A Computational Approach to Concentration Robustness in Power Law Kinetic Systems of Shinar–Feinberg Type

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Abstract

There have been recent theoretic results that provide sufficient conditions for the existence of a species displaying *absolute concentration robustness* (ACR) in a power law kinetic (PLK) system. One such result involves the detection of ACR among networks of high deficiency by considering a lower deficiency subnetwork with ACR as a local property. In turn, this "smaller" subnetwork serves as a "building block" for the larger ACR-possessing network. Here, with this theorem as foundation, we construct an algorithm that systematically checks ACR in a PLK system. By slightly modifying the algorithm, we also provide a procedure that identifies *balanced concentration robustness* (BCR), a weaker form of concentration robustness than ACR, in a PLK system.

1 Introduction

In 2010, Shinar and Feinberg [16] introduced the concept of *absolute concentration robustness* (ACR) for a system endowed with mass action kinetics (MAK). A system possesses

ACR for a particular species if for every positive steady state of the system, the concentration of that species does not change. Their important contribution is a theorem that identifies some sufficient conditions to guarantee the existence of ACR in a MAK system.

Almost a decade after, Fortun et al. [10] showed that this result can be readily extended to *power law kinetic systems with reactant-determined interactions* (PL-RDK), a kinetic system more general than MAK. They called this result the Shinar-Feinberg Theorem on ACR for PL-RDK systems (SFTACR). In a later paper, Fortun and Mendoza [9] utilized the concept of dynamic equivalence (through the method discussed in [14]) and decomposition theory to come up with results motivated by SFTACR. In the same paper, the concept of *balanced concentration robustness* (BCR), a weaker form of concentration robustness than ACR, was also introduced. Furthermore, the study established results that can detect ACR and BCR on some subclasses of PLK system which do not have any deficiency restriction unlike other earlier results on concentration robustness. As future outlook, the paper recommended to build computational approaches that could identify ACR and BCR in a PLK system based on these findings. The said recommendation serves as the motivation of this paper.

We present here an algorithm that determines if a PLK system with a positive equilibrium and an *independent decomposition* has ACR. We also present an analogous algorithm which can determine if a PLK system having an *incidence independent decomposition* and a complex balanced equilibrium possesses BCR. These algorithms are based on Propositions 2 and 3 (Propositions 8 and 9 in [9]). For an ACR or BCR to occur in a PLK-system, each of these propositions require the existence of a building block (which is defined here as a *Shinar-Feinberg* (SF)-*type subnetwork*) satisfying some conditions. We call the algorithms the *building block algorithms for* PLK *systems of* SF-*type*.

These building block algorithms are first of their kind. However, the attempt to analyze a network's concentration robustness computationally is not entirely new. For instance, Kuwahara et al. [12] developed a computer tool which can construct new biochemical networks, endowed with MAK, by combinatorially interchanging user-specified species of existing biochemical networks. The tool was called ACRE which stands for Absolute Concentration Robustness Exploration since it is also capable of recognizing which among the constructed networks have ACR.

The algorithms we have developed employ a *bottom-up* approach which works by

initially considering an SF-type subnetwork where the desired decomposition is to be constructed. We chose this approach over a *top-down* approach, which initially searches for an appropriate decomposition with the desired SF-type subnetwork, because the former approach makes the search for a suitable decomposition and subnetwork simpler and computationally cheaper.

The paper is organized as follows. Fundamental concepts on chemical reaction networks, kinetic systems, and decomposition theory are presented in section 2. Concepts and related results on concentration robustness for PLK sytems are reviewed in section 3. In section 4, the structure of the algorithms as well as the procedures of the ACR building block algorithm are discussed. The BCR building block algorithm and examples are given in section 5. Section 6 provides a summary and an outlook.

2 Fundamentals of chemical reaction networks and kinetic systems

2.1 Structure of chemical reaction networks

We review in this section some necessary concepts and results on chemical reaction network, the details of which can be found in [1, 5, 9, 17].

Definition 1. A **chemical reaction network** is a triple $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ of three non-empty finite sets:

1. a set **species** $\mathscr{S}$;

2. a set $\mathscr{C}$ of **complexes**, which are nonnegative integer linear combinations of the species; and

3. a set $\mathscr{R} \subseteq \mathscr{C} \times \mathscr{C}$ of reactions such that

   - $(y, y) \notin \mathscr{R}$ for all $y \in \mathscr{C}$, and

   - for each $y \in \mathscr{C}$, there exists a $y' \in \mathscr{C}$ such that $(y, y') \in \mathscr{R}$ or $(y', y) \in \mathscr{R}$.

The nonnegative coefficients of the species in a complex are referred to as **stoichiometric coefficients**. In this paper, a reaction $R_i = (y_i, y_i')$ is also denoted by $R_i : y_i \to y_i'$ and y_i and y_i' are called the **reactant** and **product complexes** of R_i, respectively. Further, we reserve the letters m, n, and r to denote the numbers of species, complexes, and reactions,

respectively. The following example shows that a CRN can be represented by a digraph where the complexes and reactions serve as the digraph's vertices and arcs, respectively.

Running example 1

Consider the CRN represented by the digraph below.

$$
\begin{array}{c}
\text{(2.1)}
\end{array}
$$
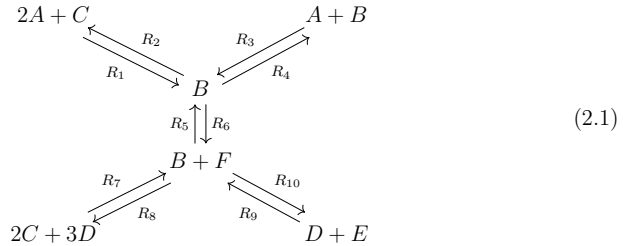
This CRN has $m = 6, n = 6$, and $r = 10$. It also has the following sets:

$$\mathscr{S} = \{A, B, C, D, E, F\};$$
$$\mathscr{C} = \{2A + C, A + B, B, B + F, 2C + 3D, D + E\}; \text{ and}$$
$$\mathscr{R} = \{R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}\}.$$

We call the connected components of a CRN **linkage classes** whose number is denoted by ℓ. The **strong linkage classes** refer to the strongly connected components and the **terminal strong linkage classes** are the strongly connected components without outgoing arrows. If each of the linkage classes of a CRN is also a strong linkage class, we call it **weakly reversible**. The CRN in Running example 1 is weakly reversible since it has only one linkage class which is also a strong linkage class. A complex is called **terminal** if it belongs to a terminal strong linkage class.

CRNs are studied with the aid of finite dimensional spaces $\mathbb{R}^{\mathscr{S}}$, $\mathbb{R}^{\mathscr{C}}$, and $\mathbb{R}^{\mathscr{R}}$, respectively referred to as **species space, complex space**, and **reaction space**. For every reaction $y \to y'$, we associate a vector, called **reaction vector**, resulted from subtracting the reactant complex y from the product complex y'. The linear subspace of $\mathbb{R}^{\mathscr{S}}$ defined by $S := \text{span}\{y' - y \in \mathbb{R}^{\mathscr{S}} | y \to y' \in \mathscr{R}\}$ is called the **stoichiometric subspace** S of a CRN. Its dimension s also refers to the **rank** of the CRN. A CRN can be characterized by a nonnegative integer δ called **deficiency** which is given by $\delta = n - \ell - s$. The CRN in Running example 1 has $S = \text{span}\{r_1, r_2, r_3, r_4, r_5\}$ where

$$r_1 = \begin{bmatrix} 2 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, r_2 = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, r_3 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}, r_4 = \begin{bmatrix} 0 \\ -1 \\ 2 \\ 3 \\ 0 \\ -1 \end{bmatrix}, r_5 = \begin{bmatrix} 0 \\ -1 \\ 0 \\ 1 \\ 1 \\ -1 \end{bmatrix}.$$

Furthermore, its rank and deficiency is $s = 5$ and $\delta = 6 - 1 - 5 = 0$, respectively.

Definition 2. Let $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a CRN. The **incidence map** $I_a : \mathbb{R}^{\mathcal{R}} \to \mathbb{R}^{\mathcal{C}}$ is the linear map defined by mapping for each reaction $R_i : y_i \to y_i' \in \mathcal{R}$, the basis vector ω_i to the vector $\omega_{y_i'} - \omega_{y_i} \in \mathcal{C}$.

As a linear map, the incidence map has an $n \times r$ matrix representation, called **incidence matrix**, whose entries are described by the following.

$$(I_a)_{(i,j)} = \begin{cases} -1 & \text{if } i \text{ is the reactant complex of reaction } j \in \mathcal{R}, \\ 1 & \text{if } i \text{ is the product complex of reaction } j \in \mathcal{R}, \\ 0 & \text{otherwise.} \end{cases}$$

The CRN in Running example 1 has the following incidence matrix.

$$I_a = \begin{bmatrix} R_1 & R_2 & R_3 & R_4 & R_5 & R_6 & R_7 & R_8 & R_9 & R_{10} \\ -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 1 & -1 & 1 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 1 & 1 & -1 & 1 & -1 \\ 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 \end{bmatrix} \begin{matrix} 2A + C \\ A + B \\ B \\ B + F \\ 2C + 3D \\ D + E \end{matrix} \tag{2.2}$$

For the incidence matrix (of a directed graph), it is known that $\dim \operatorname{Im} I_a = n - \ell$ [2].

2.2 Dynamics of chemical reaction networks

A **kinetics** is an assignment of a rate function to each reaction in a CRN. A network $\mathcal{N}$ together with a kinetics K is called a **chemical kinetic system** (CKS) and is denoted here by $(\mathcal{N}, K)$. **Power law kinetics** (PLK) is identified by the **kinetic order matrix** which is an $r \times m$ matrix $F = [F_{ij}]$, and vector $k \in \mathbb{R}_{>0}^{\mathcal{R}}$, called the **rate vector**.

Definition 3. A kinetics $K : \mathbb{R}_{>0}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{R}}$ is a **power law kinetics** if

$$K_i(x) = k_i x^{F_{i,\cdot}} \text{ for } i = 1, \ldots, r$$

where $k_i \in \mathbb{R}_{>0}$, $F_{i,j} \in \mathbb{R}$, and $F_{i,\cdot}$ is the row of F associated to reaction R_i.

We can classify a PLK system based on the kinetic orders assigned to its **branching reactions** (i.e., reactions sharing a common reactant complex).

Definition 4. A PLK system has **reactant-determined kinetics** (of type PL-RDK) if for any two branching reactions $R_i, R_j \in \mathscr{R}$, the corresponding rows of kinetic orders in F are identical, i.e., $F_{ih} = F_{jh}$ for $h = 1, \ldots, m$. Otherwise, a PLK system has **non-reactant-determined kinetics** (of type PL-NDK).

Suppose the CRN in Running example 1 is a PLK system with the following kinetic order matrix.

$$
F = \begin{array}{c}
\begin{array}{cccccc} A & B & C & D & E & F \end{array} \\
\begin{bmatrix}
2 & 0 & 1 & 0 & 0 & 0 \\
0 & 2 & 0 & 0 & 0 & 0 \\
1 & 0.5 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 1 \\
0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 2 & 3 & 0 & 0 \\
0 & 0.5 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 1 & 1 & 0 \\
0 & 1 & 0 & 0 & 0 & 1
\end{bmatrix}
\begin{array}{l} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ R_7 \\ R_8 \\ R_9 \\ R_{10} \end{array}
\end{array}
\qquad (2.3)
$$

R_2 and R_4 are two branching reactions whose corresponding rows in F (or **kinetic order vectors**) are not the same since $F_{22} = 2 \neq 1 = F_{42}$. Hence, the system is of type PL-NDK.

The well-known **mass action kinetic system** (MAK) forms a subset of PL-RDK systems. In particular, MAK is given by $K_i(x) = k_i x^{Y_{.j}}$ for all reactions $R_i : y_i \to y'_i \in \mathscr{R}$ with $k_i \in \mathbb{R}_{>0}$ (called **rate constant**). The vector $Y_{.j}$ contains the stoichiometric coefficients of a reactant complex $y_i \in \mathscr{C}$.

Definition 5. The **species formation rate function** of a chemical kinetic system is the vector field

$$
f(c) = NK(c) = \sum_{y_i \to y'_i \in \mathscr{R}} K_i(c)(y'_i - y_i), \text{ where } c \in \mathbb{R}^{\mathscr{S}}_{\geq 0},
$$

where N is the $m \times r$ matrix, called **stoichiometric matrix**, whose columns are the reaction vectors of the system. The equation $dc/dt = f(c(t))$ is the **ODE or dynamical system** of the chemical kinetic system. An element c^* of $\mathbb{R}^{\mathscr{S}}_{\geq 0}$ such that $f(c^*) = 0$ is called a **positive equilibrium** or **steady state** of the system. We use $E_+(\mathscr{N}, K)$ to denote the set of all positive equilibria of a CKS.

Analogous to the species formation rate function, we also have the complex formation rate function.

Definition 6. The **complex formation rate function** $g : \mathbb{R}_{>0}^{\mathscr{S}} \to \mathbb{R}^{\mathscr{C}}$ of a chemical kinetic system is the vector field

$$g(c) = I_a K(c) = \sum_{y_i \to y_i' \in \mathscr{R}} K_i(c)(\omega_{y_i'} - \omega_{y_i}), \text{ where } c \in \mathbb{R}_{\geq 0}^{\mathscr{S}}.$$

where I_a is the incidence map. A CKS is **complex balanced** if it has complex balanced steady state, i.e., there is a composition $c^{**} \in \mathbb{R}_{>0}^{\mathscr{S}}$ such that $g(c^{**}) = 0$. We denote by $Z_+(\mathscr{N}, K)$ the set of all complex balanced steady states of the system.

Theorem 1 (Corollary 4.8, [6]). *If a CKS has deficiency 0, then its steady states are all complex balanced.*

2.3 Decomposition theory

We briefly discuss here two decomposition types which are important components of our findings.
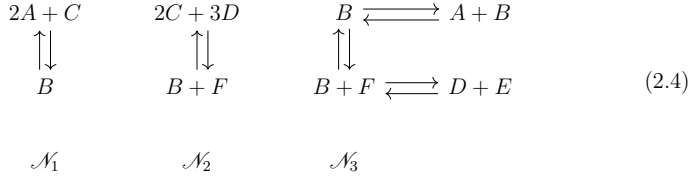
Definition 7. Let $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a CRN. A **covering** of $\mathscr{N}$ is a collection of subsets $\{\mathscr{R}_1, \ldots, \mathscr{R}_k\}$ whose union is $\mathscr{R}$. A covering is called a **decomposition** of $\mathscr{N}$ if the sets $\mathscr{R}_i$ form a partition of $\mathscr{R}$.

$\mathscr{R}_i$ defines a subnetwork $\mathscr{N}_i$ of $\mathscr{N}$ where $\mathscr{N}_i = (\mathscr{S}_i, \mathscr{C}_i, \mathscr{R}_i)$ such that $\mathscr{C}_i$ consists of all complexes occurring in $\mathscr{R}_i$ and $\mathscr{S}_i$ has all the species occurring in $\mathscr{C}_i$. From here on, we will use $\{\mathscr{N}_1, \mathscr{N}_2, \ldots, \mathscr{N}_k\}$ to denote the decomposition induced by $\mathscr{R}_i$'s. Also, for convenience, we will sometimes refer to $\mathscr{N}$, given that it has been "decomposed", as the parent network.

The idea of network decomposition originally came from Feinberg [4]. He introduced a decomposition subclass called independent decomposition, which is identified based on the subnetworks' stoichiometric subspaces.

Definition 8. A decomposition is **independent** if S is the direct sum of the subnetworks' stoichiometric subspaces S_i or equivalently, $s = s_1 + \cdots + s_k$.

Consider the decomposition $\{\mathscr{N}_1, \mathscr{N}_2, \mathscr{N}_3\}$ of the CRN in Running example 1 (see (2.4)). Notice that $\mathscr{N}_1, \mathscr{N}_2$, and $\mathscr{N}_3$ have $1, 1$, and 3 as ranks, respectively. Since the parent network is of rank 5, the decomposition is independent.

$$
\begin{array}{cccc}
2A + C & 2C + 3D & B \rightleftharpoons A + B \\
\updownarrow & \updownarrow & \updownarrow \\
B & B + F & B + F \rightleftharpoons D + E
\end{array}
\qquad (2.4)
$$

$$
\mathscr{N}_1 \qquad\qquad \mathscr{N}_2 \qquad\qquad \mathscr{N}_3
$$

The following observation relates the images of the incidence maps of the parent network and its subnetworks.

Proposition 1 (Proposition 6, [3]). *Let $\{\mathscr{N}_1, \mathscr{N}_2, \cdots, \mathscr{N}_k\}$ be a covering of $\mathscr{N}$. Further, let $I_{a,i}$ be the incidence map of the subnetwork $\mathscr{N}_i$ with $n_i - \ell_i = \dim I_{a,i}$. Then,*

  i. $Im\ I_a = Im\ I_{a,1} + Im\ I_{a,2} + \cdots + Im\ I_{a,k}$

 ii. $n - \ell \leq (n_1 - \ell_1) + (n_2 - \ell_2) + \cdots + (n_k - \ell_k)$

Motivated by the idea of independent decomposition and Proposition 1, Farinas et al. [3] introduced the concept of incidence independent decomposition.

Definition 9. A decomposition of a CRN $\mathscr{N}$ is **incidence independent** if and only if the image of the incidence map of $\mathscr{N}$ is the direct sum of the images of the incidence maps of the subnetworks or equivalently, $n - \ell = \sum(n_i - \ell_i)$.

The decomposition of the CRN in Running example 1 whose subnetworks are given in (2.4) is incidence independent since $n - \ell = 5$, $n_1 - \ell_1 = n_2 - \ell_2 = 1$, and $n_3 - \ell_3 = 3$.

Interestingly, incidence independent decompositions are more commonly observed in CRNs compared to independent decompositions. In particular, linkage class decomposition (i.e., a decomposition where the subnetworks are the linkage classes) is always incidence independent but not necessarily independent [3].

3 Concentration robustness in PLK systems of Shinar–Feinberg type

In this section, we first review concepts and results on concentration robustness in PLK systems. We then introduce a running example to illustrate the different steps of the algorithm in the following sections.

3.1 Review of concentration robustness in PLK systems of Shinar–Feinberg type

Details of the concepts and results reviewed below can be found in Fortun and Mendoza [9].

Definition 10. A PLK system $(\mathscr{N}, K)$ has **absolute concentration robustness** in a species $X \in \mathscr{S}$ if there exists $c^* \in E_+(\mathscr{N}, K)$ and for every other $c^{**} \in E_+(\mathscr{N}, K)$, we have $c_X^* = c_X^{**}$.

Balanced concentration robustness (BCR), a concentration robustness that is weaker than ACR, was also introduced in [9].

Definition 11. A complex balanced CKS $(\mathscr{N}, K)$ has **balanced concentration robustness** in a species $X \in \mathscr{S}$ if X has the same value for all $c \in Z_+(\mathscr{N}, K)$.

If a system has ACR in a species, then it also has BCR for that species. The converse, however, of this observation is not always true.

Definition 12. A pair of reactions in a PLK system is called a **Shinar-Feinberg pair** (or SF-pair) in a species X if their kinetic order vectors differ only in X. A network that contains an SF-pair is called a **Shinar-Feinberg type** (SF-type).

A reactant complex in a PL-NDK system of some branching reactions is said to be an **NDK node** if the kinetic order vectors of the branching reactions are different. A **complex factorizable** (CF)-**subset** of a reactant complex is a subset of the branching reactions whose kinetic order vectors are the same.

Definition 13. A PL-NDK system containing a single NDK node which has two CF-subsets, at least one of which contains only one reaction, is called **minimally PL-NDK**.

The next proposition enables us to determine if a PLK system has ACR. Unlike other similar results on ACR [9, 10, 16], this proposition does not have any deficiency restriction imposed on the underlying network. This allows us to deal with higher deficiency systems including higher deficiency MAK systems.

Proposition 2 (Proposition 8, [9]). *Let $(\mathscr{N}, K)$ be a* PLK *system with a positive equilibrium and an independent decomposition $\{\mathscr{N}_1, \mathscr{N}_2, \cdots, \mathscr{N}_k\}$. If there is an $\mathscr{N}_i$ with $(\mathscr{N}_i, K_i)$ of* SF-type *in $X \in \mathscr{S}$ such that*

   i. $\delta_i = 0$ and is PL-RDK *or minimally* PL-NDK, *or*

   ii. $\delta_i = 1$ and is PL-RDK.

Then $(\mathcal{N}, K)$ has ACR *in X.*

The next proposition, which is analogous to Proposition 2, can determine the existence of BCR.

Proposition 3 (Proposition 9, [9])**.** *Let $(\mathcal{N}, K)$ be a* PLK *system with a complex balanced equilibrium and an incidence independent decomposition $\{\mathcal{N}_1, \mathcal{N}_2, \cdots, \mathcal{N}_k\}$. If there is an $\mathcal{N}_i$ with $(\mathcal{N}_i, K_i)$ of* SF-type *in $X \in \mathscr{S}$ such that*
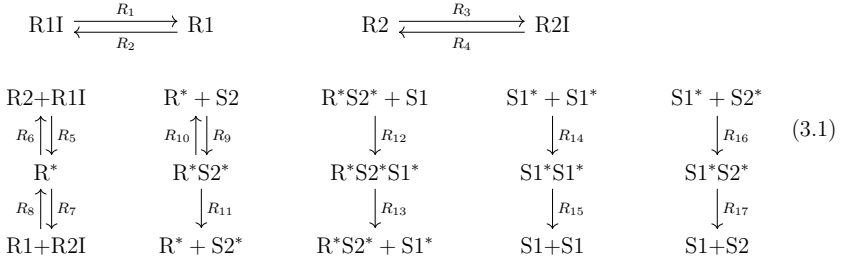
   i. $\delta_i = 0$ and is PL-RDK *or minimally* PL-NDK, *or*

   ii. $\delta_i = 1$ and is PL-RDK.

Then $(\mathcal{N}, K)$ has BCR *in X.*

For a PLK system to have the desired concentration robustness, Proposition 2 requires the system to have a positive equilibrium and independent decomposition while Proposition 3 requires it to have an incidence independent decomposition and a complex balanced equilibrium. In addition, both requires having a **building block** or an SF-type subnetwork, taken from the attained decomposition, which satisfies certain conditions. Notice that after ensuring that a system has the desired decomposition and equilibrium, the said propositions translate the problem of identifying ACR or BCR to a search for a building block, eventually shifting the focus of the analysis on this smaller subnetwork.
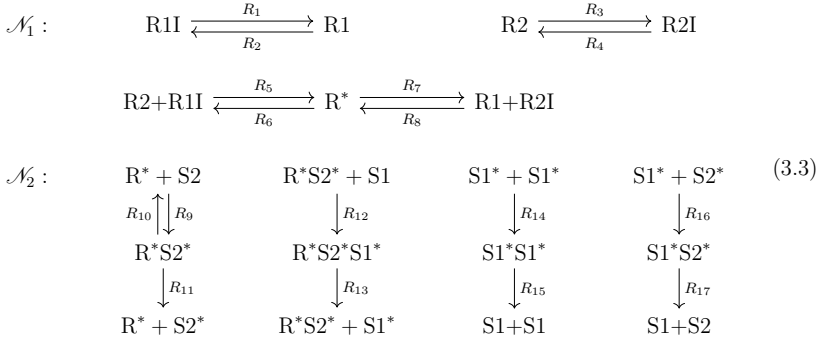
Running example 2

We consider the following MAK system representing the early STAT signaling network coupled with the receptor complex formation upon interferon (IFN) induction which was studied in [15] (see (3.1) for the CRN and (3.2) for the kinetic order matrix). It has a positive equilibrium, but its deficiency is 3.

$$\text{R1I} \underset{R_2}{\overset{R_1}{\rightleftarrows}} \text{R1} \qquad \text{R2} \underset{R_4}{\overset{R_3}{\rightleftarrows}} \text{R2I}$$

$$
\begin{array}{ccccc}
\text{R2+R1I} & \text{R}^* + \text{S2} & \text{R}^*\text{S2}^* + \text{S1} & \text{S1}^* + \text{S1}^* & \text{S1}^* + \text{S2}^* \\
R_6 \Big\uparrow\!\Big\downarrow R_5 & R_{10} \Big\uparrow\!\Big\downarrow R_9 & \Big\downarrow R_{12} & \Big\downarrow R_{14} & \Big\downarrow R_{16} \qquad (3.1)\\
\text{R}^* & \text{R}^*\text{S2}^* & \text{R}^*\text{S2}^*\text{S1}^* & \text{S1}^*\text{S1}^* & \text{S1}^*\text{S2}^* \\
R_8 \Big\uparrow\!\Big\downarrow R_7 & \Big\downarrow R_{11} & \Big\downarrow R_{13} & \Big\downarrow R_{15} & \Big\downarrow R_{17} \\
\text{R1+R2I} & \text{R}^* + \text{S2}^* & \text{R}^*\text{S2}^* + \text{S1}^* & \text{S1+S1} & \text{S1+S2}
\end{array}
$$

$$
F =
\begin{array}{c}
\begin{array}{ccccccccccccc}
\text{R1} & \text{R1I} & \text{R2} & \text{R2I} & \text{R}^* & \text{S1} & \text{S1}^* & \text{S2} & \text{S2}^* & \text{S1}^*\text{S1}^* & \text{S1}^*\text{S2}^* & \text{R}^*\text{S2}^* & \text{R}^*\text{S2}^*\text{S1}^*
\end{array} \\
\left[
\begin{array}{ccccccccccccc}
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 2 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0
\end{array}
\right]
\begin{array}{l}
R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ R_7 \\ R_8 \\ R_9 \\ R_{10} \\ R_{11} \\ R_{12} \\ R_{13} \\ R_{14} \\ R_{15} \\ R_{16} \\ R_{17}
\end{array}
\end{array}
\qquad (3.2)
$$

Take the decomposition $\{\mathcal{N}_1, \mathcal{N}_2\}$ of the system where $\mathscr{R}_1 = \{R_1, R_3, R_5\}$ and $\mathscr{R}_2 = \{R_9, R_{11}, R_{12}, R_{13}, R_{14}, R_{16}\}$ (see (3.3)). The decomposition is independent since $\mathcal{N}_1$ and $\mathcal{N}_2$ have, respectively, 3 and 6 as ranks while the given system is of rank 9. Observe that $\mathcal{N}_1$ is an SF-type subnetwork for containing reactions R_1 and R_5 which are SF-pair in R2 since their kinetic order vectors differ only in that species. The subsystem $(\mathcal{N}_1, K_1)$ is of deficiency $\delta_1 = 7 - 3 - 3 = 1$ and is clearly a PL-RDK implying that it has ACR in R2.

$$\mathscr{N}_1: \qquad \text{R1I} \underset{R_2}{\overset{R_1}{\rightleftarrows}} \text{R1} \qquad\qquad \text{R2} \underset{R_4}{\overset{R_3}{\rightleftarrows}} \text{R2I}$$

$$\text{R2+R1I} \underset{R_6}{\overset{R_5}{\rightleftarrows}} \text{R}^* \underset{R_8}{\overset{R_7}{\rightleftarrows}} \text{R1+R2I}$$

$$\mathscr{N}_2: \qquad \text{R}^* + \text{S2} \qquad \text{R}^*\text{S2}^* + \text{S1} \qquad \text{S1}^* + \text{S1}^* \qquad \text{S1}^* + \text{S2}^* \qquad (3.3)$$

$$\Big\updownarrow\substack{R_{10}\\R_9} \qquad\qquad \Big\downarrow R_{12} \qquad\qquad \Big\downarrow R_{14} \qquad\qquad \Big\downarrow R_{16}$$

$$\text{R}^*\text{S2}^* \qquad\qquad \text{R}^*\text{S2}^*\text{S1}^* \qquad\quad \text{S1}^*\text{S1}^* \qquad\quad \text{S1}^*\text{S2}^*$$

$$\Big\downarrow R_{11} \qquad\qquad \Big\downarrow R_{13} \qquad\qquad \Big\downarrow R_{15} \qquad\qquad \Big\downarrow R_{17}$$

$$\text{R}^* + \text{S2}^* \qquad \text{R}^*\text{S2}^* + \text{S1}^* \qquad\quad \text{S1+S1} \qquad\qquad \text{S1+S2}$$

4 The ACR building block algorithm for PLK systems of Shinar-Feinberg type

4.1 General structure and flow of the algorithm

Propositions 2 and 3 require four things in a PLK system to guarantee the existence of ACR or BCR. These are: (1) the system must have an equilibrium (positive/complex balanced); (2) the system must have a decomposition (independent/incidence independent); (3) the decomposition must have an SF-type subnetwork; and (4) the subnetwork must be a building block. These requirements are the key factors that we have considered in the development of the algorithms. The major stages of the algorithms dwell on the checking of these requirements (see Table 4.1).

STAGE 1	Check if the PLK system has multiple equilibria
STAGE 2	Check if the PLK system has an SF-type subnetwork.
STAGE 3	Check if the PLK system has an appropriate decomposition induced by the SF-type subnetwork.
STAGE 4	Check if the SF-type subnetwork is a building block.

Table 4.1. Stages of the algorithm.

Since the first stage includes equilibrium checking, we clarify that this paper does not focus on the checking of the capacity of a system to admit an equilibrium. Readers are advised to refer to papers such as [7, 8, 11] for discussions regarding this topic. Furthermore, in this stage, we require the system to have an equilibrium that is not unique in the

whole species space, otherwise the system will trivially have a concentration robustness in all species [9].

With these stages in mind, we developed the algorithms employing a **bottom-up** (BU) approach. This approach works by initially identifying a subnetwork which contains an SF-pair beginning with the smallest possible such subnetwork, i.e., the subnetwork consisting only the SF-pairs. Finding every SF-pair is done by tracking the difference of every two kinetic order vectors in the system. A decomposition is constructed from the identified SF-type subnetwork. Once the desired decomposition has been obtained, the subnetwork is subjected to a series of tests (called **building block tests**) to determine if the necessary conditions enumerated in Propositions 2 and 3 are met. In case the chosen subnetwork does not give the desired output, another subnetwork is considered and tested until all the possible subnetworks containing the SF-pairs have been checked.

Finding a suitable decomposition from of an SF-type subnetwork is not always an easy task. The challenge is even greater when the network system at hand is large. Nevertheless, a good algorithm needs to have an efficient mechanism in finding such decomposition. Apparently, it is not efficient to consider a decomposition with arbitrary number of subnetworks. Hence, we must consider a decomposition with the smallest possible number of subnetworks that will do the job. This led us to design the algorithms to just consider binary decompositions. This decision is further justified by the following reasons. First, a more refined decomposition is difficult to handle especially if we want to achieve efficiency. Second, note that we are only interested in the subnetwork which contains the SF-pair leaving the other subnetworks with no purpose in the analysis. So, having a decomposition with many subnetworks leads to some impractical labor loss. For the last reason, we turn our attention to the following results of Farinas et al. [3] on the coarsening of independent and incidence independent decompositions. The results are stated as follows.

Proposition 4 (Propositions 5 and 8, [3])**.** *If a decomposition is independent (incidence independent), then any coarsening of the decomposition is also independent (incidence independent).*

These results mean that a network possessing an independent/incidence independent decomposition also possesses a binary independent/incidence independent decomposition. In particular, given that a network $\mathcal{N}$ has an independent/incidence independent decom-

position say $\{\mathcal{N}_1, \mathcal{N}_2, \cdots, \mathcal{N}_k\}$ where $\mathcal{N}_1$ contains an SF-pair. Then, $\{\mathcal{N}_1, \mathcal{N}^*\}$, where $\mathcal{N}^* = \mathcal{N}_2 \cup \mathcal{N}_3 \cup \cdots \cup \mathcal{N}_k$, must also be an independent/incidence independent decomposition. These tell us that it does not matter if we consider a binary decomposition since the independence or incidence independence of a finer decomposition is inherited by it.

It is also important to note that even if we can decompose a network in so many ways there is no guarantee that it possesses an independent/incidence independent decomposition. Take network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ with $\mathcal{S} = \mathcal{C} = \{A, B\}$ and $\mathcal{R} = \{A \to B, B \to A\}$ as an example. Observe that $\mathcal{N}$ can be only decomposed as $\{\mathcal{N}_1, \mathcal{N}_2\}$ where $\mathcal{R}_1 = \{A \to B\}$ and $\mathcal{R}_2 = \{B \to A\}$. However, this decomposition is not independent nor incidence independent. So, Propositions 2 and 3 can no longer handle this network. Consequently, this kind of CRN limits the scope of the algorithms. This implies that the algorithms may determine if a system has the desired concentration robustness but not the nonexistence of such.

On the other hand, a network may have so many independent or incidence independent decompositions. Unfortunately, it is not always the case that one decomposition gives everything we need to have an ACR or BCR. This means that a good algorithm must be capable of analyzing every possible independent/incidence decomposition a network may have. In Example 2, we illustrate how one of our algorithms is unable to determine if the network has the desired concentration robustness. However, it also shows how it is able to generate and analyze every necessary binary decomposition of the network.

4.2 Detailed step-by-step description of the ACR building block algorithm

The following are the details on how we proceed with the ACR building block algorithm for PLK systems of Shinar-Feinberg type.

1. The inputs are the network $\mathcal{N}$ and its kinetic order matrix F.

2. From the inputs, vital information including the set of reaction vectors $\mathcal{R}^* = \{y' - y \in \mathbb{R}^{\mathcal{S}} | y \to y' \in \mathcal{R}\}$ and the network's rank will be collected (STEP 1).

3. Every SF-pair will also be collected and stored (STEP 2).

4. From an SF-pair $\{R_u, R_v\}$, corresponding vectors r_u and r_v will be obtained. Then, $\{r_u, r_v\}$ will be extended to a basis $B = \{r_u, r_v, r'_1, r'_2, \cdots, r'_p\}$ of the stoichiometric

subspace S. The rank obtained in STEP 1 determines the number of elements of B (STEPS 3-5).

5. After setting $B_1 = \{r_u, r_v\}$ and $B_2 = \{r'_1, r'_2, \cdots, r'_p\}$, the occurrence of a decomposition will be tested by checking if $\mathscr{R}^* \subseteq span B_1 \cup span B_2$. A positive test result means that B_1 and B_2 generate all the reaction vectors of the system, i.e., a binary decomposition $\{\mathscr{N}_1, \mathscr{N}_2\}$ is obtained where $\mathscr{N}_1$ and $\mathscr{N}_2$ have the reactions which corresponds to the vectors in $span B_1$ and $span B_2$, respectively. $B_1 \cap B_2 = \emptyset$ and $B_1 \cup B_2 = B$ ensure that the decomposition is independent (STEPS 6-7).

6. If in case the initial B_1 and B_2 will not be able to generate the desired decomposition, some vectors in B_2 will be transferred to B_1 and the process of checking for a possible decomposition will be repeated. This method of transferring vectors from B_2 to B_1 aims to preserve the disjointness of B_1 and B_2 while maintaining that their union is B (STEP 8).

7. Once a decomposition has been established, the generated subsystem $(\mathscr{N}_1, K_1)$ undergoes the building block tests. If the testing does not yield a positive result, the process will be repeated (STEPS 9-12).

4.3   The ACR building block algorithm

We now present the ACR building block algorithm for PLK systems of SF-type.

Algorithm 1 ACR building block algorithm

INPUT
Network: $\mathscr{N}$ with positive equilibrium
Kinetic order matrix: F

STEP 1 Determine the following information about $\mathscr{N}$
Set of reaction vectors: $\mathscr{R}^* = \{y' - y \in \mathbb{R}^{\mathscr{S}} | y \to y' \in \mathscr{R}\}$
Rank of $\mathscr{N}$

STEP 2 Find all SF-pairs
if there is none **then**
    exit the algorithm
else
    store these SF-pairs as $\{\{R_u, R_v\}\}$ and proceed to STEP 3
end if

STEP 3 Choose SF-pair $\{R_u, R_v\}$

STEP 4 Get the vectors r_u and r_v corresponding to R_u and R_v

STEP 5 Extend $\{r_u, r_v\}$ to a basis $B = \{r_u, r_v, r'_1, r'_2, \cdots, r'_p\}$ of S

STEP 6 Set $B_1 = \{r_u, r_v\}$ and $B_2 = \{r'_1, r'_2, \cdots, r'_p\}$

STEP 7 Test if $\mathscr{R}^* \subseteq span B_1 \cup span B_2$
if $\mathscr{R}^* \subseteq span B_1 \cup span B_2$ **then**
  proceed to STEP 9
else
  proceed to STEP 8
end if

STEP 8 Choose a $P \in \wp(\{r'_1, r'_2, \cdots, r'_p\}) - \{\emptyset, \{r'_1, r'_2, \cdots, r'_p\}\}$ where
$\wp(\{r'_1, r'_2, \cdots, r'_p\})$ is the set of all subsets of $\{r'_1, r'_2, \cdots, r'_p\}$
if P has not been chosen before **then**
  set $B_1 = \{r_u, r_v\} \cup P$ and $B_2 = \{r'_1, r'_2, \cdots, r'_p\} - P$ and repeat STEP 7
else
  if there is another $P \in \wp(\{r'_1, r'_2, \cdots, r'_p\}) - \{\emptyset, \{r'_1, r'_2, \cdots, r'_p\}\}$ to choose **then**
    repeat STEP 8
  else
    if there is another SF-pair that can be chosen **then**
      repeat STEP 3
    else
      exit the algorithm
    end if
  end if
end if

STEP 9 Get the subnetwork $\mathscr{N}_1$ generated by the reactions whose vectors are contained in $span B_1$

STEP 10 Determine the deficiency δ_1 of $\mathscr{N}_1$
if $\delta_1 \leq 1$ **then**
  proceed to STEP 11
else
  repeat STEP 8
end if

STEP 11 Test if $(\mathcal{N}_1, K_1)$ is a PL-RDK
if $(\mathcal{N}_1, K_1)$ is a PL-RDK **then**
  a building block is found and the system has ACR
else
  proceed to STEP 12
end if

STEP 12 Test if $(\mathcal{N}_1, K_1)$ is a minimally PL-NDK and $\delta_1 = 0$
if $(\mathcal{N}_1, K_1)$ is a minimally PL-NDK and $\delta_1 = 0$ **then**
  a building block is found and the system has ACR
else
  repeat STEP 8
end if

The following proposition proves that the decomposition produced in STEP 9 is an independent decomposition.

Proposition 5. *The decomposition* $\{\mathcal{N}_1, \mathcal{N}_2\}$ *induced by* B_1 *and* B_2 *where* $\mathscr{R}^* \subseteq spanB_1 \cup spanB_2$ *is an independent decomposition.*

Proof. Clearly, B_1 and B_2 are nonempty. Now, note that $\mathcal{N}_1$ and $\mathcal{N}_2$ are generated by the reactions whose vectors are contained in $S_1 = spanB_1$ and $S_2 = spanB_2$, respectively. Let R be any reaction in $\mathcal{N}$. Since $\mathscr{R}^* \subseteq spanB_1 \cup spanB_2$, then the reaction vector r of R is contained in either S_1 or S_2. Suppose $r \in S_1$. Then, R is a reaction in $\mathcal{N}_1$. Now, if $r \in S_2$, then $r_u, r_v, r'_1, r'_2, \cdots, r'_p$ are going to be linearly dependent violating the fact that B is a basis for S. This means that R cannot be a reaction in $\mathcal{N}_2$ suggesting that $\{\mathcal{N}_1, \mathcal{N}_2\}$ is a decomposition. Finally, since $B_1 \cap B_2 = \emptyset$ and $B_1 \cup B_2 = B$, then $S_1 + S_2 = S$ is a direct sum implying that $\{\mathcal{N}_1, \mathcal{N}_2\}$ is an independent decomposition. ∎

Example 1. (from Running example 2) We illustrate the algorithm by showing how it can produce the independent binary decomposition of the system in Running example 2 and subject the SF-type subnetwork to the building block tests.

STEP 1: The set of all reaction vectors of the system is $\mathscr{R}^* = \{r_1, r_2, \cdots, r_{17}\}$ where

$$
r_1 = \begin{bmatrix} 1 \\ -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},\;
r_3 = \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},\;
r_5 = \begin{bmatrix} 0 \\ -1 \\ -1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},\;
r_7 = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 1 \\ -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},\;
r_9 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix},\;
r_{11} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ -1 \\ 0 \end{bmatrix},
$$

$$
r_{12} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 1 \end{bmatrix},\;
r_{13} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ -1 \end{bmatrix},\;
r_{14} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -2 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix},\;
r_{15} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 2 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ 0 \end{bmatrix},\;
r_{16} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 0 \\ -1 \\ 0 \\ 1 \\ 0 \end{bmatrix},\;
r_{17} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \\ 0 \\ 0 \\ -1 \\ 0 \\ 0 \end{bmatrix},
$$

$r_2 = -r_1, r_4 = -r_3, r_6 = -r_5, r_8 = -r_7, r_{10} = -r_9.$

The system is of rank 9.

STEPS 2-6: The system has seven SF-pairs namely, $\{R_2, R_8\}, \{R_1, R_5\}, \{R_3, R_5\}, \{R_4, R_8\}, \{R_{10}, R_{12}\}, \{R_6, R_9\}$, and $\{R_7, R_9\}$. We deliberately choose R_1 and R_5. These reactions correspond to r_1 and r_5. We extend $\{r_1, r_5\}$ to a basis $B = \{r_1, r_5, r_3, r_9, r_{11}, r_{12}, r_{13}, r_{14}, r_{16}\}$ of the stoichiometric subspace S of the system. Now, we set $B_1 = \{r_1, r_5\}$ and $B_2 = \{r_3, r_9, r_{11}, r_{12}, r_{13}, r_{14}, r_{16}\}$. It can be verified that $r_7 \notin \operatorname{span} B_1 \cup \operatorname{span} B_2$, i.e. $\mathscr{R}^* \nsubseteq \operatorname{span} B_1 \cup \operatorname{span} B_2$. Hence, we go to STEP 8.
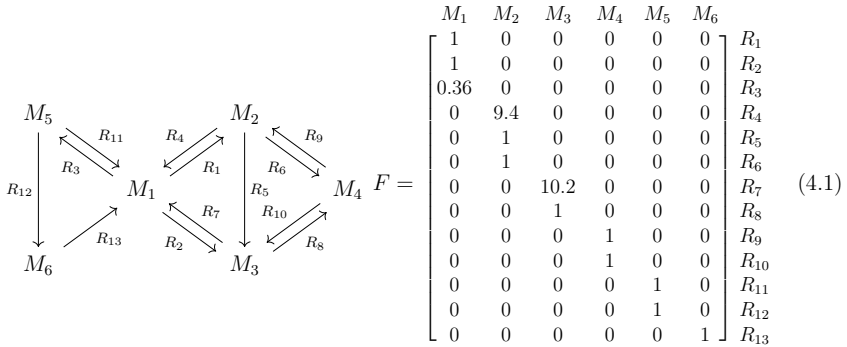
STEP 8: Note that $\wp(\{r_3, r_9, r_{11}, r_{12}, r_{13}, r_{14}, r_{16}\})$ has $2^8 = 256$ elements. So, we have 254 other iterations of B_1 and B_2. We can see in the following table a few of these iterations. From the table, notice that we get a decomposition when $B_1 = \{r_1, r_5, r_3\}$ and $B_2 = \{r_9, r_{11}, r_{12}, r_{13}, r_{14}, r_{16}\}$. We proceed to STEP 9.

B_1	B_2	Element(s) not contained in $spanB_1 \cup spanB_2$
$\{r_1, r_5, r_3\}$	$\{r_9, r_{11}, r_{12}, r_{13}, r_{14}, r_{16}\}$	(none)
$\{r_1, r_5, r_9\}$	$\{r_3, r_{11}, r_{12}, r_{13}, r_{14}, r_{16}\}$	r_7, r_8, r_{17}
$\{r_1, r_5, r_{11}\}$	$\{r_3, r_9, r_{12}, r_{13}, r_{14}, r_{16}\}$	r_7, r_8, r_{17}
$\{r_1, r_5, r_{12}\}$	$\{r_3, r_9, r_{11}, r_{13}, r_{14}, r_{16}\}$	r_7, r_8, r_{15}, r_{17}
$\{r_1, r_5, r_{13}\}$	$\{r_3, r_9, r_{11}, r_{12}, r_{14}, r_{16}\}$	r_7, r_8, r_{15}, r_{17}
$\{r_1, r_5, r_{14}\}$	$\{r_3, r_9, r_{11}, r_{12}, r_{13}, r_{16}\}$	r_7, r_8, r_{15}, r_{17}
$\{r_1, r_5, r_{16}\}$	$\{r_3, r_9, r_{11}, r_{12}, r_{13}, r_{14}\}$	r_7, r_8, r_{17}
$\{r_1, r_5, r_3, r_9\}$	$\{r_{11}, r_{12}, r_{13}, r_{14}, r_{16}\}$	r_{17}
$\{r_1, r_5, r_3, r_{11}\}$	$\{r_9, r_{12}, r_{13}, r_{14}, r_{16}\}$	r_{17}
$\{r_1, r_5, r_3, r_{12}\}$	$\{r_9, r_{11}, r_{13}, r_{14}, r_{16}\}$	r_{15}, r_{17}
$\{r_1, r_5, r_3, r_{13}\}$	$\{r_9, r_{11}, r_{12}, r_{14}, r_{16}\}$	r_{15}, r_{17}
$\{r_1, r_5, r_3, r_{14}\}$	$\{r_9, r_{11}, r_{12}, r_{13}, r_{16}\}$	r_{15}
$\{r_1, r_5, r_3, r_{16}\}$	$\{r_9, r_{11}, r_{12}, r_{13}, r_{14}\}$	r_{17}

Table 4.2. Some iterations of B_1 and B_2

STEPS 9-11: From STEP 8, we get the subnetwork $\mathcal{N}_1$ induced by the reactions whose vectors are contained in $spanB_1$ (see (3.3)). As mentioned, $\mathcal{N}_1$ has deficiency 1 and the subsystem $(\mathcal{N}_1, K_1)$ is a PL-RDK, i.e., a building block is found and the system has ACR in R2.

Example 2. (a non-example) We show a system where the ACR building block algorithm is silent. Consider the PLK system for R. Schmitz's preindustrial carbon cycle model (see (4.1)) which appeared as an example in [8]. The system has a positive equilibrium and is of deficiency 0.

$$F = \begin{array}{c} \begin{array}{cccccc} M_1 & M_2 & M_3 & M_4 & M_5 & M_6 \end{array} \\ \left[\begin{array}{cccccc} 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 0.36 & 0 & 0 & 0 & 0 & 0 \\ 0 & 9.4 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 10.2 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{array}\right] \begin{array}{c} R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ R_7 \\ R_8 \\ R_9 \\ R_{10} \\ R_{11} \\ R_{12} \\ R_{13} \end{array} \end{array} \quad (4.1)$$

STEP 1: The set of reaction vectors is given by $\mathscr{R}^* = \{r_1, r_2, \cdots, r_{13}\}$ where

$$r_1 = \begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, r_2 = \begin{bmatrix} -1 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, r_3 = \begin{bmatrix} -1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}, r_4 = -r_1, r_5 = \begin{bmatrix} 0 \\ -1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, r_6 = \begin{bmatrix} 0 \\ -1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, r_7 = -r_2,$$

$$r_8 = \begin{bmatrix} 0 \\ 0 \\ -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, r_9 = -r_6, r_{10} = -r_8, r_{11} = -r_3, r_{12} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ -1 \\ 1 \end{bmatrix}, r_{13} = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ -1 \end{bmatrix}.$$
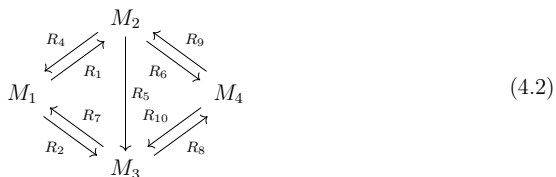
STEPS 2-7: The system has five SF-pairs, but we only choose the pair $\{R_4, R_5\}$. Reactions R_4 and R_5 correspond to r_4 and r_5. We get a basis $B = \{r_4, r_5, r_3, r_8, r_{12}\}$ of the stoichiometric subspace after extending $\{r_4, r_5\}$. We let $B_1 = \{r_4, r_5\}$ and $B_2 = \{r_3, r_8, r_{12}\}$. Notice that $r_4, r_5, r_1, r_2, r_7 \in span B_1$ while $r_3, r_8, r_{12}, r_{11}, r_{10}, r_{13} \in span B_2$. On the other hand, $r_6, r_9 \notin span B_1 \cup span B_2$, i.e., $\mathscr{R}^* \nsubseteq span B_1 \cup span B_2$. We proceed to STEP 8.

STEP 8: Before transferring some elements of B_2 to B_1, we point out that $\wp(B_2)$ has $2^3 = 8$ elements. Excluding $\emptyset$ and B_2 from $\wp(B_2)$ gives us 6 ways to rewrite B_1 and B_2. We can see from the table below that only the case where $B_1 = \{r_4, r_5, r_8\}$ and $B_2 = \{r_3, r_{12}\}$ induces a partition of $\mathscr{R}^*$ resulting to a decomposition of the given network. The algorithm will ultimately pick this iteration.

B_1	B_2	element(s) not contained in $span B_1 \cup span B_2$
$\{r_4, r_5, r_3\}$	$\{r_8, r_{12}\}$	r_6, r_9, r_{13}
$\{r_4, r_5, r_8\}$	$\{r_3, r_{12}\}$	(none)
$\{r_4, r_5, r_{12}\}$	$\{r_3, r_8\}$	r_6, r_9, r_{13}
$\{r_4, r_5, r_3, r_8\}$	$\{r_{12}\}$	r_{13}
$\{r_4, r_5, r_3, r_{12}\}$	$\{r_8\}$	r_6, r_9, r_{10}, r_{13}
$\{r_4, r_5, r_8, r_{12}\}$	$\{r_3\}$	r_{11}, r_{13}

Table 4.3. The other iterations of B_1 and B_2

STEPS 9-10: Given below is the subnetwork $\mathscr{N}_1$ generated by the reactions whose vectors are contained in $span B_1 = span\{r_4, r_5, r_8\}$. It has deficiency $\delta_1 = 4 - 1 - 3 = 0 \leq 1$.

$$
\begin{array}{c}
M_2 \\
R_4 \nearrow \quad \uparrow R_1 \quad R_6 \downarrow \quad \nwarrow R_9 \\
M_1 \qquad\qquad R_5 \qquad\qquad M_4 \\
R_7 \searrow \quad R_2 \swarrow \qquad R_{10} \nearrow \quad R_8 \nwarrow \\
M_3
\end{array}
\tag{4.2}
$$

STEPS 11-12: Notice that in the subsystem $(\mathcal{N}_1, K_1)$, the branching reactions R_4 and R_5 have different kinetic order vectors. This means that the subsystem is NOT PL-RDK. Unfortunately, M_2 and M_3 are both NDK nodes in the subsystem implying that it is also not minimally PL-NDK. No building block is found and the algorithm cannot determine if the system has ACR using the SF-pair $\{R_4, R_5\}$.

We note that testing every other SF-pair yields similar result, i.e., no decomposition gives an SF-type subnetwork that passes the building block tests. In short, the algorithm cannot determine if the given system has ACR. Nevertheless, though the result is not affirmative, this example also illustrates the capability of the algorithm to extract and analyze every binary decomposition of the network. This feature of the algorithm can be seen as an opportunity for those who are also working on decomposition theory.

5   The BCR building block algorithm: essential modifications

By modifying some steps of the ACR building block algorithm, we get the BCR building block algorithm. The following are the alterations we have made in the procedure of ACR building block algorithm. We first remove the step that determines the set of reaction vectors and the rank of the network. Replace this step with the step that determines the incidence matrix I_a and its rank. We take advantage of the column space $\mathrm{ColS}(I_a)$ of I_a here since a basis of $\mathrm{ColS}(I_a)$ provides a basis for the image of I_a. Then, we replace items 4 and 5, with the following.

- From an SF-pair $\{R_u, R_v\}$, corresponding column vectors c_u and c_v of I_a will be obtained. Then, $\{c_u, c_v\}$ will be extended to a basis $B = \{c_u, c_v, c'_1, c'_2, \cdots, c'_q\}$ of $\mathrm{ColS}(I_a)$ (STEPS 3-5).

- Let $B_1 = \{c_u, c_v\}$ and $B_2 = \{c'_1, c'_2, \cdots, c'_q\}$ and check if $C \subseteq span B_1 \cup span B_2$,

where C is the set of all column vectors of I_a. This testing aims to check if $spanB_1$ and $spanB_2$ generate all the column vectors of I_a. A binary decomposition $\{\mathcal{N}_1, \mathcal{N}_2\}$ is obtained when the test result is positive. Note that $\mathcal{N}_1$ and $\mathcal{N}_2$ consist of the reactions which are associated to the column vectors in $spanB_1$ and $spanB_2$, respectively. Finally, note that $B_1 \cap B_2 = \emptyset$ and $B_1 \cup B_2 = B$ ensure that the decomposition is incidence independent (STEPS 6-7).

Similar to Proposition 5, the following result tells us that STEP 9 of BCR building block algorithm produced an incidence independent decomposition.

Proposition 6. *The decomposition $\{\mathcal{N}_1, \mathcal{N}_2\}$ induced by B_1 and B_2 where $C \subseteq spanB_1 \cup spanB_2$ is an incidence independent decomposition.*

We now give the BCR building block algorithm for PLK systems of SF-type.

Algorithm 2 BCR building block algorithm

INPUT
Network: $\mathcal{N}$ with complex balanced equilibrium
Kinetic order matrix: F

STEP 1 Determine the following information about $\mathcal{N}$
Incidence matrix I_a
Rank of I_a

STEP 2 Find all SF-pairs
if there is none **then**
    exit the algorithm
else
    store these SF-pairs as $\{\{R_u, R_v\}\}$ and proceed to STEP 3
end if

STEP 3 Choose SF-pair $\{R_u, R_v\}$

STEP 4 Get the column vectors c_u and c_v of I_a corresponding to R_u and R_v

STEP 5 Extend $\{c_u, c_v\}$ to a basis $B = \{c_u, c_v, c'_1, c'_2, \cdots, c'_q\}$ of $\text{ColS}I_a$

STEP 6 Set $B_1 = \{c_u, c_v\}$ and $B_2 = \{c'_1, c'_2, \cdots, c'_q\}$.

STEP 7 Test if $C \subseteq spanB_1 \cup spanB_2$.
if $C \subseteq spanB_1 \cup spanB_2$ **then**
   proceed to STEP 9
else
   proceed to STEP 8
end if

STEP 8 Choose a $P \in \wp(\{c'_1, c'_2, \cdots, c'_p\}) - \{\emptyset, \{c'_1, c'_2, \cdots, c'_q\}\}$ where
$\wp(\{c'_1, c'_2, \cdots, c'_p\})$ is the set of all subsets of $\{c'_1, c'_2, \cdots, c'_p\}$
if P has not been chosen before **then**
   set $B_1 = \{c_u, c_v\} \cup P$ and $B_2 = \{c'_1, c'_2, \cdots, c'_p\} - P$ and repeat STEP 7
else
   if there is another $P \in \wp(\{c'_1, c'_2, \cdots, c'_p\}) - \{\emptyset, \{c'_1, c'_2, \cdots, c'_p\}\}$ to choose **then**
      repeat STEP 8
   else
      if there is another SF-pair that can be chosen **then**
         repeat STEP 3
      else
         exit the algorithm
      end if
   end if
end if

STEP 9 Get the subnetwork $\mathcal{N}_1$ generated by the reactions which correspond to the column vectors of I_a contained in $spanB_1$

STEP 10 Determine the deficiency δ_1 of $\mathcal{N}_1$
if $\delta_1 \leq 1$ **then**
   proceed to STEP 11
else
   repeat STEP 8
end if

STEP 11 Test if $(\mathcal{N}_1, K_1)$ is a PL-RDK
if $(\mathcal{N}_1, K_1)$ is a PL-RDK **then**
   a building block is found and the system has BCR
else
   proceed to STEP 12
end if

STEP 12 Test if $(\mathcal{N}_1, K_1)$ is a minimally PL-NDK and $\delta_1 = 0$
if $(\mathcal{N}_1, K_1)$ is a minimally PL-NDK and $\delta_1 = 0$ **then**
   a building block is found and the system has BCR
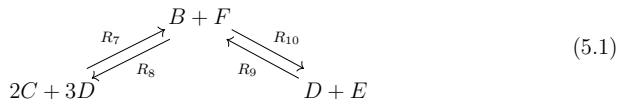**else**
   repeat STEP 8
end if

Example 3. (from Running example 1) Consider the system given in Running example 1. See (2.1) for the CRN and (2.3) for the kinetic order matrix. It is a deficiency zero PL-NDK system which contains two NDK nodes: B and $B + F$. It has a positive equilibrium according to Theorem 4 of [8]. By Theorem 1, the equilibrium is also complex balanced. Using the BCR building block algorithm, we show that the system has BCR in F.

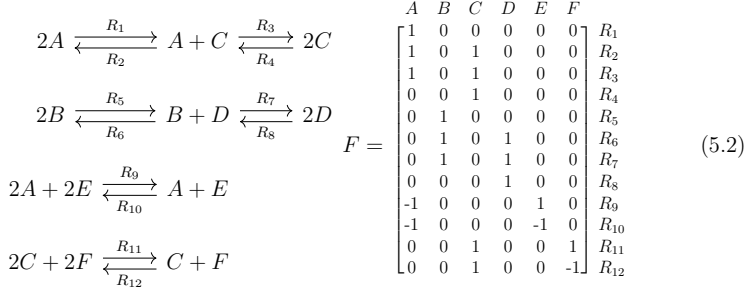STEP 1: The incidence matrix, given in (2.2), is of rank 5.

STEPS 2-7: The system has six SF-pairs, namely, $\{R_2, R_4\}$, $\{R_2, R_6\}$, $\{R_4, R_5\}$, $\{R_4, R_{10}\}$, $\{R_5, R_8\}$, $\{R_8, R_{10}\}$. Being one of the two SF-pairs that corresponds to F, we pick $\{R_8, R_{10}\}$. We consider c_8 and c_{10}, the column vectors of I_a that correspond to R_8 and R_{10}. We get the basis $B = \{c_8, c_{10}, c_1, c_3, c_5\}$ of $\text{ColS}(I_a)$ after extending $\{c_8, c_{10}\}$. Let $B_1 = \{c_8, c_{10}\}$ and $B_2 = \{c_1, c_3, c_5\}$. It can be noticed that $c_7, c_8, c_9, c_{10} \in span B_1$ and $c_1, c_2, c_3, c_4, c_5, c_6 \in span B_2$ suggesting that $span B_1 \cup span B_2$ generates all the column vectors of I_a. Then, we proceed to STEP 9.

STEPS 9-12: Consider the subnetwork $\mathcal{N}_1$ (see (5.1)) generated by the reactions associated to the vectors in $span B_1$. The deficiency of $\mathcal{N}_1$ is $\delta_1 = 3 - 2 - 1 = 0 \leq 1$. However, it is PL-NDK having $B + F$ as the sole NDK node. This NDK node has two CF-subsets, namely, $\{R_8\}$ and $\{R_{10}\}$ where each contains exactly one reaction. Hence, $\mathcal{N}_1$ is a minimally PL-NDK which means that we found a building block and so the given system has BCR in F.

$$
\begin{array}{ccccc}
& & B + F & & \\
& \overset{R_7}{\nearrow} & & \overset{R_{10}}{\nwarrow} & \\
& \underset{R_8}{\swarrow} & & \underset{R_9}{\searrow} & \\
2C + 3D & & & & D + E
\end{array}
\qquad (5.1)
$$

Example 4. The following PLK system was used as an example in [13].

$$2A \underset{R_2}{\overset{R_1}{\rightleftharpoons}} A + C \underset{R_4}{\overset{R_3}{\rightleftharpoons}} 2C$$

$$2B \underset{R_6}{\overset{R_5}{\rightleftharpoons}} B + D \underset{R_8}{\overset{R_7}{\rightleftharpoons}} 2D$$

$$2A + 2E \underset{R_{10}}{\overset{R_9}{\rightleftharpoons}} A + E$$

$$2C + 2F \underset{R_{12}}{\overset{R_{11}}{\rightleftharpoons}} C + F$$

$$F = \begin{bmatrix} A & B & C & D & E & F & \\ 1 & 0 & 0 & 0 & 0 & 0 & R_1 \\ 1 & 0 & 1 & 0 & 0 & 0 & R_2 \\ 1 & 0 & 1 & 0 & 0 & 0 & R_3 \\ 0 & 0 & 1 & 0 & 0 & 0 & R_4 \\ 0 & 1 & 0 & 0 & 0 & 0 & R_5 \\ 0 & 1 & 0 & 1 & 0 & 0 & R_6 \\ 0 & 1 & 0 & 1 & 0 & 0 & R_7 \\ 0 & 0 & 0 & 1 & 0 & 0 & R_8 \\ -1 & 0 & 0 & 0 & 1 & 0 & R_9 \\ -1 & 0 & 0 & 0 & -1 & 0 & R_{10} \\ 0 & 0 & 1 & 0 & 0 & 1 & R_{11} \\ 0 & 0 & 1 & 0 & 0 & -1 & R_{12} \end{bmatrix}$$ (5.2)

It has a complex balanced equilibrium and deficiency $\delta = 3$. Let us show using BCR building block algorithm that this system has a BCR in C. The system's incidence matrix I_a of rank 6 is given by the following.

$$I_a = \begin{bmatrix} R_1 & R_2 & R_3 & R_4 & R_5 & R_6 & R_7 & R_8 & R_9 & R_{10} & R_{11} & R_{12} & \\ -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 2A \\ 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & A+C \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 2C \\ 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 2B \\ 0 & 0 & 0 & 0 & 1 & -1 & -1 & 1 & 0 & 0 & 0 & 0 & B+D \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 2D \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 2A+2E \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & A+E \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 2C+2F \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & C+F \end{bmatrix}$$ (5.3)

The system has the following SF-pairs: $\{R_1, R_2\}, \{R_1, R_3\}, \{R_2, R_4\}, \{R_3, R_4\}, \{R_5, R_6\}, \{R_5, R_7\}, \{R_6, R_8\}, \{R_7, R_8\}, \{R_9, R_{10}\}, \{R_{11}, R_{12}\}$. We choose the pair $\{R_1, R_2\}$ since the kinetic order vectors of R_1 and R_2 differ only at C. The column vectors c_1 and c_2 of I_a correspond to R_1 and R_2. Extending $\{c_1, c_2\}$ to a basis of $\mathrm{ColS}(I_a)$, we get $B = \{c_1, c_3, c_5, c_7, c_9, c_{11}\}$. We let $B_1 = \{c_1, c_2\}$ and $B_2 = \{c_3, c_5, c_7, c_9, c_{11}\}$. Observe that $span B_1$ contains c_1 and c_2 while $span B_2$ contains $c_3, c_4, c_5, \cdots, c_{12}$, i.e., $span B_1 \cup span B_2$ contains all the column vectors of the matrix of I_a. Hence, we proceed by subjecting the subnetwork $\mathcal{N}_1$ (see (5.4)) generated by the reactions whose corresponding column vectors are contained in $span B_1$ to the building block tests.

$$2A \underset{R_2}{\overset{R_1}{\rightleftharpoons}} A + C$$ (5.4)

$\mathcal{N}_1$ has deficiency $\delta_1 = 2 - 1 - 1 = 0$ and clearly, $(\mathcal{N}_1, K_1)$ is a PL-RDK. So, a building block is found, and we conclude that the system has BCR in C.

6 Summary and outlook

We summarize the results we have obtained and give some recommendations for further research.

We have developed algorithms that enable us to identify ACR and BCR on PLK systems. The algorithms are based on Propositions 8 and 9 of [9]. Each of the algorithms works by searching for an SF-type subnetwork taken from a suitable decomposition. This subnetwork undergoes several tests to determine if it is a building block.

While the algorithms can determine the existence of a concentration robustness in a PLK system given that the system has all the required conditions, these procedures are not capable of determining if a PLK system does not have a concentration robustness.

ACR building block algorithm is also capable of finding every binary independent decomposition (such that one subnetwork of each decomposition contains a fixed pair of reactions) of a given network. Hence, as implied by Proposition 4 (Proposition 5 in [3]), this algorithm also enables us to detect if a network does not have a more refined independent decomposition. In other words, if a binary independent decomposition does not exist, then an independent refinement of such decomposition also does not exist. Similarly, BCR building block algorithm can also be used to determine if a network does not have a refined incidence independent decomposition. These observations imply that the algorithms can be utilized as tools in analyzing decompositions of a network. In this regard, further studies could be done to achieve computational techniques that generate all independent and incidence independent decompositions of a network.

Each of the algorithms here generates decompositions by considering subsets of a power set. Since power set easily gets large, a computationally less expensive strategy in finding those subsets will improve the efficiency of the algorithms.

The creation of computer programs applying the algorithms is a good next step for this study. If successful, such project will be beneficial for those who study concentration robustness in PLK systems, or other systems that can be represented as PLK systems.

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