

# An Efficient Algorithm for Determining the Equivalence of Zero-one Reaction Networks

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## Abstract

Zero-one reaction networks play a crucial role in cell signaling. Determining the equivalence of reaction networks is a fundamental computational problem in the field of chemical reaction networks. In this work, we develop an efficient method for determining the equivalence of zero-one networks. The efficiency comes from several criteria for determining the equivalence of the steady-state ideals arising from zero-one networks, which helps for cutting down the expenses on computing Gröbner bases. Experiments show that our method can successfully classify over three million networks according to their equivalence in a reasonable time.

*Keywords:* Chemical reaction network, Gröbner basis, Steady-state ideal

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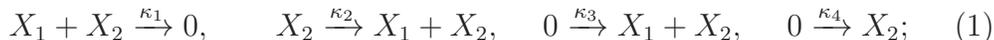
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## 1. Introduction

For the dynamical systems that arise from biochemical reaction networks, the following computational question is fundamental.

**Question 1.** *Which reaction networks have the same steady-state ideal?*

The equivalence of steady-state ideals is one of the equivalence problem in the field of chemical reaction networks. The dynamical features of chemical reaction networks such as multistability, Hopf-bifurcation, and absolute concentration robustness (ACR) are linked to switch-like behavior, decision-making process, oscillation, and so on in cellular signaling [7, 23, 27, 9, 3, 25]. Usually, looking at the steady states is the first step for studying the dynamical behaviors of a chemical reaction system arising under mass-action kinetics. However, it is possible for two different networks to have the same steady-state ideal (notice that the steady states can be considered as real points located in the algebraic variety generated by the steady-state ideal). For instance, consider the two reaction networks:



They respectively have the following steady-state systems (see how to write down the system for a given network later in (8))

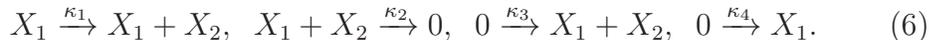
$$\{-\kappa_1 x_1 x_2 + \kappa_2 x_2 + \kappa_3, -\kappa_1 x_1 x_2 + \kappa_3 + \kappa_4\}; \quad (3)$$

$$\{-\kappa_1 x_1 x_2 + \kappa_2 x_2 + \kappa_3, -\kappa_2 x_2 + \kappa_4\}. \quad (4)$$

It is straightforward to compute the reduced Gröbner bases [8] for the above two steady-state systems, and we find that in  $\mathbb{Q}(\kappa)[x]$  they have the same reduced Gröbner basis

$$\{\kappa_2 x_2 - \kappa_4, \kappa_1 \kappa_4 x_1 - \kappa_2 \kappa_3 - \kappa_2 \kappa_4\}. \quad (5)$$

In many cases, the above two networks are considered to be equivalent because when we only care about the dynamical behaviors determined by the steady states such as multistationarity, multistability, Hopf-bifurcation and ACR, we only need to study one of the networks that have the same steady-state ideal. Notice that relabeling the species or the reactions in a network naturally gives another kind of equivalence (see more details in [5] on the “dynamical equivalence” of networks). For instance, if we relabel the species  $X_1$  and  $X_2$  and we relabel the first and the second reactions in the network (1), then we get the following network



Of course, the network (6) should be considered to be equivalent to the network (1) and so, it is also equivalent to the network (2). Hence, in our context, we say two networks are equivalent if they have the same steady-state ideal after relabeling (see Definition 1).

Determining the equivalence is computationally challenging since a standard approach is to compute the reduced Gröbner bases. In a recent related work [12], the authors point out that there are few works on looking at the equivalence of the steady-state ideals, and we see that deriving explicit conditions for the equivalence is difficult in general. So, we might need to focus on a special class of networks for making this problem more feasible. The standard way (computing Gröbner bases [17, 15, 13, 14, 1, 16]) might be efficient for small networks such as one-species networks or two-reaction networks. However, in the studying of small networks, we usually need to deal with a substantial amount of networks. The idea of studying the small networks is motivated by the fact that many important dynamical features have inheritance from a large network to a smaller “subnetwork” such as multistability [20, 6], oscillation [2] and local bifurcations [4]. In many recent works, people are searching for the smallest networks from a big class of networks that admit these dynamical behaviors. In these studies, we need to first determine the equivalence of networks for making the searching process easier. For instance, Banaji and Boros [3] recently completely classify the smallest at-most-bimolecular networks that admit Hopf bifurcations

(they contain three species and four reactions). Tang and Wang [27] find that the smallest zero-one networks that admit Hopf bifurcations are four-dimensional (they contain four species and five reactions). Kaihnsa, Nguyen and Shiu [21] prove that an at-most-bimolecular network admitting both multistationarity and ACR has at least three species and three reactions, and it is at least two-dimensional. The focus of this work is the zero-one networks since many biological significant networks in cell signaling are zero-one such as phosphorylation-dephosphorylation cycle [18], cell cycle [24], hybrid histidine kinase [26], and so on.

In this work, our main contribution is an efficient algorithm (Algorithm 1) for determining the equivalence of zero-one networks. The efficiency of the proposed new method comes from several criteria for determining the equivalence of the steady-state ideals arising from zero-one networks, which dramatically cuts down the expenses on computing Gröbner bases since many computations are avoided. We have successfully applied the new method to determining the equivalence of the smallest zero-one networks that admit multistationarity (these networks are three-dimensional, three-species and five-reaction [19]). The input contains over three millions such networks, and the new algorithm returns 32394 networks after determining the equivalence. The computation is completed in a short time (see Table 1).

The rest of this paper is organized as follows. In Section 2, we review the basic concepts on reaction networks and the dynamical systems arising from mass-action kinetics. Also, we formally define the steady-state ideal and the equivalence of networks in our context. In Section 3, we prove a series of sufficient conditions (Theorems 1–3) for determining the equivalence of networks. In Section 4, we present the main algorithm (Algorithm 1) with two sub-algorithms (Algorithms 2–3) for determining the equivalence of zero-one networks. In Section 5, we illustrate how the main algorithm performs by applying it to the three-dimensional zero-one networks with three species and five reactions. Also, we explain the implementation details and present the computational timings.

## 2. Background

In this section, we briefly recall the standard notions and definitions for reaction networks and computational algebraic geometry, see [10] and [11] for more details.

A **reaction network**  $G$  (or **network** for short) consists of a set of  $s$  species  $\{X_1, X_2, \dots, X_s\}$  and a set of  $m$  reactions:



where all **stoichiometric coefficients**  $\alpha_{ij}$  and  $\beta_{ij}$  are non-negative integers, and we assume that  $(\alpha_{1j}, \dots, \alpha_{sj}) \neq (\beta_{1j}, \dots, \beta_{sj})$ . Each  $\kappa_j \in \mathbb{R}_{>0}$  is called a **rate constant** corresponding to the  $j$ -th reaction in (7). We say a reaction is a **zero-one reaction**, if the stoichiometric coefficients  $\alpha_{ij}$  and  $\beta_{ij}$  in (7) belong to  $\{0, 1\}$ . We say a network (7) is a **zero-one network** if it only has zero-one reactions. For any reaction defined in (7), the **stoichiometric vector** is  $(\beta_{1j} - \alpha_{1j}, \dots, \beta_{sj} - \alpha_{sj})^\top \in \mathbb{Q}^s$ . We say finitely many reactions are linearly independent if their corresponding stoichiometric vectors are linearly independent. We call the  $s \times m$  matrix with  $(i, j)$ -entry equal to  $\beta_{ij} - \alpha_{ij}$  the **stoichiometric matrix** of  $G$ , denoted by  $\mathcal{N}$ . The **dimension** of  $G$  is defined as the rank of  $\mathcal{N}$ . We call the  $s \times m$  matrix the **reactant matrix** of  $G$  with  $(i, j)$ -entry equal to  $\alpha_{ij}$ , denoted by  $\mathcal{Y}$ .

Denote by  $x_1, \dots, x_s$  the concentrations of the species  $X_1, \dots, X_s$ , respectively. Under the assumption of mass-action kinetics, we describe how these concentrations change in time by the following system of ODEs:

$$\dot{x} = f(\kappa, x) := \mathcal{N}v(\kappa, x) = \mathcal{N} \begin{pmatrix} \kappa_1 \prod_{i=1}^s x_i^{\alpha_{i1}} \\ \kappa_2 \prod_{i=1}^s x_i^{\alpha_{i2}} \\ \vdots \\ \kappa_m \prod_{i=1}^s x_i^{\alpha_{im}} \end{pmatrix}, \quad (8)$$

where  $x = (x_1, x_2, \dots, x_s)^\top$ ,  $v(\kappa, x) = (v_1(\kappa, x), \dots, v_m(\kappa, x))^\top$  and

$$v_j(\kappa, x) := \kappa_j \prod_{i=1}^s x_i^{\alpha_{ij}}. \quad (9)$$

By viewing the rate constants as a real vector of parameters  $\kappa := (\kappa_1, \kappa_2, \dots, \kappa_m)^\top$ , we have polynomials  $f_i(\kappa, x) \in \mathbb{Q}(\kappa)[x]$ , for  $i \in \{1, \dots, s\}$ . The polynomial ideal generated by  $f$  in  $\mathbb{Q}(\kappa)[x]$ , denoted by  $\langle f \rangle$ , is called the **steady-state ideal**.

**Definition 1.** Two reaction networks are **equivalent** if they have the same steady-state ideal in the sense of relabeling.

For any given rate-constant vector  $\kappa^* \in \mathbb{R}_{>0}^m$ , a **steady state** of (8) is a vector of concentrations  $x^* \in \mathbb{R}_{\geq 0}^s$  such that  $f(\kappa^*, x^*) = \vec{0}$ , where  $f(\kappa, x)$  is on the right-hand side of the ODEs (8), and  $\vec{0}$  denotes the column vector whose coordinates are all zero. If all the coordinates of a steady state  $x^*$  are strictly positive (i.e.,  $x^* \in \mathbb{R}_{>0}^s$ ), then we call  $x^*$  a **positive steady state**. For the stoichiometric matrix  $\mathcal{N} \in \mathbb{Q}^{s \times m}$ , the **positive flux cone** of  $\mathcal{N}$  is defined as

$$\mathcal{F}^+(\mathcal{N}) := \{\gamma \in \mathbb{R}_{>0}^m \mid \mathcal{N}\gamma = \vec{0}\}. \quad (10)$$

In applications, we usually only care about positive steady states of a network. It is well-known that a network admits positive steady states if and only if  $\mathcal{F}^+(\mathcal{N}) \neq \emptyset$ .

### 3. Theorem

#### 3.1. Sufficient conditions for vacuous ideals

For any matrix  $\mathcal{A}$ , we denote by  $\text{row}_i(\mathcal{A})$  and  $\text{col}_i(\mathcal{A})$  the  $i$ -th row and the  $i$ -th column of  $\mathcal{A}$ , respectively. For any vector  $a$ , we denote by  $a_i$  the  $i$ -th coordinate of  $a$ .

**Theorem 1.** For any network  $G$  (7), let  $f$  be the steady-state system defined as in (8). If there exists  $a \in \mathbb{Q}^s$  such that

- (1)  $P := \mathcal{N}^\top a \neq \vec{0}$ , and
- (2) for any  $i \in \{1, \dots, s\}$ , if  $P_i \neq 0$ , then we have  $\text{col}_i(\mathcal{Y}) = \vec{0}$ ,

then  $\langle f \rangle = \langle 1 \rangle$  in  $\mathbb{Q}(\kappa)[x]$ .

*Proof.* Let  $v = (v_1, \dots, v_m)^\top$  be defined as in (9). By the condition (1), we have

$$P^\top v = \sum_{i=1}^s a_i \text{row}_i(\mathcal{N})v. \quad (11)$$

Note that  $P \neq \vec{0}$ . We denote by  $P_{i_1}, \dots, P_{i_n}$  all the non-zero coordinates in  $P$ . So, by (11), we have

$$\sum_{i=1}^s a_i \text{row}_i(\mathcal{N})v = \sum_{j=1}^n P_{i_j} v_{i_j}. \quad (12)$$

By the condition (2), for any  $j \in \{1, \dots, n\}$ , we have  $\text{col}_{i_j}(\mathcal{Y}) = \vec{0}$ . Hence, by (9), for any  $j \in \{1, \dots, n\}$ ,

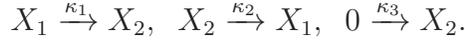
$$v_{i_j} = \kappa_{i_j}.$$

Then, by (8) and by (12), we have

$$\sum_{i=1}^s a_i f_i = \sum_{i=1}^s a_i \text{row}_i(\mathcal{N})v = \sum_{j=1}^n P_{i_j} \kappa_{i_j} \in \langle f \rangle.$$

Thus, we have  $\langle f \rangle = \langle 1 \rangle$  in  $\mathbb{Q}(\kappa)[x]$ .  $\square$

**Example 1.** We illustrate how Theorem 2 works by the following network:



The corresponding reactant matrix is

$$\mathcal{Y} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}. \quad (13)$$

The corresponding stoichiometric matrix is

$$\mathcal{N} = \begin{pmatrix} -1 & 1 & 0 \\ 1 & -1 & 1 \end{pmatrix}.$$

Let  $a = (1, 1)^\top$ . Then, we have  $P := \mathcal{N}^\top a = (0, 0, 1)^\top$ . Note that  $P_3 \neq 0$ . By (13),  $\text{col}_3(\mathcal{Y}) = \vec{0}$ . Hence, by Theorem 1, we have  $\langle f \rangle = \langle 1 \rangle$ .

A row (column) of a matrix is called a **non-zero row (column)** if there exists a non-zero element in this row (column). If a row (column) has both positive and negative elements, we say **the row (column) changes signs**.

**Theorem 2.** For any  $d$ -dimensional zero-one network  $G$  (7), let  $f$  be the steady-state system defined as in (8). We denote by  $c$  the number of zero columns of the reactant matrix  $\mathcal{Y}$ . Assume that all the rows of the stoichiometric matrix  $\mathcal{N}$  are non-zero and change signs. Then, we have the following statements.

1. There is at least one non-zero column in  $\mathcal{Y}$  (i.e.,  $c < m$ ).
2. If  $c = m - 1$  and  $d \geq 2$ , then  $\langle f \rangle = \langle 1 \rangle$  in  $\mathbb{Q}(\kappa)[x]$ .
3. If  $c = m - 2$  and  $d = s \geq 3$ , then  $\langle f \rangle = \langle 1 \rangle$  in  $\mathbb{Q}(\kappa)[x]$ .
4. If  $c = 0$ , then  $\langle f \rangle \neq \langle 1 \rangle$  in  $\mathbb{Q}(\kappa)[x]$ .

*Proof.* 1. Recall that any stoichiometric coefficients  $\alpha_{ij}$  and  $\beta_{ij}$  are defined as in (7). By the definition of zero-one network, for any  $(i, j) \in \{1, \dots, s\} \times \{1, \dots, m\}$ , we have  $\beta_{ij} \in \{0, 1\}$ . So, if there exists  $(i, j)$  such that  $\alpha_{ij} = 0$ , then the  $(i, j)$ -entry of  $\mathcal{N}$  (i.e.,  $\beta_{ij} - \alpha_{ij}$ ) can only be 0 or 1. Hence, if all entries of  $\mathcal{Y}$  are 0 (i.e.,  $c = m$ ), then all entries of  $\mathcal{N}$  are 0 or 1. It is contrary to the assumption that all the rows of  $\mathcal{N}$  are non-zero and change signs. Therefore, there is at least one non-zero column in  $\mathcal{Y}$  (i.e.,  $c < m$ ).

2. Since all the rows of  $\mathcal{N}$  are non-zero and change signs, there exists the element  $-1$  in every row of  $\mathcal{N}$ . By the definition of zero-one network, we have  $\alpha_{ij} \in \{0, 1\}$  and  $\beta_{ij} \in \{0, 1\}$ . Hence, if there exists an  $(i, j)$ -entry of  $\mathcal{N}$  such that the entry is  $-1$  (i.e.,  $\beta_{ij} - \alpha_{ij} = -1$ ), then  $\alpha_{ij} = 1$ . Hence, there exists the element 1 in every row of  $\mathcal{Y}$ . Since the number of zero columns is  $m - 1$ , we can assume that the first  $m - 1$  columns of  $\mathcal{Y}$  are the zero vector. Note that there exists the element 1 in every row of  $\mathcal{Y}$ . So, all the coordinates of the the  $m$ -th column of  $\mathcal{Y}$  must be 1. Then, we have

$$\mathcal{Y} = \begin{pmatrix} 0 & \cdots & 0 & 1 \\ & \ddots & & \vdots \\ 0 & \cdots & 0 & 1 \end{pmatrix}.$$

By the definition of zero-one network, if there exists  $(i, j)$  such that  $\alpha_{ij} = 0$ , then the  $(i, j)$ -entry of  $\mathcal{N}$  (i.e.,  $\beta_{ij} - \alpha_{ij}$ ) can only be 0 or 1. Hence, every coordinate of the first  $m - 1$  columns of  $\mathcal{N}$  can only be 0 or 1. Note that there exists  $-1$  in every row vector of  $\mathcal{N}$ . So, all the coordinates of the the  $m$ -th column of  $\mathcal{N}$  are  $-1$ . Thus,  $\mathcal{N}$  has the following form

$$\mathcal{N} = \begin{pmatrix} & -1 \\ \mathcal{A}_1 & \vdots \\ & -1 \end{pmatrix}, \quad (14)$$

where all the entries of the  $s \times (m-1)$  submatrix  $\mathcal{A}_1$  are 0 or 1. Recall that for any  $i \in \{1, \dots, s\}$ , we denote by  $row_i(\mathcal{N})$  the  $i$ -th row of  $\mathcal{N}$ . Since  $d \geq 2$  (note here,  $\mathbf{rank}(\mathcal{N}) = d$ ), there exist  $i, j \in \{1, \dots, s\}$  such that  $P^\top := row_i(\mathcal{N}) - row_j(\mathcal{N}) \neq \vec{0}^\top$ . So, if  $P_k \neq 0$ , then by (14), we have  $k \in \{1, \dots, m-1\}$ . Note that for any  $k \in \{1, \dots, m-1\}$ , the  $k$ -th column vector of  $\mathcal{Y}$  is a zero vector. Therefore, by Theorem 1, we have  $\langle f \rangle = \langle 1 \rangle$ .

3. Assume that the first  $m-2$  columns of  $\mathcal{Y}$  are the zero vector. Then, by the definition of zero-one network, we have

$$\mathcal{Y} = \begin{pmatrix} 0 & \cdots & 0 & \\ & & \ddots & \mathcal{A}_2 \\ 0 & \cdots & 0 & \end{pmatrix},$$

where the entries of the  $s \times 2$  submatrix  $\mathcal{A}_2$  are 0 or 1. Then, similar to the proof of (2), by the definition of zero-one network, we have

$$\mathcal{N} = (\mathcal{A}_3 \quad \mathcal{A}_4), \tag{15}$$

where the entries of the  $s \times (m-2)$  submatrix  $\mathcal{A}_3$  are 0 or 1. Since all rows of  $\mathcal{N}$  are non-zero and change signs, there exists the element  $-1$  in every row of  $\mathcal{N}$ . Hence, the rows of the  $s \times 2$  submatrix  $\mathcal{A}_4$  must be in the set

$$\{(0, -1), (-1, 0), (1, -1), (-1, 1), (-1, -1)\}. \tag{16}$$

- (i) Assume that there exist  $k < s$  different row vectors in (16) appearing in  $\mathcal{A}_4$ . Since  $k < s$ , at least two rows in  $\mathcal{A}_4$  are the same. Assume that the  $i$ -th and the  $j$ -th ( $i, j \in \{1, \dots, s\}$ ) rows in  $\mathcal{A}_4$  are the same. Define  $P^\top := row_i(\mathcal{N}) - row_j(\mathcal{N})$ . Then, we have  $P_{m-1} = P_m = 0$ . Since  $\mathbf{rank}(\mathcal{N}) = d = s$ , we have  $P \neq \vec{0}$ . Therefore, for any  $k \in \{1, \dots, m\}$ , if  $P_k \neq 0$ , we have  $k \in \{1, \dots, m-2\}$ . Note that for any  $k \in \{1, \dots, m-2\}$ , the  $k$ -th column of  $\mathcal{Y}$  is the zero vector. Hence, by Theorem 1, we have  $\langle f \rangle = \langle 1 \rangle$ .
- (ii) Assume that there exist  $s$  different row vectors in (16) appearing in  $\mathcal{A}_4$ . Note that any matrix consisting of  $s \geq 3$  different row vectors in (16) is rank-two. Hence,  $\mathbf{rank}(\mathcal{A}_4) = 2$ . Note that there are  $s \geq 3$  rows in  $\mathcal{A}_4$ . So, there exists  $a \in \mathbb{Q}^s \setminus \{\vec{0}\}$  such that

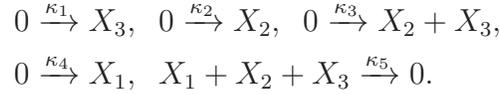
$\mathcal{A}_4^\top a = \vec{0}$ . Recall that  $a = (a_1, \dots, a_s)^\top$ . By (15),  $\mathcal{A}_4^\top a$  is equal to the last two coordinates of  $P^\top := \sum_{i=1}^s a_i \text{row}_i(\mathcal{N})$ . Hence, we have  $P_{m-1} = P_m = 0$ . Note that  $\text{rank}(\mathcal{N}) = d = s$ . So,  $P \neq \vec{0}$  since  $a \neq \vec{0}$ . Hence, for any  $k \in \{1, \dots, m\}$ , if  $P_k \neq 0$ , then we have  $k \in \{1, \dots, m-2\}$ . Note that for any  $k \in \{1, \dots, m-2\}$ , the  $k$ -th column of  $\mathcal{Y}$  is the zero vector. Therefore, by Theorem 1, we have  $\langle f \rangle = \langle 1 \rangle$ .

4. Since there is no zero columns in  $\mathcal{Y}$ , by (9), for any  $i \in \{1, \dots, m\}$ ,  $v_i = \kappa_i \prod_{j=1}^s x^{\alpha_{ji}}$ , where  $\sum_{j=1}^s \alpha_{ji} \geq 0$  since  $\alpha_{ji} \in \{0, 1\}$ . Hence, by (8), all terms in  $f$  contain the variables  $x_i$ 's. So, in  $\mathbb{Q}(\kappa)[x]$ ,  $1 \notin \langle f \rangle$ . Hence, we have  $\langle f \rangle \neq \langle 1 \rangle$ .

□

**Example 2.** We illustrate how Theorem 2 works by the following examples.

(1) Consider the following zero-one network:



The stoichiometric matrix  $\mathcal{N}$  is

$$\begin{pmatrix} 0 & 0 & 0 & 1 & -1 \\ 0 & 1 & 1 & 0 & -1 \\ 1 & 0 & 1 & 0 & -1 \end{pmatrix}.$$

Note that  $\text{rank}(\mathcal{N}) = 3$ . The reactant matrix  $\mathcal{Y}$  is

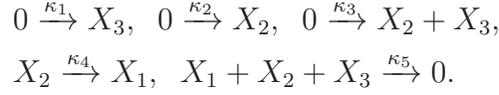
$$\begin{pmatrix} 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}.$$

Note that there are 4 zero columns in  $\mathcal{Y}$  (i.e.,  $c = 4 = m - 1$ ). Hence, by Theorem 2 (2), we have  $\langle f \rangle = \langle 1 \rangle$ . Note that

$$\begin{aligned} f_1 &= \kappa_4 - \kappa_5 x_1 x_2 x_3, \\ f_2 &= \kappa_2 + \kappa_3 - \kappa_5 x_1 x_2 x_3, \\ f_3 &= \kappa_1 + \kappa_3 - \kappa_5 x_1 x_2 x_3. \end{aligned}$$

It is straightforward to check that  $\frac{f_1 - f_2}{\kappa_4 - \kappa_2 - \kappa_3} = 1$ .

(2) Consider the following zero-one network:



The stoichiometric matrix  $\mathcal{N}$  is

$$\begin{pmatrix} 0 & 0 & 0 & 1 & -1 \\ 0 & 1 & 1 & -1 & -1 \\ 1 & 0 & 1 & 0 & -1 \end{pmatrix}.$$

Note that  $\text{rank}(\mathcal{N}) = 3$ , i.e.,  $d = s = 3$ . The reactant matrix  $\mathcal{Y}$  is

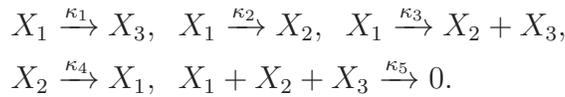
$$\begin{pmatrix} 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}.$$

Note that there are 3 zero columns in  $\mathcal{Y}$  (i.e.,  $c = 3 = m - 2$ ). Hence, by Theorem 2 (3), we have  $\langle f \rangle = \langle 1 \rangle$ . Note that

$$\begin{aligned} f_1 &= \kappa_4 x_2 - \kappa_5 x_1 x_2 x_3, \\ f_2 &= \kappa_2 + \kappa_3 - \kappa_4 x_2 - \kappa_5 x_1 x_2 x_3, \\ f_3 &= \kappa_1 + \kappa_3 - \kappa_5 x_1 x_2 x_3. \end{aligned}$$

It is straightforward to check that  $\frac{f_1 + f_2 - 2f_3}{-2\kappa_1 + \kappa_2 - \kappa_3} = 1$ .

(3) Consider the following zero-one network:



The stoichiometric matrix  $\mathcal{N}$  is

$$\begin{pmatrix} -1 & -1 & -1 & 1 & -1 \\ 0 & 1 & 1 & -1 & -1 \\ 1 & 0 & 1 & 0 & -1 \end{pmatrix}.$$

The reactant matrix  $\mathcal{Y}$  is

$$\begin{pmatrix} 1 & 1 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}.$$

Note that there is no zero columns in  $\mathcal{Y}$  (i.e.,  $c = 0$ ). Hence, by Theorem 2 (4), we have  $\langle f \rangle \neq \langle 1 \rangle$ . Note that

$$\begin{aligned} f_1 &= -\kappa_1 x_1 - \kappa_2 x_1 - \kappa_3 x_1 + \kappa_4 x_2 - \kappa_5 x_1 x_2 x_3, \\ f_2 &= \kappa_2 x_1 + \kappa_3 x_1 - \kappa_4 x_2 - \kappa_5 x_1 x_2 x_3, \\ f_3 &= \kappa_1 x_1 + \kappa_3 x_1 - \kappa_5 x_1 x_2 x_3. \end{aligned}$$

It is straightforward to check that  $1 \notin \langle f \rangle$ .

### 3.2. Sufficient conditions for equivalence

**Theorem 3.** For any two networks  $G$  and  $G'$ , let  $\mathcal{N}$  and  $\mathcal{N}'$  be the corresponding stoichiometric matrices, and let  $\mathcal{Y}$  and  $\mathcal{Y}'$  be the reactant matrices. Let  $f$  and  $f'$  be the steady-state systems defined as in (8). If

(1)  $\mathcal{Y} = \mathcal{Y}'$ , and

(2) for any  $i \in \{1, \dots, s\}$ , we have

$$\text{row}_i(\mathcal{N}) \in \text{span}_{\mathbb{Q}}\{\text{row}_1(\mathcal{N}'), \dots, \text{row}_s(\mathcal{N}')\},$$

and

$$\text{row}_i(\mathcal{N}') \in \text{span}_{\mathbb{Q}}\{\text{row}_1(\mathcal{N}), \dots, \text{row}_s(\mathcal{N})\},$$

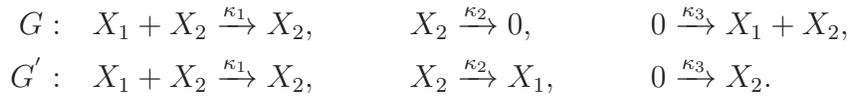
where  $\text{span}_{\mathbb{Q}}\{\cdot\}$  means the rational vector space spanned by a set of rational vectors, then  $\langle f \rangle = \langle f' \rangle$  in  $\mathbb{Q}(\kappa)[x]$ .

*Proof.* Let  $v = (v_1, \dots, v_m)^\top$  and  $v' = (v'_1, \dots, v'_m)^\top$  be defined as in (9) corresponding to  $G$  and  $G'$  respectively, where

$$v_i = \kappa_i \prod_{j=1}^s x_j^{\alpha_{ji}}, \quad v'_i = \kappa_i \prod_{j=1}^s x_j^{\alpha'_{ji}}. \quad (17)$$

By  $\mathcal{Y} = \mathcal{Y}'$ , for any  $i \in \{1, \dots, s\}$  and for any  $j \in \{1, \dots, s\}$ ,  $\alpha_{ij} = \alpha'_{ij}$ . Hence, by (17), we have  $v = v'$ . So, the conclusion follows from (8) and the condition (2).  $\square$

**Example 3.** Consider the following two networks  $G$  and  $G'$ .



Note that the two networks  $G$  and  $G'$  have the same set of reactants. Hence, the reactant matrices  $\mathcal{Y}$  and  $\mathcal{Y}'$  are equal. The stoichiometric matrices  $\mathcal{N}$  and  $\mathcal{N}'$  are as follows.

$$\mathcal{N} = \begin{pmatrix} -1 & 0 & 1 \\ 0 & -1 & 1 \end{pmatrix}, \quad \mathcal{N}' = \begin{pmatrix} -1 & 1 & 0 \\ 0 & -1 & 1 \end{pmatrix}.$$

Note that  $\text{row}_1(\mathcal{N}) = \text{row}_1(\mathcal{N}') + \text{row}_2(\mathcal{N}')$ ,  $\text{row}_2(\mathcal{N}) = \text{row}_2(\mathcal{N}')$  and  $\text{row}_1(\mathcal{N}') = \text{row}_1(\mathcal{N}) - \text{row}_2(\mathcal{N})$ . So, by Theorem 3, the ideals generated by  $f$  and  $f'$  are equal.

**Remark 1.** We remark that although Theorem 1 and Theorem 3 are straightforward to prove, the hypotheses in these theorems can not be directly checked by a computer, while Theorem 2 is explicit enough. In the next section, we will solve this issue by Algorithms 2 and 3.

#### 4. Algorithm

In this section, we propose a main algorithm (Algorithm 1) to determine the equivalence of zero-one networks with two sub-algorithms (Algorithm 2 and 3). The goal of the main algorithm is to efficiently classify all  $d$ -dimensional  $s$ -species  $m$ -reaction zero-one networks according to the equivalence determined by their steady-state ideals. The correctness of Algorithm 1 follows from Theorem 3 and the correctness of the two sub-algorithms.

**Algorithm 1.** *DetermineEquivalence*

**Input.** *The number of the species  $s$ , the number of the reactions  $m$  and the dimension  $d$*

**Output.** *Finitely many classes of  $d$ -dimensional  $s$ -species  $m$ -reaction zero-one networks such that the networks in the same class have the same steady-state ideal*

**Step 1.** *Enumerate all  $d$ -dimensional  $s$ -species  $m$ -reaction zero-one networks.*

**Step 2.** *Pick the networks satisfying the following two conditions simultaneously.*

1. *All the rows of the stoichiometric matrix  $N$  are non-zero and change signs.*

2. The set  $\mathcal{F}^+(\mathcal{N})$  defined as in (10) is not empty.

(#By this step, we remove the networks definitely admitting no positive steady states.)

**Step 3.** For each remaining network, do the following steps:

**Step 3.1.** If  $c = m - 1$  and  $d \geq 2$ , then delete the network.

**Step 3.2.** If  $c = m - 2$  and  $d = s \geq 3$ , then delete the network.

(#Note here,  $c$  denotes the number of zero columns of the reactant matrix  $\mathcal{Y}$ .)

**Step 4.** We call *CoefficientsForVacuous*( $s, d$ ), and we get a set  $S \subset \mathbb{Q}^s$ .

**Step 5.** For each remaining network, if there exists  $a \in S$  such that

- (1)  $\mathcal{N}^\top a \neq 0$ , and
- (2) for any  $i \in \{1, \dots, s\}$ , if the  $i$ -th coordinate of  $\mathcal{N}^\top a$  is non-zero, then  $\text{col}_i(\mathcal{Y}) = \vec{0}$ ,

then delete the network.

**Step 6.** Delete the same networks after relabeling the species.

**Step 7.** We call *CoefficientsForEquivalence*( $s, d$ ), and we get a set  $S_a \subset \mathbb{Q}^s$ .

**Step 8.** For each pair of networks  $G$  and  $G'$  from the remaining networks in Step 6, do the following steps.

**Step 8.1.** If there exists a permutation on the rows of  $\mathcal{Y}$  and  $\mathcal{Y}'$  such that  $\mathcal{Y}$  and  $\mathcal{Y}'$  are equal after permutating their rows in the same way, then permutate the rows of  $\mathcal{N}$  and  $\mathcal{N}'$  in the same way, and go to Step 8.2. Otherwise, consider the next pair of networks.

**Step 8.2.** Check if  $\mathcal{N}$  and  $\mathcal{N}'$  satisfy the following condition: for any  $i \in \{1, \dots, s\}$ , there exist  $(a_{i1} \dots, a_{is})^\top \in S_a$  and  $(b_{i1}, \dots, b_{is})^\top \in S_a$  such that

$$\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a_{ij} \text{row}_j(\mathcal{N}), \quad \text{row}_i(\mathcal{N}) = \sum_{j=1}^s b_{ij} \text{row}_j(\mathcal{N}').$$

If yes, then put the networks  $G$  and  $G'$  into the same class. If not, then consider the next pair of networks.

**Step 9.** For every class generated in Step 8, choose the first network as the representative element. Calculate the reduced Gröbner bases for these representative networks. Delete the networks whose reduced Gröbner base are  $\{1\}$  or have a monomial as an element.

**Step 10.** Combine the networks with the same reduced Gröbner basis into the same class. Choose the first network as the representative element. Return these representative elements.

**Algorithm 2.** *CoefficientsForVacuous*

**Input.** The number of species  $s$  and the dimension  $d$

**Output.** A set  $S \subset \mathbb{Q}^s$  such that for any  $d$ -dimensional  $s$ -species zero-one network, if there exists  $a \in \mathbb{Q}^s$  such that the conditions (1) and (2) of Theorem 1 hold, then there exists  $\tilde{a} \in S$  satisfying the conditions (1) and (2) of Theorem 1

**Step 1.** Enumerate all  $s$ -species zero-one reactions.

**Step 2.** Let  $S := \emptyset$ . For every  $n \in \{1, \dots, d-1\}$ , choose  $n$  linearly independent reactions from the reactions enumerated in Step 1. For every choice, do the following steps.

**Step 2.1.** Denote by

$$\mathcal{M} = \begin{pmatrix} M_1 \\ \vdots \\ M_n \end{pmatrix}$$

an  $n \times s$  matrix, where each row  $M_j$  is the transpose of the stoichiometric vector of a reaction from the chosen  $n$  independent reactions.

**Step 2.2.** Calculate the basis of the null space of  $\mathcal{M}$  and add all the vectors in the basis into the set  $S$ .

(#Note here, all these vectors in the basis are in  $\mathbb{Q}^s$ .)

**Step 3.** Return the set  $S$ .

**Proof of the Correctness of Algorithm 2.** Define

$$\Delta_1 := \{i \in \{1, \dots, m\} | \text{col}_i(\mathcal{Y}) \neq \vec{0}\}, \quad (18)$$

$$\Delta_2 := \{1, \dots, m\} \setminus \Delta_1. \quad (19)$$

Let  $M$  and  $M_k$  ( $k \in \{1, 2\}$ ) be the real vector spaces spanned by the columns of  $\mathcal{N}$  and the set of column vectors  $\{\text{col}_i(\mathcal{N}) | i \in \Delta_k\}$ , respectively. By (18) and the condition (2) of Theorem 1, we have

$$a \in M_1^\perp.$$

Since  $\mathcal{N}^\top a \neq \vec{0}$  (the condition (1) of Theorem 1), we have  $a \notin M^\perp$ . Since  $M_1 \subset M$ , we have  $\dim(M_1) < \dim(M) = d$ . So, by Step 2 of Algorithm 2, there exists  $B \subset S$  such that  $B$  is the basis of  $M_1^\perp$ . Notice that there exists  $\tilde{a} \in B$  such that  $\tilde{a} \notin M^\perp$ , i.e.,  $\mathcal{N}^\top \tilde{a} \neq \vec{0}$ . Otherwise, we have  $B \subset M^\perp$  and hence, we have  $M_1^\perp \subset M^\perp$ , which is contrary to the fact that  $a \in M_1^\perp \setminus M^\perp$ . So, the conditions (1) and (2) of Theorem 1 hold for  $\tilde{a} \in \mathbb{Q}^s$ .

**Example 4.** We illustrate how Algorithm 2 works for  $s = d = 3$ .

*Step 1. Enumerate all three-species zero-one reactions (there are 56 reactions in total).*

*Step 2. Let  $S := \emptyset$ . Note that  $d = 3$ . For every  $n \in \{1, 2\}$ , choose  $n$  linearly independent reactions from the 56 reactions enumerated in Step 1 and for every choice, do the following steps (below we only give details on the first round).*

*Step 2.1 Suppose  $(0, 0, 1)$  is the stoichiometric vector corresponding to the first reaction from the 56 reactions. Let  $\mathcal{M} := (0, 0, 1)$ .*

*Step 2.2 The basis of the null space of  $\mathcal{M}$  is  $\{(1, 0, 0)^\top, (0, 1, 0)^\top\}$ . Add the vectors in the basis into the set  $S$ .*

*Similarly, we do Steps 2.1 and 2.2 for all the other choices of reactions. Then, we get the set  $S$ :*

$$\begin{aligned} & \{0, 1\}^3 \cup (\{-1, 1\}^s \times \{2\}) \cup \\ & (\{-1, 1\} \times \{-2, 2\} \times \{1\}) \cup (\{-2, 2\} \times \{-1, 1\} \times \{1\}) \cup \\ & \{(-1, -1, 1)^\top, (1, -1, 1)^\top, (-1, 1, 1)^\top, (-1, 0, 1)^\top, \\ & (-1, 1, 0)^\top, (0, -1, 1)^\top\} \setminus (0, 0, 0)^\top. \end{aligned} \tag{20}$$

**Algorithm 3.** *CoefficientsForEquivalence*

**Input.** *The number of species  $s$  and the dimension  $d$*

**Output.** A set  $S_a \subset \mathbb{Q}^s$  such that if two  $d$ -dimensional  $s$ -species zero-one networks satisfy

- (1)  $\mathcal{Y} = \mathcal{Y}'$ , and
- (2) for any  $i \in \{1, \dots, s\}$ ,

$$\text{row}_i(\mathcal{N}') \in \text{span}_{\mathbb{Q}}\{\text{row}_1(\mathcal{N}), \dots, \text{row}_s(\mathcal{N})\}, \quad (21)$$

then for any  $i \in \{1, \dots, s\}$ , there exists  $(a_{i1}, \dots, a_{is})^\top \in S_a$  such that

$$\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a_{ij} \text{row}_j(\mathcal{N})$$

**Step 1.** Enumerate all possible zero-one reactions with  $s$  species (here, we only enumerate one direction in a pair of reversible reactions). Write the corresponding stoichiometric vectors into a set  $E \subset \mathbb{Q}^s$  (here, it is possible for different reactions to have the same stoichiometric vector, and we only put different vectors into the set  $E$ ).

**Step 2.** Let  $S_a := \emptyset$ . For any  $d$  column vectors from  $E$ , do the following steps.

**Step 2.1.** Let  $\mathcal{A}$  be the  $s \times d$  matrix consisting of the  $d$  column vectors. If  $\mathcal{A}$  has any zero rows, then stop and go to the next group of  $d$  vectors chosen from  $E$ .

**Step 2.2.** Denote by  $\vec{1}$  and  $-\vec{1}$  the column vectors whose coordinates are all 1 and  $-1$ , respectively. Define

$$\Lambda_1 := \{i \in \{1, \dots, d\} \mid \text{col}_i(\mathcal{A}) = \vec{1}\}, \quad (22)$$

$$\Lambda_2 := \{i \in \{1, \dots, d\} \mid \text{col}_i(\mathcal{A}) = -\vec{1}\}, \quad (23)$$

$$\Lambda_3 := \{1, \dots, d\} \setminus (\Lambda_1 \cup \Lambda_2). \quad (24)$$

Define a set of vectors

$$F := \{0, 1\}^{|\Lambda_1|} \times \{-1, 0\}^{|\Lambda_2|} \times \{-1, 0, 1\}^{|\Lambda_3|} \subset \mathbb{Q}^d. \quad (25)$$

(#Notice here  $|\Lambda_1| + |\Lambda_2| + |\Lambda_3| = d$ .)

For any column vector  $b$  in the set  $F$ , do the following steps.

**Step 2.2.1.** Solve  $a \in \mathbb{Q}^s$  from  $\mathcal{A}^\top a = b$ .

**Step 2.2.2.** If there exists finitely many solutions, then add the solutions into the set  $S_a$ . If there exists infinitely many solutions, then add one of the solutions into the set  $S_a$ . If there is no solutions, then go to the next vector  $b \in F$ .

**Step 3.** Return the set  $S_a$ .

**Proof of the Correctness of Algorithm 3.** Consider two  $d$ -dimensional  $s$ -species zero-one networks  $G$  and  $G'$ . Assume that their reactant matrices are equal, i.e.,  $\mathcal{Y} = \mathcal{Y}'$ . First, we prove a claim.

**Claim.** If there exists  $\mathcal{A}$  in Step 2.1 of Algorithm 3 such that  $\mathcal{A} = \mathcal{N}$ , then for any  $j \in \{1, \dots, s\}$ , there exists  $b \in F$  (defined as in (25)) such that  $\text{row}_j(\mathcal{N}')^\top = b$ .

In fact, by (22), for any  $i \in \Lambda_1$ , all the coordinates of  $\text{col}_i(\mathcal{A})$  are 1. Then, since  $\mathcal{N} = \mathcal{A}$ , for any  $i \in \Lambda_1$ , all the coordinates of  $\text{col}_i(\mathcal{N})$  are 1. By the definition of zero-one network, all the coordinates of  $\text{col}_i(\mathcal{Y})$  are 0. Then, since  $\mathcal{Y} = \mathcal{Y}'$ , all the coordinates of  $\text{col}_i(\mathcal{Y}')$  are 0. Thus, by the definition of zero-one network again, we have all the coordinates of  $\text{col}_i(\mathcal{N}')$  are 0 or 1. Hence, for any  $j \in \{1, \dots, s\}$  and for any  $i \in \Lambda_1$ , the  $i$ -th coordinate of  $\text{row}_j(\mathcal{N}')$  is 0 or 1. Similarly, we can derive that for any  $j \in \{1, \dots, s\}$  and for any  $i \in \Lambda_2$ , the  $i$ -th coordinate of  $\text{row}_j(\mathcal{N}')$  is  $-1$  or 0. Note that by the definition of zero-one network, for any  $j \in \{1, \dots, s\}$  and for any  $i \in \Lambda_3$ , the  $i$ -th coordinate of  $\text{row}_j(\mathcal{N}')$  is  $-1$ , 0 or 1. Hence, by (25), for any  $j \in \{1, \dots, s\}$ ,  $\text{row}_j(\mathcal{N}')^\top \in F$ . So, for any  $j \in \{1, \dots, s\}$ , there exists  $b \in F$  such that  $\text{row}_j(\mathcal{N}')^\top = b$ .

Below, we prove the correctness of Algorithm 3 by discussing two cases.

Case 1. Assume that all the columns of  $\mathcal{N}$  are in the set  $E$  generated in Step 1 of Algorithm 3.

- (i) Assume that all the columns of  $\mathcal{N}$  are different. Since all the columns in  $E$  are different. by the choice of  $\mathcal{A}$  in Step 2 of Algorithm 3, there exists  $\mathcal{A}$  such that  $\mathcal{A} = \mathcal{N}$ . By (21), for any  $i \in \{1, \dots, s\}$ , there exists  $a' := (a'_{i1}, \dots, a'_{is})^\top \in \mathbb{Q}^s$  such that

$$\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a'_{ij} \text{row}_j(\mathcal{N}). \quad (26)$$

Hence, by (26), for any  $i \in \{1, \dots, s\}$ , we have

$$\mathcal{N}^\top a' = \text{row}_i(\mathcal{N}')^\top. \quad (27)$$

By  $\mathcal{A} = \mathcal{N}$  and by the claim, for any  $i \in \{1, \dots, s\}$ , there exists  $b \in F$  such that  $\text{row}_i(\mathcal{N}')^\top = b$ . Hence, by  $\mathcal{N} = \mathcal{A}$  and (27), we have  $\mathcal{A}^\top a' = b$ , i.e., there exists a solution to the equation  $\mathcal{A}^\top a = b$ . By Step 2.2.2, there exists  $a \in S_a$  such that  $\mathcal{A}^\top a = b$ . Hence, for any  $i \in \{1, \dots, s\}$ , by  $\mathcal{A} = \mathcal{N}$  and  $\text{row}_i(\mathcal{N}')^\top = b$ , we have  $\mathcal{N}^\top a = \text{row}_i(\mathcal{N}')^\top$ , i.e.,  $\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a_{ij} \text{row}_j(\mathcal{N})$ , where  $(a_{i1}, \dots, a_{is})^\top = a \in S_a$ .

- (ii) Assume that at least two columns in  $\mathcal{N}$  are the same. Without loss of generality, assume that the first  $m_1$  columns of  $\mathcal{N}$  are different and for any  $i \in \{m_1 + 1, \dots, m\}$ , there exists  $j \in \{1, \dots, m_1\}$  such that  $\text{col}_i(\mathcal{N}) = \text{col}_j(\mathcal{N})$ . By (21), for any  $i \in \{1, \dots, s\}$ , there exists  $(a'_{i1}, \dots, a'_{is})^\top \in \mathbb{Q}^s$  such that

$$\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a'_{ij} \text{row}_j(\mathcal{N}). \quad (28)$$

We denote by  $\mathcal{N}_1$  and  $\mathcal{N}'_1$  the first  $m_1$  columns of  $\mathcal{N}$  and  $\mathcal{N}'$ . Then, by (28), we have for any  $i \in \{1, \dots, s\}$ ,

$$\text{row}_i(\mathcal{N}'_1) = \sum_{j=1}^s a'_{ij} \text{row}_j(\mathcal{N}_1).$$

Note that all the columns of  $\mathcal{N}_1$  are different. Then, by (i), for any  $i \in \{1, \dots, s\}$ , there exists  $(a_{i1}, \dots, a_{is})^\top \in S_a$  such that

$$\text{row}_i(\mathcal{N}'_1) = \sum_{j=1}^s a_{ij} \text{row}_j(\mathcal{N}_1). \quad (29)$$

Note that for any  $k \in \{m_1 + 1, \dots, m\}$ , there exists  $j \in \{1, \dots, m_1\}$  such that  $\text{col}_k(\mathcal{N}) = \text{col}_j(\mathcal{N})$ . Hence, by (28), the  $k$ -th and the  $j$ -th coordinates of  $\text{row}_i(\mathcal{N}')$  are equal. So, by (29), for any  $i \in \{1, \dots, s\}$ ,  $\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a_{ij} \text{row}_j(\mathcal{N})$ , where  $(a_{i1}, \dots, a_{is})^\top \in S_a$ .

Case 2. Assume that some columns of  $\mathcal{N}$  are not in the set  $E$ . By (21), for any  $i \in \{1, \dots, s\}$ , there exists  $(a'_{i1}, \dots, a'_{is})^\top \in \mathbb{Q}^s$  such that

$$\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a'_{ij} \text{row}_j(\mathcal{N}). \quad (30)$$

Define two new matrices  $\tilde{\mathcal{N}}$  and  $\tilde{\mathcal{N}}'$  as follows. For any  $j \in \{1, \dots, m\}$ , if  $\text{col}_j(\mathcal{N}) \in E$ , then define

$$\text{col}_j(\tilde{\mathcal{N}}) := \text{col}_j(\mathcal{N}), \text{ and } \text{col}_j(\tilde{\mathcal{N}}') := \text{col}_j(\mathcal{N}').$$

If  $\text{col}_j(\mathcal{N}) \notin E$ , then define

$$\text{col}_j(\tilde{\mathcal{N}}) := -\text{col}_j(\mathcal{N}), \text{ and } \text{col}_j(\tilde{\mathcal{N}}') := -\text{col}_j(\mathcal{N}').$$

Then, by the definition of  $E$ , all the columns of  $\tilde{\mathcal{N}}$  are in the set  $E$ . Note that by (30), for any  $i \in \{1, \dots, s\}$ ,

$$\text{row}_i(\tilde{\mathcal{N}}') = \sum_{j=1}^s a'_{ij} \text{row}_j(\tilde{\mathcal{N}}). \quad (31)$$

Then, by (31) and by (Case 1)–(ii), for any  $i \in \{1, \dots, s\}$ , there exists  $(a_{i1}, \dots, a_{is})^\top \in S_a$  such that

$$\text{row}_i(\tilde{\mathcal{N}}') = \sum_{j=1}^s a_{ij} \text{row}_j(\tilde{\mathcal{N}}).$$

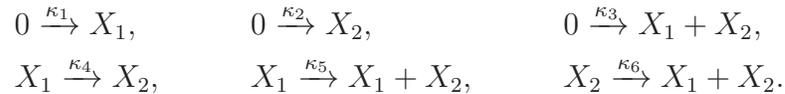
Therefore, by the definition of  $\tilde{\mathcal{N}}$  and  $\tilde{\mathcal{N}}'$ , we have

$$\text{row}_i(\mathcal{N}') = \sum_{j=1}^s a_{ij} \text{row}_j(\mathcal{N}),$$

where  $(a_{i1}, \dots, a_{is})^\top \in S_a$ .

**Example 5.** We illustrate how Algorithm 3 works for  $s = d = 2$ .

*Step 1 Enumerate all possible zero-one reactions with two species (only enumerate one direction in a pair of reversible reactions).*



Put the corresponding stoichiometric vectors (only consider different vectors) into a set:

$$E = \{(1, 0)^\top, (0, 1)^\top, (1, 1)^\top, (-1, 1)^\top\}. \quad (32)$$

Step 2 Let  $S_a := \emptyset$ . Note that  $d = 2$ . Choose 2 column vectors from (32). There are six possibilities as follows:

$$\left\{ \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}, \begin{pmatrix} 1 & 1 \\ 0 & 1 \end{pmatrix}, \begin{pmatrix} 1 & -1 \\ 0 & 1 \end{pmatrix}, \begin{pmatrix} 0 & 1 \\ 1 & 1 \end{pmatrix}, \begin{pmatrix} 0 & -1 \\ 1 & 1 \end{pmatrix}, \begin{pmatrix} 1 & -1 \\ 1 & 1 \end{pmatrix} \right\}.$$

For each matrix in the above set, do the following steps (we only show the details for the first matrix).

Step 2.1.  $\mathcal{A} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \end{pmatrix}$ .

Step 2.2. By (22)–(24), we have

$$\Lambda_1 = \Lambda_2 = \emptyset, \Lambda_3 = \{1, 2\}.$$

Then, by (25), we have

$$F = \{(-1, -1)^\top, (-1, 0)^\top, (-1, 1)^\top, (0, -1)^\top, (0, 0)^\top, (0, 1)^\top, (1, -1)^\top, (1, 0)^\top, (1, 1)^\top\}.$$

For any  $b \in F$ , solve  $a$  from  $\mathcal{A}^\top a = b$ . Then, we get the set of the solutions is

$$\{-1, 0, 1\} \times \{-1, 0, 1\}.$$

Add all these solutions into the set  $S_a$ .

Similarly, we do Steps 2.1 and 2.2 for all other matrices. Then, we get the set  $S_a$ :

$$\{-1, 0, 1\}^2 \cup \{(2, -1)^\top, (2, 1)^\top, (-1, 2)^\top, (1, 2)^\top, (-1, -2)^\top, (-2, -1)^\top, \left(\frac{1}{2}, \frac{1}{2}\right)^\top, \left(-\frac{1}{2}, \frac{1}{2}\right)^\top, \left(\frac{1}{2}, -\frac{1}{2}\right)^\top\}.$$

## 5. Implementation

We have implemented the procedure in Algorithm 1. The supporting codes are available online <https://github.com/YueJ13/equivalence>. As a larger example, we apply the algorithm to all the three-dimensional three-species five-reaction zero-one networks.

**Step 1.** We enumerate all three-species five-reaction zero-one networks. There are 3819816 networks.

**Step 2.** We call `CoefficientsForVacuous(3, 3)`, and by the computation carried out in Example 4, we get the set of rational vectors  $S$  in (20). For each network from the 3819816 networks, we do the following steps.

**Step 2.1.** If the stoichiometric matrix  $\mathcal{N}$  of the network is rank three (i.e., the network is three-dimensional), and all rows of  $\mathcal{N}$  are non-zero and change signs, then pick the network.

**Step 2.2.** If the set  $\mathcal{F}^+(\mathcal{N})$  is not empty, then pick the network.

**Step 2.3.** If  $c = 3$  or  $4$ , then delete the network. (Note here,  $c$  denotes the number of zero columns of the reactant matrix  $\mathcal{Y}$ .)

**Step 2.4.** If there exists  $a \in S$  such that

- (1)  $\mathcal{N}^\top a \neq \vec{0}$ , and
- (2) for any  $i \in \{1, 2, 3\}$ , if the  $i$ -th coordinate of  $\mathcal{N}^\top a$  is non-zero, then  $col_i(\mathcal{Y}) = \vec{0}$ ,

then delete the network.

Then, we get 484477 networks.

**Step 3.** Delete the same networks after relabeling the species. Then, we get 76752 networks.

**Step 4.** We call `CoefficientsForEquivalence(3, 3)`, and we get a set of vectors  $S_a \subset \mathbb{Q}^3$ , where for any  $a = (a_1, a_2, a_3) \in S_a$ , we have

$$a_i \in \{\pm 4, \pm 3, \pm 2, \pm \frac{3}{2}, \pm \frac{4}{3}, \pm 1, \pm \frac{3}{4}, \pm \frac{2}{3}, \pm \frac{1}{2}, \pm \frac{1}{3}, \pm \frac{1}{4}, 0\}.$$

For each pair of networks  $G$  and  $G'$  from the 76752 networks in Step 3, check if  $\mathcal{N}$  and  $\mathcal{N}'$  (after permutation according to the description

in Step 8.1 of Algorithm 1) satisfy the following condition: for any  $i \in \{1, 2, 3\}$ , there exist  $(a_1, a_2, a_3)^\top \in S_a$  and  $(b_1, b_2, b_3)^\top \in S_a$  such that

$$\text{row}_i(\mathcal{N}') = \sum_{j=1}^3 a_j \text{row}_j(\mathcal{N}), \quad \text{row}_i(\mathcal{N}) = \sum_{j=1}^3 b_j \text{row}_j(\mathcal{N}').$$

If yes, then put the networks  $G$  and  $G'$  into the same class. Then, we get 40522 classes of networks. Choosing the first network from every class, we get 40522 networks.

**Step 5.** Calculate the reduced Gröbner bases of the 40522 networks. Delete the networks whose reduced Gröbner bases are 1 or have a monomial as an element. Then, we get 32668 networks.

**Step 6.** Combine the networks having the same reduced Gröbner basis into the same class. Choosing the first network from every class, we get 32394 networks.

We record the timings for carrying out the above steps in the following Table 1. In the experiments, we use the command `Basis` [13] in `Maple` [22] to calculate the reduced Gröbner bases. Note that if we do not apply Algorithm 1, then we need about 60 hours to check the reduced Gröbner bases of all three-dimensional three-species five-reaction zero-one networks. Our purpose is to show the improvement Algorithm 1 makes comparing with purely computing Gröbner bases. One can improve the computational timings presented in Table 1 by applying any more advanced tools for computing Gröbner bases rather than the standard `Maple` package.

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Table 1: Computational time (min: minutes; s: seconds)

STEP	NUMBER OF NETWORKS	TIME
Step 1	3819816	1 min
Step 2	484477	30 min
Step 3	76752	145 s
Step 4	40522	40 min
Step 5	32668	100 s
Step 6	32394	30 min

**Notes:** (i) The column “STEP” lists the steps in the procedure shown in Algorithm 1. (ii) The middle column records the number of networks we get after carrying out each step. (iii) The column “TIME” records the computational time for each step.

We run the procedure by a 3.60 GHz Inter Core i9 processor (64GB total memory) under Windows 10.

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