

TECHNICAL REPORT

Stoichiometric Network Analysis

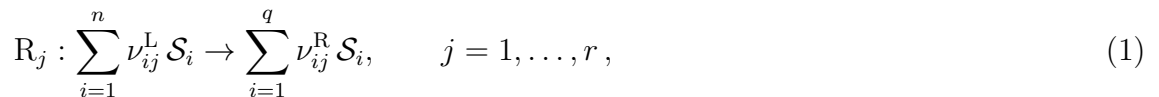
We describe how the stoichiometric network analysis decomposes complex reaction networks into elementary subnetworks. The problem can be converted into the geometrical problem of finding the vertices, edges, and higher dimensional faces of a convex polyhedron (polytope) in a high-dimensional space.

1 Introduction

Before we will continue, we should have to recall several concepts from chemical kinetics. Good understanding of these concepts is necessary condition for further reading.

1.1 Elements of chemical kinetics

Chemical species can be different atoms, molecules, photons, etc. In this work we will denote a chemical species by the calligraphic symbol \mathcal{S}_i . The italic symbol x_i will stand for the molar concentration of species \mathcal{S}_i . We will assume that the number q of chemical species participating in the r chemical reactions will be always finite and specified



where $\nu_{ij}^L \geq 0$ and $\nu_{ij}^R \geq 0$ are the left-hand and right-hand stoichiometric coefficients of species \mathcal{S}_i in the reaction R_j .

In general, the rate laws for these chemical reactions have a form of rational polynomials. However, the most common form for the reactions R_j from Eq. (1) is *power law kinetics*

$$v_j(\mathbf{x}, \mathbf{k}, \underline{\kappa}) = k_j \prod_{i=1}^n x_i^{\kappa_{ij}}, \quad j = 1, \dots, r, \quad (2)$$

where the exponents κ_{ij} are the *reaction orders*, and k_j are the *rate coefficients* of the reactions R_j .

The reaction orders κ_{ij} are small numbers, frequently integers, and form the *kinetic order matrix* $\underline{\kappa} = [\kappa_{ij}] \in \mathbb{R}^{n \times r}$. We define the *effective power function* for the general rate laws

$$\kappa_{ij} \equiv \frac{\partial \ln v_j(\mathbf{x}, \mathbf{k})}{\partial \ln x_i}. \quad (3)$$

Hence $\kappa_{ij} = \kappa_{ij}(\mathbf{x}, \mathbf{k})$ is a function of concentrations \mathbf{x} , and rate coefficients \mathbf{k} , respectively. For power law kinetics, κ_{ij} is constant but it must not equal to ν_{ij} , i.e. $\kappa_{ij} \neq \nu_{ij}$. If the *elementary reaction* takes place, then the effective reaction orders equal to the corresponding stoichiometric coefficients

$$\kappa_{ij} = \nu_{ij}. \quad (4)$$

The reaction rate coefficient k quantifies the rate of a chemical reaction. k has a temperature dependence, which is usually known as the Arrhenius equation

$$k(T) = A \exp\left(-\frac{E_a}{RT}\right), \quad (5)$$

where A is the pre-exponential factor or frequency factor, E_a is the activation energy, R is the universal gas constant and T is the thermodynamic temperature. The reaction rate coefficients are often poorly known experimentally and can range over many orders of magnitude. They also cannot change sign and may always be considered positive $\mathbf{k} \in \mathbb{R}_+^r$.

When we use the multi-index notation for a monomial

$$\mathbf{x}^{\kappa_j} = \prod_{i=1}^n x_i^{\kappa_{ij}}, \quad (6)$$

we may rewrite Eq. (2) into a short form

$$v_j(\mathbf{x}, \mathbf{k}, \underline{\kappa}) = k_j \mathbf{x}^{\kappa_j}. \quad (7)$$

1.2 Division of chemical species

We may divide chemical species into three groups according to where they appear in chemical reactions. First, *reactants* appear on the left-hand sides of some reactions in Eq. (1) only. Second, *products* appear on the right-hand sides. Finally, *intermediates* must appear on both sides of some reactions in Eq. (1).

From the point of view of chemical kinetics, we can divide chemical species into two groups according to time variation of their concentrations. The concentrations of *internal*

species have a significant time variation and therefore are dynamical variables. *External species* are reactants or intermediates present in such surplus so that their concentrations are effectively time invariant. Products are also external species; they may vary in time, but such dynamics is not expressed by independent equations. Thus we can omit external species from independent dynamical variables. Assume the reaction



with the rate law $v = k'x_1x_2$. When we omit the external species \mathcal{S}_2 and \mathcal{S}_4 in the reaction R' , we give the *pseudoreaction*



with the rate law $v = kx_1$, where $k = k'x_2$. The external species \mathcal{S}_2 provides a means whereby the rate coefficient k of the pseudoreaction may be adjusted throughout the range $0 < k < \infty$ for any fixed $k' > 0$. We do not include $k_i = 0$ in the accessible domain because when a reaction vanishes, the system is a network with fewer reactions. Physical limits on the concentration of \mathcal{S}_2 (e.g. solubility) plus detailed dependence of the rate laws on external species determine the *physically accessible domain* of \mathbf{k} -space. We will consider a whole \mathbf{k} -space to avoid a complicated structure of physically accessible domain of \mathbf{k} -space (Clarke, 1980).

Clarke (1980) introduced to use the symbol \square when one side of a pseudoreaction becomes blank after the omission of external species. This symbol is analogous to the number 0, the vector $\mathbf{0}$, and the empty set \emptyset . However, a new symbol is required because the expressions on each side of a reaction arrow are not numbers, vectors, or sets.

We will use the symbol \square in the sense of the surroundings of the system. Then the pseudoreaction



could represent diffusive exchange with an external reservoir, or a phase equilibrium with an unreactive phase. The pseudoreaction



represents the inflow of \mathcal{S}_i into the system. Conversely, the pseudoreaction



represents the outflow of \mathcal{S}_i from the system. This idea comes from the topic of mass balances in engineering.

Moreover, we will sometimes use the notation



when we highlight the fact that \mathcal{S}_1 reacts with some external species denoted by brackets $[]$, i.e. a bimolecular reaction. Conversely, sometimes the right-hand side of the pseudo-reaction will be left blank



when only inert products are formed.

2 Chemical networks

Now we make an important distinction between a chemical system and a chemical network. A *chemical system* is a set of reaction *stoichiometries*, which specify the number of molecules produced or consumed in each reaction, and a function $v_j(\mathbf{x})$ for each reaction (i.e., all parameters have a numerical value). The stoichiometries and rate laws completely determine a system of nonlinear ordinary differential equations that may be further studied.

When we specify a *mechanism*, we again give a set of reaction stoichiometries. However, the form of the rate laws $v_j(\mathbf{x}, \mathbf{k}, \underline{\kappa})$ is assumed to be determined by the stoichiometries if the mechanism consists of *elementary reactions*. Otherwise, we must define the rate form explicitly but without assigning numerical values to parameters. In either case, the mechanism does not specify the rate coefficients \mathbf{k} , which are left as experimental parameters. Thus a mechanism is not a chemical system, but a set of chemical systems, one system for each choice of $\mathbf{k} \in \mathbb{R}_+^r$. We will use the term *network* in the same sense as mechanism. A chemical network is a set of chemical systems, one system for each value of a parameter vector $\mathbf{p} \in \mathbb{R}^q$ (analogous to \mathbf{k}), which lies in a specified domain D of parameter space.

Let us have a set of q internal species \mathcal{S}_i . Reordering q species in such way that the first n species, $n \leq q$, enter the pseudoreactions

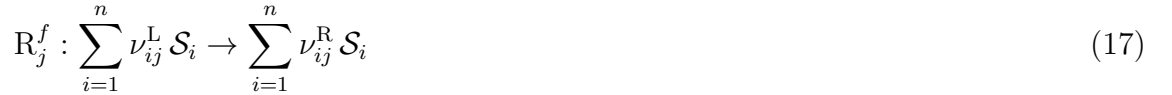
$$\mathbf{R}_j : \sum_{i=1}^n \nu_{ij}^L \mathcal{S}_i \rightarrow \sum_{i=1}^q \nu_{ij}^R \mathcal{S}_i, \quad j = 1, \dots, r. \tag{15}$$

The first n species are reactants or intermediates and the remaining $q - n$ are inert products.

When the reaction mechanism contains the elementary reversible reaction



then we have to expand \mathbf{R}_j^m into the forward reaction



with the rate law $v_j = k_j^f \mathbf{x}^{\nu_j^L}$, and the backward reaction



with the rate law $v_{j+1} = k_j^b \mathbf{x}^{\nu_j^R}$. Note that reversible reactions increase the total number of reactions in the reaction mechanism.

Clarke (1980) defines a *chemical network* as a set of n internal species $\mathcal{S}_1, \dots, \mathcal{S}_n$, a set of r pseudoreactions $\mathbf{R}_1, \dots, \mathbf{R}_r$, a matrix of net reaction stoichiometries $\underline{\nu}$, and a vector function $\mathbf{v}(\mathbf{x}, \mathbf{k})$ whose j th component gives the rate of the j th reaction when the concentration vector is $\mathbf{x} \in \mathbb{R}_+^n$ and the rate constants are $\mathbf{k} \in \mathbb{R}_+^r$. Each element ν_{ij} of the net stoichiometric matrix $\underline{\nu}$ is the difference between the number of units of \mathcal{S}_i on the right and on the left sides of \mathbf{R}_j , i.e. $\nu_{ij} = \nu_{ij}^R - \nu_{ij}^L$. In a spatially homogeneous system (open or closed) the *dynamic* (or *evolution*) *equation*

$$\frac{d\mathbf{x}}{dt} = \dot{\mathbf{x}} = \underline{\nu} \mathbf{v}(\mathbf{x}, \mathbf{k}) \quad (19)$$

determines the dynamics of a set of chemical systems, one system for each $\mathbf{k} \in \mathbb{R}_+^r$.

In other words, the set of autonomous ordinary differential equations (19) represents mass balance equations of internal species. In an open system, inputs and outputs are treated as pseudoreactions of zeroth and first order, respectively.

Example 1: This example demonstrates how the following theory works. We choose some

reactions from a reaction mechanism of catalytic oxidation of CO (Marek *et al.*, 2006):



To form a network we must rewrite chemical reactions into pseudoreactions:



Denote concentrations of species as follows: $[\text{CO}] = x_1$, $[\text{CO}^*] = x_2$, $[\text{CO}_2] = x_3$, $[\text{O}_2] = x_4$, $[\text{O}^*] = x_5$, $[*] = x_6$. Reaction kinetics is given by the kinetic matrix:

$$\underline{\kappa} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} . \quad (36)$$

Stoichiometric matrix:

$$\underline{\nu} = \begin{bmatrix} -1 & 1 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & -1 & 0 & 0 & 0 & 1 & -1 & 0 & 0 \\ 0 & 0 & 2 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & 1 & -2 & 2 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}. \quad (37)$$

Vector of reaction rates:

$$\mathbf{v}(\mathbf{x}, \mathbf{k}) = (k_1 x_1 x_6, k_2 x_2, k_3 x_4 x_6, k_4 x_2 x_5, k_5, k_6 x_1, k_7, k_8 x_4, k_9, k_{10} x_3)^T.$$

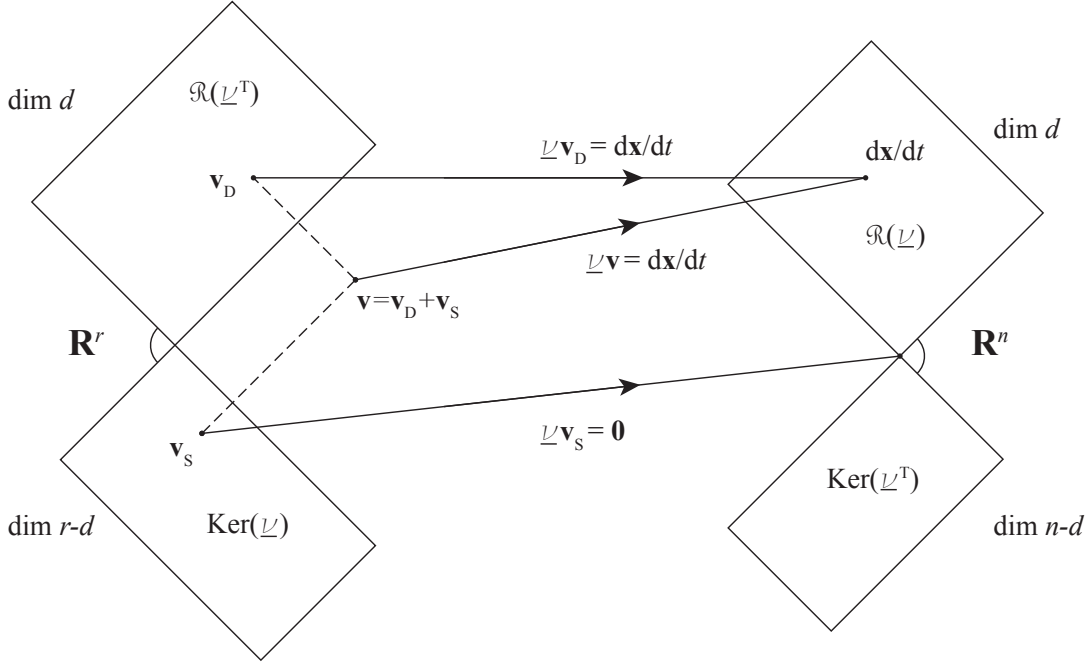
Dynamic equations:

$$\begin{aligned} \dot{x}_1 &= -k_1 x_1 x_6 + k_2 x_2 + k_5 - k_6 x_1, \\ \dot{x}_2 &= k_1 x_1 x_6 - k_2 x_2 - k_4 x_2 x_5, \\ \dot{x}_3 &= k_4 x_2 x_5 + k_9 - k_{10} x_3, \\ \dot{x}_4 &= -k_3 x_4 x_6 + k_7 - k_8 x_4, \\ \dot{x}_5 &= 2k_3 x_4 x_6 - k_4 x_2 x_5, \\ \dot{x}_6 &= -k_1 x_1 x_6 + k_2 x_2 - 2k_3 x_4 x_6 + 2k_4 x_2 x_5. \end{aligned}$$

3 Stoichiometric matrix

The matrix $\underline{\nu} \in \mathbb{R}^{n \times r}$ commonly called the *stoichiometric matrix* defines a linear transformation of the reaction rate vector $\mathbf{v} \in \mathbb{R}_+^r$ to the vector of time derivatives of the concentration vector $\dot{\mathbf{x}} \in \mathbb{R}^n$ as Eq. (19). The stoichiometric matrix $\underline{\nu}$ is organised in a such way that every column corresponds to a reaction and every row corresponds to a species. Each column that corresponds to a reaction is constrained by the rules of chemistry, such as elemental balancing. Every row describes the reactions in which that species participates and thus how the reactions are interconnected. Thus the stoichiometric matrix contains chemical and network information.

Now we may apply the fundamental theorem of linear algebra to the stoichiometric matrix $\underline{\nu}$. In general, each matrix $\underline{\nu}$ defines column space $\mathcal{R}(\underline{\nu})$, nullspace $\text{Ker}(\underline{\nu})$, row space $\mathcal{R}(\underline{\nu}^T)$ and left nullspace $\text{Ker}(\underline{\nu}^T)$ schematically shown in Fig. 1. These four fundamental subspaces contain important information about the reaction network. Chemical engineering interpretation of the fundamental subspaces of $\underline{\nu}$ is as follows (Palsson, 2006):



Obrázek 1: The stoichiometric matrix $\underline{\nu}$ as a linear transformation. The four fundamental subspaces of $\underline{\nu}$ are shown.

- The *nullspace* of $\underline{\nu}$, $\text{Ker}(\underline{\nu})$, contains all the steady-state reaction rate vectors available in the network.
- The *row space* of $\underline{\nu}$, $\mathcal{R}(\underline{\nu}^T)$, contains all the dynamic reaction rate vectors of the network. These are the thermodynamic driving forces that change the rate of reaction activity.
- The *left nullspace* of $\underline{\nu}$, $\text{Ker}(\underline{\nu}^T)$, contains all the conservation relationships, or *time invariants*, that the network contains. The sum of conserved subunits is time invariant (they do not change with time).
- The *column space* of $\underline{\nu}$, $\mathcal{R}(\underline{\nu})$, contains all the possible time derivatives of \mathbf{x} which show how the thermodynamic forces move the concentration state of the network.

4 Accessible states of concentration space

According the fundamental theorem of linear algebra $\underline{\nu}$ induces two subspaces $\text{Ker}(\underline{\nu}^T)$ and $\mathcal{R}(\underline{\nu})$ of the concentration space \mathbb{R}^n , see Fig. 1. These subspaces will be described

below.

4.1 Conservation constraint cone

If an atom or other subunit appear only in the internal species, the reaction stoichiometries must conserve the subunit. Assume that the species \mathcal{S}_i contains γ_{ki} subunits of type k . Then the total concentration of subunit k is

$$\sum_{i=1}^n \gamma_{ki} x_i = C_k, \quad (38)$$

which is a time invariant (conserved) quantity. When we differentiate Eq. (38) we obtain

$$\sum_{i=1}^n \gamma_{ki} \frac{dx_i}{dt} = 0. \quad (39)$$

Since the vector $\boldsymbol{\gamma}_k^T$ is orthogonal to the vector $\dot{\mathbf{x}}$, and $\dot{\mathbf{x}} \in \mathcal{R}(\boldsymbol{\nu})$ then $\boldsymbol{\gamma}_k^T \in \text{Ker}(\boldsymbol{\nu}^T)$. The dimension of $\text{Ker}(\boldsymbol{\nu}^T)$ corresponds to the number of conserved subunits in the network. We may write mass balance equations for $n - d$ conserved subunits

$$\underline{\boldsymbol{\gamma}} \mathbf{x} = \mathbf{C}, \quad (40)$$

where $\underline{\boldsymbol{\gamma}} \in \mathbb{R}^{(n-d) \times n}$ is the *conservation matrix* formed from row vectors $\boldsymbol{\gamma}_k^T$. $\mathbf{C} \in \overline{\mathbb{R}}_+^{n-d}$ is the conservation constraint vector. $\overline{\mathbb{R}}_+^{n-d}$ is called the *conservation constraint cone*. Since any reaction R_j cannot destroy conserved subunits, summing over all species \mathcal{S}_i yields

$$\underline{\boldsymbol{\gamma}} \boldsymbol{\nu} = \mathbf{0}. \quad (41)$$

This equation proves that $\underline{\boldsymbol{\gamma}}$ forms the left nullspace $\text{Ker}(\boldsymbol{\nu}^T)$.

4.2 Concentration polyhedron

For each $\mathbf{C} \in \overline{\mathbb{R}}_+^{n-d}$, the set of \mathbf{x} that are stoichiometrically compatible with \mathbf{C} and physically meaningful (nonnegative) is

$$\Pi_x(\mathbf{C}) \equiv \{\mathbf{x} \in \overline{\mathbb{R}}_+^n \mid \underline{\boldsymbol{\gamma}} \mathbf{x} = \mathbf{C}\}. \quad (42)$$

In general, this set forms an unbounded convex polyhedron. There are d independent dynamical variables and the remaining $n - d$ species are determined from Eq. (40). We will call $\Pi_x(\mathbf{C})$ the *concentration polyhedron*.

The representation $\Pi_x(\mathbf{C})$ in Eq. (42) is called *external representation*. It gives a test for determining whether any arbitrary chosen \mathbf{x}^* is in the set. An internal representation is an algorithm for constructing points in the set directly.

If the concentration state is initially \mathbf{x} , a new stoichiometrically accessible concentration state \mathbf{x}^* may be obtained by shifting each reaction R_j by an amount ξ_j , called the *extent of reaction*. Then

$$\mathbf{x}^* = \mathbf{x} + \underline{\nu}\xi. \quad (43)$$

Substitution in (40) shows that every $\xi \in \mathbb{R}^r$ determines \mathbf{x}^* satisfying $\underline{\gamma}\mathbf{x}^* = \underline{\gamma}\mathbf{x}$. Then this is a point of $\Pi_x(\underline{\gamma}\mathbf{x})$ provided $\mathbf{x}_i^* \geq 0$. Hence

$$\Pi_x(\underline{\gamma}\mathbf{x}) = \{\mathbf{x} + \underline{\nu}\xi \mid \xi \in \mathbb{R}^r, \mathbf{x} + \underline{\nu}\xi \geq 0\}, \quad (44)$$

which is only partly internal representation because it still contains a test (inequality).

For some $k > 0$, there exists a $n \times k$ matrix \mathbf{H} such that

$$\Pi_x(\underline{\gamma}\mathbf{x}) = \{\mathbf{H}\eta \mid \eta \in \mathbb{R}_+^k, \sum \eta_i = 1\} \quad (45)$$

and the representation of $\Pi_x(\underline{\gamma}\mathbf{x})$ is *internal representation*.

5 Reaction rate space

We now turn our attention from the n -dimensional concentration space to the r -dimensional reaction velocity space. According the fundamental theorem of linear algebra $\underline{\nu}$ induces two subspaces $\text{Ker}(\underline{\nu})$ and $\mathcal{R}(\underline{\nu}^T)$ of the reaction rate space \mathbb{R}^r , see Fig. 1. These subspaces will be describes below.

5.1 Current cone and polytope

In general reaction rates comply the physical constraint

$$v_i(\mathbf{x}, \mathbf{k}) \geq 0. \quad (46)$$

For any reversible reaction the forward and reverse reaction rates are given by two non-negative numbers and the corresponding columns of $\underline{\nu}$ sum to zero.

When we apply the definition of the steady state

$$\left. \frac{d\mathbf{x}}{dt} \right|_{\mathbf{x}=\mathbf{x}^0} = \mathbf{0} \quad (47)$$

to Eq. (19), we obtain the steady-state condition for reaction rates

$$\underline{\nu} \mathbf{v}^0(\mathbf{x}^0, \mathbf{k}) = \mathbf{0}. \quad (48)$$

Since any stationary state \mathbf{x}^0 solves Eq. (48) therefore the corresponding stationary rate vector $\mathbf{v}^0 = \mathbf{v}^0(\mathbf{x}^0, \mathbf{k})$ lies in the nullspace of $\underline{\nu}$, i.e. $\mathbf{v}^0 \in \text{Ker}(\underline{\nu})$. The set of all \mathbf{v}^0 form an unbounded $(r - d)$ -dimensional convex cone \mathcal{C}_v which dimension corresponds to $\dim(\text{Ker}(\underline{\nu}))$. Clarke (1980) noticed that the steady-state condition in Eq. (48) is similar to Kirchhoff's current law for electrical networks. Hence \mathbf{v}^0 are called *currents*. The set of all currents is a set called *current cone*

$$\mathcal{C}_v \equiv \{\mathbf{v}^0 \in \overline{\mathbb{R}}_+^r \mid \underline{\nu} \mathbf{v}^0 = \mathbf{0}\}. \quad (49)$$

This is an external representation of \mathcal{C}_v . We may rewrite \mathcal{C}_v into the form

$$\mathcal{C}_v = \{\lambda \mathbf{v}^0 \mid \mathbf{v}^0 \in \Pi_v, \lambda \geq 0\}, \quad (50)$$

where Π_v is the convex polyhedron defined

$$\Pi_v \equiv \{\mathbf{v}^0 \in \overline{\mathbb{R}}_+^r \mid \underline{\nu} \mathbf{v}^0 = \mathbf{0}, \mathbf{e}_r^T \cdot \mathbf{v}^0 = 1\}, \quad (51)$$

where $\mathbf{e}_r^T = (1, \dots, 1) \in \mathbb{R}^r$. Clarke (1980) called Π_v the *current polytope*. According Theorem IV in Subsection we may express Π_v as a convex combination of its extreme points

$$\Pi_v = \{\mathbf{E} \mathbf{j} \mid \mathbf{j} \in \overline{\mathbb{R}}_+^f, \mathbf{e}_f^T \mathbf{j} = 1\}, \quad (52)$$

where $\mathbf{E} \in \mathbb{R}^{r \times f}$ and $\mathbf{e}_f^T = (1, \dots, 1) \in \mathbb{R}^f$. When we omit the second restriction on \mathbf{j} and combine with Eq. (50) we give the internal representation for \mathcal{C}_v

$$\mathcal{C}_v = \{\mathbf{E} \mathbf{j} \mid \mathbf{j} \in \overline{\mathbb{R}}_+^f\}. \quad (53)$$

We will call vectors \mathbf{E}_i s as *extreme currents* which point along the edges of the current cone \mathcal{C}_v and form the cone's frame. The edges of the current cone \mathcal{C}_v represent the simplest solutions \mathbf{v}^0 of Eq. (48) which define *elementary subnetworks* (or *extreme subnetworks*).

The equations (49) and (53) imply that every $\mathbf{v}^0 \in \mathcal{C}_v$ has the form

$$\mathbf{v}^0 = \mathbf{E} \mathbf{j} \quad (54)$$

for some $\mathbf{j} \in \overline{\mathbb{R}}_+^f$. Substituting into Eq. (48) gives $\underline{\nu} \mathbf{E} \mathbf{j} = \mathbf{0}$ for all $\mathbf{j} \in \overline{\mathbb{R}}_+^f$, hence we may write

$$\underline{\nu} \mathbf{E} = \mathbf{0}. \quad (55)$$

The restriction $\mathbf{v}^0 \in \overline{\mathbb{R}}_+^r$ in Eq. (49) with Eq. (55) says that every \mathbf{E}_j must lie in the intersection of the null space of $\text{Ker}(\underline{\boldsymbol{\nu}})$ and the closed positive orthant $\overline{\mathbb{R}}_+^r$, i.e. $\mathbf{E}_j \in \text{Ker}(\underline{\boldsymbol{\nu}}) \cap \overline{\mathbb{R}}_+^r$. Recall that $\dim \mathcal{C}_v = \dim \text{Ker}(\underline{\boldsymbol{\nu}}) = r - d$. A cone of this dimension cannot be spanned by fewer than $r - d$ frame vectors, so

$$f \geq r - d. \quad (56)$$

The current cone \mathcal{C}_v has no boundary other than the boundary of $\overline{\mathbb{R}}_+^r$. This boundary consists entirely of the coordinate hyperplanes $v_i^0 = 0$, $i = 1, \dots, r$. If \mathcal{C}_v intersects the i th hyperplane other than at the origin, we can investigate this intersection by setting $v_i^0 = 0$ in Equation (48). We obtain $(r - d - 1)$ -dimensional facet of \mathcal{C}_v lying within $\text{Ker}(\underline{\boldsymbol{\nu}}) \cap \{\mathbf{v}^0 \in \overline{\mathbb{R}}_+^r \mid v_i = 0\}$. We are interested in edges (1-dimensional facet) of the cone \mathcal{C}_v which do not intersect any coordinate hyperplane except at the origin. This half-line is a frame vector of \mathcal{C}_v , and any point $\mathbf{v}^0 \neq \mathbf{0}$ on it is an extreme current. Thus we have to investigate all intersections of any $r - d$ hyperplanes.

Before we will continue we explicitly show the calculation of the extreme current matrix \mathbf{E} . Hence below follows a detailed discussion of how this is done.

5.2 Linear programming algorithm for calculation of \mathbf{E}

This algorithm comes from linear programming literature (Hadley, 1962).

Let us combine the two restrictions on \mathbf{v}^0 in Eq. (51) into the equation

$$\mathbf{B}\mathbf{v}^0 = \mathbf{b}, \quad (57)$$

where $\mathbf{B} \in \mathbb{R}^{(d+1) \times r}$ is obtained by adding a bottom row of 1's, i.e. $(1, \dots, 1) \in \mathbb{R}^r$, to d linearly independent rows forming the row space $\mathcal{R}(\underline{\boldsymbol{\nu}}^T)$, and $\mathbf{b} = (0, \dots, 0, 1)^T \in \mathbb{R}^{d+1}$. We must set to zero $r - d$ components of \mathbf{v}^0 and then solve Eq. (57) to get a unique solution for the remaining components. If the final row of \mathbf{B} were a linear combination of the remaining rows, every solution of Eq. (57) would satisfy $\mathbf{e}_r^T \mathbf{v}^0 = 0$ and Eq. (57) would be inconsistent. Since $\mathbf{e}_r^T \mathbf{v}^0 = 1$, \mathbf{B} has rank $d + 1$.

To find an extreme current, we select $d + 1$ columns of \mathbf{B} and construct a square matrix that usually may be inverted to obtain \mathbf{v}^0 . All possible extreme currents are found by selecting the $d + 1$ columns in all possible ways and then keeping only solutions satisfying Eq. (46). Maximally, we may obtain $r!/(d + 1)!(r - d - 1)!$ extreme currents.

It often happens that for certain choices of $d + 1$ columns, the resulting matrix has rank less than $d + 1$. Then Eq. (57) cannot be solved because the linearly dependent columns

of \mathbf{B} form a singular matrix. For these choices of columns we terminate the calculation because we obtain every extreme solution of Eq. (48) satisfying constraints of Eq. (46) from Eq. (57) with a linearly independent set of columns.

5.3 Pathway oriented algorithm for calculation of \mathbf{E}

Many authors have used the linear programming algorithm described in Subsection 5.2. The number of chemical reactions r increases the number of tasks which has to be computed. In general, networks may also consist of hundreds of chemical species. Since there are only several (typically two, three, or four) species that participate in a reaction out of hundreds of species participating in a network, the stoichiometric matrix $\underline{\nu}$ is a *sparse*. A sparse matrix mostly comprises zero elements. Schilling *et al.* (2000) published a pathway oriented algorithm which is another algorithm for calculation of \mathbf{E} . The pathway oriented algorithm saves computation time by dealing with nonzero elements only. For clarity, we describe this algorithm using the Example 1.

The pathway oriented algorithm for calculation of \mathbf{E} begins with the formulation of an initial matrix. The *initial matrix* $\mathbf{T}^{(ini)}$ is a block matrix formed from two blocks. The left hand side block is the $r \times r$ identity matrix \mathbf{I}_r . Whereas the right hand side block forms the transpose of the stoichiometric matrix $\underline{\nu}^T \in \mathbb{R}^{n \times r}$. Then

$$\mathbf{T}^{(ini)} = [\mathbf{I}_r \mid \underline{\nu}^T] \in \mathbb{R}^{r \times (r+n)}, \quad (58)$$

where each element of this matrix will be denoted T_{ij} .

Example 1 (*continued from Section 2*) Immediately, we may write the initial matrix

$$\mathbf{T}^{(ini)} = \left[\begin{array}{cccccccccc|cccccc} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & -1 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 2 & -2 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & -1 & 2 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{array} \right]. \quad (59)$$

Examine constraints on chemical species in the fictitious reactions of the network. We may divide species into two disjoint sets. The first set contains only *unconstrained*

species that can both enter and exit the system. Each unconstrained species \mathcal{S}_i brings the fictitious reaction defined by Eq. (10) into the network. The rest species belong to the set of *constrained species* because these species either enter or exit the system or remain in the system.

Then we move all rows corresponding to the fictitious reactions of unconstrained species from the matrix $\mathbf{T}^{(ini)}$ into a temporary matrix $\mathbf{T}^{(E)}$ row by row. Finally, we obtain the initial matrix $\mathbf{T}^{(0)}$ consisting of the remaining rows of the matrix $\mathbf{T}^{(ini)}$.

Example 1 (*continued*) The reaction system defines matrices $\mathbf{T}^{(0)}$ and $\mathbf{T}^{(E)}$

$$\mathbf{T}^{(0)} = \left[\begin{array}{cccccccccccc|cccccc} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & -1 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 2 & -2 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & -1 & 2 \end{array} \right] \quad (60)$$

and

$$\mathbf{T}^{(E)} = \left[\begin{array}{cccccccccccc|cccccc} 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \end{array} \right]. \quad (61)$$

Let k be an integer. Start with $k = 1$ then $\mathbf{T}^{(k-1)} = \mathbf{T}^{(0)}$ and the next matrix $\mathbf{T}^{(k)}$ is generated in the following manner:

1. Identify all constrained species. The total number of such species is denoted by ω . In this example, compounds CO^* , O^* and $*$ belong into constrained species so that $\omega = 3$.
2. Let c to be the index of the column which corresponds to the first constrained species in the $\underline{\nu}^T$, i.e. the right block of $\mathbf{T}^{(k-1)}$. Then we begin to form the new matrix $\mathbf{T}^{(k)}$ by copying all rows \mathbf{T}_i^T from $\mathbf{T}^{(k-1)}$ which satisfy the condition $T_{ic} = 0$.

Example 1: the second column of $\underline{\nu}^T$ corresponds to the first identified species CO^* , i.e. $c = 12$.

3. From the remaining rows in $\mathbf{T}^{(k-1)}$ we add together all possible combinations of rows which contain values of the opposite sign in the column c , such that the addition

produces a zero in this column. Let us have two rows \mathbf{T}_i^T and \mathbf{T}_j^T , then we add up these rows to generate a new row

$$\mathbf{T}_m^T = |T_{jc}| \mathbf{T}_i^T + |T_{ic}| \mathbf{T}_j^T. \quad (62)$$

This row will be added to the matrix $\mathbf{T}^{(k)}$.

Example 1 (*continued*) The resulting matrix $\mathbf{T}^{(1)}$ up to this point is as follows:

$$\mathbf{T}^{(1)} = \left[\begin{array}{cccccccccc|cccc} 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 2 & -2 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 1 & 0 & -1 & 1 \end{array} \right]. \quad (63)$$

4. Check all rows of the matrix $\mathbf{T}^{(k)}$ formed in steps 2 and 3. We should be sure that no row exists that is a nonnegative combination of the set of the others in $\mathbf{T}^{(k)}$. Let $A(i)$ is a set of column indices for which the elements of the i th row of $\mathbf{T}^{(k)}$ equal zero

$$A(i) \equiv \{j \mid T_{ij} = 0, 1 \leq j \leq (r+n)\}. \quad (64)$$

If there are any two distinct rows \mathbf{T}_i^T and \mathbf{T}_h^T that satisfy

$$A(i) \subseteq A(h), \quad i \neq h. \quad (65)$$

Then we have to eliminate the row \mathbf{T}_i^T from the matrix $\mathbf{T}^{(k)}$.

5. The matrix $\mathbf{T}^{(k)}$ is now complete. We will repeat steps 2–4 for all of the constrained species, incrementing k by one up to ω . The final matrix will be $\mathbf{T}^{(\omega)}$.

Example 1 (*continued*) There are three species so we need to iterate through steps 2–4 again. The second iteration gives the matrix $\mathbf{T}^{(2)}$

$$\mathbf{T}^{(2)} = \left[\begin{array}{cccccccccc|cccc} 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 2 & 0 & 1 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & -2 & 0 & 2 & -1 & 0 & 0 \end{array} \right]. \quad (66)$$

Since the column corresponding to the species * contains only zeros, the third iteration is not necessary, and $\mathbf{T}^{(3)} = \mathbf{T}^{(2)}$.

6. Create the matrix $\mathbf{T}^{(\omega+1)}$ such that $\mathbf{T}^{(\omega+1)} = \mathbf{T}^{(\omega)}$. Start with the first nonzero column in the right block of $\mathbf{T}^{(\omega+1)}$. This column corresponds to the first unconstrained species. Let $j \in [(r+1), (r+n)]$ is the index of the first unconstrained species

in the right block of $\mathbf{T}^{(\omega+1)}$. If i is the index of the row which possesses the element $T_{ij} \neq 0$, then we find the corresponding row \mathbf{T}_m^T from $\mathbf{T}^{(E)}$ such that

$$\text{sgn}(T_{ij}) = -\text{sgn}(T_{mj}).$$

Replace the i th row of the matrix $\mathbf{T}^{(\omega+1)}$ by the row that arises from the following addition of rows to produce zero in the position T_{ij}

$$\mathbf{T}_i^T = \mathbf{T}_i^T + |T_{ij}| \mathbf{T}_m^T. \quad (67)$$

Repeat this procedure for each nonzero elements in the j th column of the matrix $\mathbf{T}^{(\omega+1)}$ to create zeros in the entire j th column.

Example 1 (*continued*) We begin with the column corresponding to the species CO

$$\mathbf{T}^{(4)} = \left[\begin{array}{cccccccccc|cccc} 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 2 & 0 & 1 & 2 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 2 & -1 & 0 & 0 \end{array} \right]. \quad (68)$$

- Continue with the same procedure as in step 6 for each column $\mathbf{T}^{(\omega+1)}$ which corresponds to each unconstrained species.

Example 1 (*continued*) We need to perform step 6 for the columns corresponding to species CO, O₂, and CO₂. Then

$$\mathbf{T}^{(bal)} = \left[\begin{array}{cccccccccc|cccc} 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 2 & 0 & 1 & 2 & 2 & 0 & 1 & 0 & 0 & 2 & 0 & 0 & 0 & 0 & 0 & 0 \end{array} \right]. \quad (69)$$

- Apply steps 2–3 to the matrix $\mathbf{T}^{(E)}$. Here we replace the constrained species unconstrained ones and obtain the matrix $\mathbf{T}^{(f.r.)}$ representing elementary subnetworks of the fictitious reactions Eqs. (10–12).

Example 1 (*continued*)

$$\mathbf{T}^{(f.r.)} = \left[\begin{array}{cccccccccc|cccc} 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \end{array} \right]. \quad (70)$$

- Append $\mathbf{T}^{(f.r.)}$ to the bottom of matrix $\mathbf{T}^{(\omega+1)}$. Now we have the final matrix $\mathbf{T}^{(fin)}$.

Example 1 (*continued*)

$$\mathbf{T}^{(fin)} = \left[\begin{array}{cccccccccccc|cccccc} 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 2 & 0 & 1 & 2 & 2 & 0 & 1 & 0 & 0 & 0 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{array} \right]. \quad (71)$$

The left block of the matrix $\mathbf{T}^{(fin)} \in \mathbb{R}^{f \times (r+n)}$, i.e. the first r columns of $\mathbf{T}^{(fin)}$, forms the matrix \mathbf{E}^T that contains the extreme currents (elementary subnetworks).

$$\mathbf{T}^{(fin)} = [\mathbf{E}^T \mid \mathbf{0}] \in \mathbb{R}^{r \times (r+n)}. \quad (72)$$

Finally, we get the required matrix \mathbf{E} .

Example 1 (*continued*)

$$\mathbf{E} = \left[\begin{array}{ccccc} 1 & 2 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 2 & 0 & 0 & 0 \\ 0 & 2 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 2 & 0 & 0 & 1 \end{array} \right]. \quad (73)$$

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