supporting hyperplane at x_1. The supporting hyperplane is of the form:

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

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

$B_1(x; x_1) \equiv V(x) - V(x_1) - \nu^T(x_1)(x - x_1) \geq 0$, 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 $x_2 \in \mathbb{X}$:

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

where the inequality holds for any $x \in \mathbb{X}$. 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. □