

Absolutely Complex Balanced Mass Action Kinetic Systems via Zero Deficiency Decomposition

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Abstract

The purpose of this study is to characterize absolutely complex balanced (ACB) systems with mass action kinetics (MAK) using zero deficiency decomposition (ZDD). To do this, we first introduce the mass action, \hat{T} -independent kinetic (MA-TIK) and mass action, non- \hat{T} -independent kinetic (MA-NTIK) systems, that is, MAK systems that are also PL-TIK and non-PL-TIK systems, respectively. Then, we develop an algorithm that can generate the ZDD of both MA-TIK and MA-NTIK systems. We show that for both MA-TIK and MA-NTIK systems, ZDD implies a PL-TIK decomposition, wherein each subnetwork is a PL-TIK system. We show the existence of ACB systems for non-zero deficiency MA-NTIK systems via their weakly reversible, zero deficiency, \mathcal{C} -decomposition. On the other hand, we also show the non-existence of ACB systems for non-zero deficiency MA-TIK systems. Lastly, we apply the results to the mathematical model of a mechanism for human dihydrofolate reductase (DHFR) catalysis.

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1 Introduction

To determine the nonemptiness of positive steady states in a network, the main focus of Chemical Reaction Network Theory (CRNT) is to utilize the concept of network deficiency. For MAK systems, Horn, Jackson, and Feinberg jointly established DZT [13]. Then, Feinberg formulated and proved DOT [11]. The weak reversibility structure is a major requirement to determine if zero deficiency systems have a positive equilibrium. On the other hand, Boros found the conditions needed for non-weakly reversible, deficiency-one MAK systems to ensure the nonemptiness of positive steady states [3].

A positive vector c is called complex balanced (CB) if for a given kinetics K , $K(c)$ is contained in $\ker I_a$ [22]. In other words, the positive vector c is a complex balanced steady state, where formation and degradation are at equilibrium. So, a kinetic system is said to be complex balanced if it has a complex balanced steady state. This notion was first introduced through the works of Horn, Jackson, and Feinberg [12, 17, 18]. One of the motivations behind the study of complex balanced systems is the well-known Global Attractor Conjecture, which was formulated by Horn in 1974 [5]. This states that, in complex balanced systems, every trajectory with positive initial condition converges to the unique positive equilibrium. In MAK systems, Craciun et al. [5] referred to complex balanced mass action systems as toric dynamical systems. On the other hand, mass action systems are complex balanced if and only if it is detailed balanced [7]. Unlike the set of positive steady states, regardless of the deficiency of the network, weak reversibility is a necessary condition to ensure nonemptiness of $Z_+(\mathcal{N}, K)$.

In this study, we will probe the existence of absolutely complex balanced systems in MAK systems. A complex balanced system (\mathcal{N}, K) is said to be ACB if and only if $Z_+(\mathcal{N}, K) \neq \emptyset$ and $E_+(\mathcal{N}, K) = Z_+(\mathcal{N}, K)$. In 1972, three results on ACB systems were considered foundational [20]:

- 1) Feinberg showed that, regardless of their kinetics, complex balanced, deficiency-zero systems are ACB systems.
- 2) Horn showed that a weakly reversible, deficiency-zero MAK system

is an ACB system; and

3) Horn and Jackson [18] showed that, regardless of the network's deficiency, complex balanced MAK systems are ACB systems.

Talabis et al. in [20] showed that any complex balanced system with a bi-independent decomposition and ACB subnetworks is also ACB. Here, we will show that a class of weakly reversible and non-zero deficiency MAK systems with zero deficiency, \mathcal{C} -decomposition are ACB systems.

Our main goal is to introduce a new criterion to characterize MAK systems as ACB systems through network decomposition. In relation to this, Feinberg initiated the network decomposition theory using decomposition to investigate the existence of positive steady states in a given system [9]. One important result claims that, for any kinetic system with a given independent decomposition, the set of positive equilibria is equal to the intersection of the subnetwork's sets of positive equilibria.

Farinas et al. [8] generated an analogous result with a system's set of complex balanced equilibria and its incidence-independent decomposition. In addition, they introduced the notion of \mathcal{C} -decomposition and linked it to the complex balanced steady states of the given system. This result implied that if the set of complex balanced equilibria of each subnetwork in an incidence-independent decomposition is nonempty, then so is the parent network's. Thus, with the above property, any MAK system with a weakly reversible \mathcal{C} -decomposition has a nonempty set of complex balanced equilibria and hence a nonempty set of positive equilibria.

Moreover, Farinas et al. [8] introduced the notion of Zero Deficiency Decomposition, wherein each subnetwork in a given decomposition is a zero deficiency system. We introduce the zero deficiency decomposition (ZDD) algorithm, which elicits a ZDD from a given MAK system. This result, together with the results from Feinberg, Horn and Jackson, Talabis et al., and Farinas et al., is vital in determining the existence of ACB systems from MAK systems.

As an application, we determined whether the mechanism of human Dihydrofolate Reductase (DHFR) catalysis [6] under the assumption of mass action is an ACB system or not.

Lastly, Boros in [4] filled the gaps in the proof of the Mass Action

Conjecture by Deng et al. in 2011 and thus established the Mass Action Theorem: If (\mathcal{N}, K) is a weakly reversible mass action system, then it has a positive equilibrium.

In this study, we will show that our main result is an enhancement of the Mass Action Theorem as follows:

1. If (\mathcal{N}, K) is a weakly reversible mass action kinetic system, then it has a positive equilibrium.
2. (\mathcal{N}, K) has a complex balanced equilibrium (and hence ACB) if and only if it is MA-NTIK.

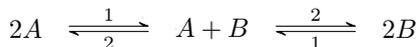
2 Basic concepts in chemical reaction network theory

This section discusses some basic concepts on chemical kinetic systems (CKS) and known results on absolutely complex balanced (ACB) systems. Also, in this section, we discuss different network decomposition classes and related results. For a more detailed discussion of the concepts, the readers can refer to [24].

2.1 Fundamentals of a chemical reaction network

A **chemical reaction network** (CRN) is an ordered triple $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ where \mathcal{S} is the finite set of all **species** or variables in the CRN, \mathcal{C} is the set of all **complexes** in the CRN, and \mathcal{R} is the set of all **reactions** involved in the CRN such that (1) $(y, y) \notin \mathcal{R}$ for any $y \in \mathcal{C}$ and (2) for each $y \in \mathcal{C}$, $\exists y' \in \mathcal{C}$ such that $(y, y') \in \mathcal{R}$ or $(y', y) \in \mathcal{R}$.

Example 1. Consider the given toy CRN with the given reaction rate constants below.



From the above CRN, $\mathcal{S} = \{A, B\}$, $\mathcal{C} = \{2A, A + B, 2B\}$, and $\mathcal{R} = \{2A \rightarrow A + B, A + B \rightarrow 2A, A + B \rightarrow 2B, 2B \rightarrow A + B\}$

On the other hand, a CRN can induce different matrices. The **molecularity matrix** Y of a CRN is the $m \times n$ matrix whose entries are stoichiometric coefficients, the entries in the i^{th} row correspond to the coefficients of the i^{th} variable X_i . The **incidence matrix** I_a of a CRN is the $n \times r$ matrix whose entries are 1, -1 , 0. If a complex is a reactant complex in the i^{th} reaction, then its corresponding entry is -1 . If a complex is a product complex in the i^{th} reaction, then its corresponding entry is 1. Otherwise, the corresponding entry in the i^{th} reaction is 0. From Running Example 1, $Y = \begin{bmatrix} 2 & 1 & 0 \\ 0 & 1 & 2 \end{bmatrix}$, and the incidence matrix is given by

$$I_a = \begin{bmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix}.$$

The **stoichiometric matrix** N is an $m \times r$ matrix whose entries are the stoichiometric coefficients of the associated reaction vector of the i^{th} reaction. The associated reaction vector of the i^{th} reaction is the difference between the reactant complex and the product complex. If $y \rightarrow y'$ is a reaction, then the associated reaction vector is $y' - y$. From Running Example 1, $N = \begin{bmatrix} -1 & 1 & -1 & 1 \\ 1 & -1 & 1 & -1 \end{bmatrix}$.

A **linkage class** is a connected component of the CRN. A **strong linkage class** is a strongly connected component of the CRN. A **terminal strong linkage class** is a strongly connected component without outgoing arcs. A CRN is called **weakly reversible** if every linkage class is a strong linkage class. It is called **t-minimal** if every linkage class has one terminal strong linkage. From Running Example 1, the linkage class, strong linkage class, and terminal linkage class coincide. So, the given CRN is both weakly reversible and t-minimal.

Arceo et al. (2017) stated that two types of terminal strong linkage classes exist. First, those **cycles** (not necessarily simple) and second, singletons (or **terminal points**) [2]. Hence, we say that a CRN is called a **cycle terminal** if $t_p = 0$, and it is called a **point terminal** if $t_c = 0$. If both t_p and t_c are positive, then the CRN is a **point-and-cycle terminal** network. Since there are no terminal points, it follows that from Running

Example 1, the given CRN is cycle terminal.

On the other hand, the **stoichiometric subspace**, denoted by S , of a CRN is the vector space generated by its reaction vectors. The **deficiency** of the CRN, denoted by δ , determines the linear independence of the reactions in a CRN. It is defined as follows:

Definition 1. The deficiency of a CRN is the integer $\delta = n - l - s$.

We list some symbols discussed in this section and provide the reaction network numbers for the Running Example. See Table 1.

Table 1. List of Symbols, their Descriptions, and Reaction Network Numbers for Running Example 1

Symbol	Description	Running Example 1
m	Cardinality of the species set	2
n	Cardinality of the complex set	3
r	Cardinality of the reaction set	4
l	Number of linkage classes	1
sl	Number of strong linkage classes	1
t	Number of terminal strong linkage classes	1
t_p	Number of terminal points	0
t_c	Number of cycles	1
s	Rank of the CRN	1
δ	Deficiency of the CRN	1

2.2 Important classes of chemical kinetic systems

A **chemical kinetic system** (CKS), denoted by (\mathcal{N}, K) , is a dynamical system consisting of a CRN \mathcal{N} together with its kinetics K . A **kinetics** K for a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ associates to each reaction $j \in \mathcal{R}$ a mapping $K_j : \mathbb{R}_{\geq 0}^m \rightarrow \mathbb{R}_{\geq 0}$, such that $K_j(c) > 0$ if and only if $\text{supp } y$ is contained in $\text{supp } c$ (positivity condition). In this study, we will focus on an important subclass of power law kinetics system. First, power law kinetics is formally defined as follows:

Definition 2. [22]. A kinetics K is a power law kinetics if

$$K_i(x) = k_i \prod_{j=1}^r x^{F_{ij}} \quad \forall i \in \overline{1, r} \text{ with } k_i, F_{ij} \in \mathbb{R}_+.$$

It is associated to an $r \times m$ matrix $F = [F_{ij}]$, called the kinetic order matrix, and a vector $k \in \mathbb{R}^r$, called the rate vector.

In particular, in a MAK system, the kinetic orders in the kinetic order matrix F are simply the stoichiometric coefficients of the reactant complexes. From Running Example 1, the kinetic order matrix is $F = \begin{bmatrix} 2 & 0 \\ 1 & 1 \\ 1 & 1 \\ 0 & 2 \end{bmatrix}$

and the rate vector is $K(x) = \begin{bmatrix} k_1 A^2 \\ k_2 AB \\ k_3 AB \\ k_4 B^2 \end{bmatrix} = \begin{bmatrix} A^2 \\ 2AB \\ 2AB \\ B^2 \end{bmatrix}$.

The dynamical system of a PLK system is written as

$$dx/dt = f(x) = N \cdot K(x).$$

A zero of f is called an **equilibrium point** or the steady state of the kinetic system. The definitions of the sets of positive steady states and complex balanced steady states are stated as follows:

Definition 3. [22]. The **set of positive equilibria**, denoted by $E_+(\mathcal{N}, K)$, is defined as

$$E_+(\mathcal{N}, K) = \{x \in \mathbb{R}_+^m | f(x) = 0\}.$$

Definition 4. [22]. A positive vector c in \mathbb{R}^m is called complex balanced (CB) if $K(c)$ is contained in $\ker I_a$. The **set of complex balanced equilibria**, denoted by $Z_+(\mathcal{N}, K)$, is defined as

$$Z_+(\mathcal{N}, K) = \{x \in \mathbb{R}_+^m | I_a \cdot K(x) = 0\} \subseteq E_+(\mathcal{N}, K).$$

From Running Example 1, the set of positive steady states and the set of complex balanced equilibria are given by

$$\begin{aligned} E_+(\mathcal{N}, K) &= -k_1 A^2 + k_2 AB - k_3 AB + k_4 B^2 = 0 \\ Z_+(\mathcal{N}, K) &= \begin{cases} -k_1 A^2 + k_2 AB = 0 \\ k_1 A^2 - k_2 AB - k_3 AB + k_4 B^2 = 0 \\ k_3 AB - k_4 B^2 = 0 \end{cases} \quad (1) \end{aligned}$$

From Definitions 3 and 4, we are now ready to define the main topic of our study, that is, absolutely complex balanced systems.

Definition 5. [20]. A complex balanced system (\mathcal{N}, K) is said to be absolutely complex balanced (ACB) if every positive equilibrium is complex balanced, that is, $E_+(\mathcal{N}, K) = Z_+(\mathcal{N}, K)$.

$$\text{From Running Example 1, since } K(x) = \begin{bmatrix} k_1 A^2 \\ k_2 AB \\ k_3 AB \\ k_4 B^2 \end{bmatrix} = \begin{bmatrix} A^2 \\ 2AB \\ 2AB \\ B^2 \end{bmatrix},$$

$$E_+(\mathcal{N}, K) = -A^2 + 2AB - 2AB + B^2 = 0$$

$$Z_+(\mathcal{N}, K) = \begin{cases} -A^2 + 2AB = 0 \\ A^2 - 2AB - 2AB + B^2 = 0 \\ 2AB - B^2 = 0 \end{cases} \quad (2)$$

Observe that $\begin{bmatrix} 1 \\ 1 \end{bmatrix} \in E_+(\mathcal{N}, K)$ but $\begin{bmatrix} 1 \\ 1 \end{bmatrix} \notin Z_+(\mathcal{N}, K)$. Hence, by definition 5, Running Example 1 is a non-ACB system.

Now, to determine when a MAK system is complex balanced, the following proposition about the existence of complex balanced steady states is important to this study.

Proposition 1. [17, 22]. *If $Z_+(\mathcal{N}, K) \neq \emptyset$, then \mathcal{N} is weakly reversible.*

On the other hand, we need to understand the concept of PL-TIK systems and combine its results with those of this paper. First, a PLK system is a PL-RDK system if for any two reactions i, j with identical reactant complexes, the corresponding rows of kinetic orders in F are identical, i.e., $f_{ik} = f_{jk}$ for $k = 1, \dots, m$.

The T -matrix is a matrix consisting of the columns from the \tilde{Y} -matrix where the non-reactant columns are deleted, and the \tilde{Y} -matrix is given by

$$(\tilde{Y})_{ij} = \begin{cases} (F)_{ki}, & \text{if } j \text{ is a reactant complex of reaction } k \\ 0, & \text{otherwise.} \end{cases}$$

On the other hand, a \hat{T} -matrix is a matrix of the form $\hat{T} = \begin{bmatrix} T \\ L^T \end{bmatrix}$, where $L = [e^1, \dots, e^l]$ and $e^1, \dots, e^l \in \{0, 1\}^n$. So, a PL-TIK system is a PL-RDK system such that the \hat{T} -matrix is column-rank maximal.

Remark. PL-TIK systems are PLK systems whose reactions with the same reactant complexes have the same kinetic order vectors (called interactions), which are linearly independent per linkage class [23].

In addition, if $\hat{q} = \text{rank}(\hat{T})$, then the kinetic reactant deficiency $\hat{\delta}$ is defined as $\hat{\delta} = n_r - \hat{q}$. Alternatively, $\hat{\delta} = \dim \ker(\hat{T})$ [23]. Talabis et al. [23] showed that a PL-TIK system is exactly the zero kinetic reactant deficiency system, as stated in the proposition below.

Proposition 2. *(\mathcal{N}, K) is a PL-TIK system if and only if $\hat{\delta} = 0$.*

The following is an alternative characterization of a PL-TIK system, which clearly showed that a PL-TIK system has a decomposition such that every subnetwork is also PL-TIK.

Proposition 3. [22]. *Let K be a PL-TIK system. Then,*

1. $\dim(\ker(\hat{T})) = 0$; and
2. $\text{Im } \hat{T} = \text{Im } \hat{T}^1 \oplus \text{Im } \hat{T}^2 \oplus \dots \oplus \text{Im } \hat{T}^l$.

For a weakly reversible PL-TIK system, Talabis et al. [23] proposed the Zero Kinetic Reactant Deficiency Theorem (ZKRDT), which established the nonemptiness of the set of complex balanced equilibria.

Theorem 4. *(Zero Kinetic Reactant Deficiency Theorem (ZKRDT)) [23]. Let K be a PL-RDK kinetics with T -matrix T on \mathcal{N} and $\hat{\delta} = 0$. Then \mathcal{N} is weakly reversible if and only if $Z_+(\mathcal{N}, K) \neq \emptyset$.*

2.3 Deficiency theorems for MAK systems

Boros [3] established a different perspective to compute a network deficiency by introducing the augmented matrix of complexes \hat{Y} , which is given by $\hat{Y} = \begin{bmatrix} Y \\ L^T \end{bmatrix}$.

Using this notion, he proposed that a network deficiency can be reformulated as follows:

Proposition 5. [3]. $\delta = \dim \ker \hat{Y}$ and $\ker \hat{Y} = \ker Y \cap \text{Im } I_a$.

Proposition 5 implies that a network deficiency is simply the number of linearly dependent column vectors in the augmented matrix of complexes. This is used in this study to relate to the kinetic reactant deficiency of a PL-TIK system under the MAK assumption, which we call a MA-TIK system. Moreover, the network deficiency per linkage class can be reformulated as follows:

Proposition 6. [3]. $\delta_i = \dim \ker \hat{Y}_i$.

As far as deficiency theorems are concerned, the well-known DZT and DOT were among the first results in CRNT [9].

In 1972, three results on ACB systems were considered foundational [20]:

- 1) Feinberg showed that, regardless of their kinetics, complex balanced, deficiency-zero systems are ACB systems.
- 2) Horn showed that a weakly reversible, deficiency-zero MAK system is an ACB system; and
- 3) Horn and Jackson [18] showed that, regardless of the network deficiency, complex balanced MAK systems are ACB systems.

2.4 Network decomposition theory

In this subsection, we listed important network decomposition classes of a CRN. For a detailed discussion of these decomposition classes, the readers can refer to [24]. Furthermore, we will enumerate some important graph-theoretic results related to this study.

If $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is a CRN, then a covering of \mathcal{N} is a set of subsets of \mathcal{R}_i whose union is \mathcal{R} and a covering is called a decomposition of \mathcal{N} if the sets \mathcal{R}_i form a partition of \mathcal{R} . A subnetwork \mathcal{N}_i of \mathcal{N} is defined by \mathcal{R}_i , that is, the set \mathcal{C}_i consisting of all complexes in \mathcal{R}_i and the set \mathcal{S}_i consisting of all species in \mathcal{C}_i . The simplest decomposition class is the linkage class decomposition. In this decomposition class, the subnetworks of the given CRN are its linkage classes.

A decomposition is independent if and only if S is the direct sum of the subnetworks' stoichiometric subspaces S_i or equivalently, $s = s_1 + \dots + s_k$. Feinberg [9] developed the first result in Network Decomposition

Theory, that is, the well-known Feinberg Decomposition Theorem. This showed that if the network decomposition is independent, then the set of positive equilibria is equal to the finite intersection of the subnetwork's set of positive equilibria.

A decomposition $\mathcal{N} = \mathcal{N}_1 \cup \dots \cup \mathcal{N}_k$ is incidence-independent if and only if the image of the incidence map of \mathcal{N} is the direct sum of the images of the incidence maps of \mathcal{N}_i 's, or equivalently, $n - l = \sum_{i=1}^k (n_i - l_i)$. For an incidence-independent decomposition, Horn [17] showed that a weakly reversible parent network implies a weakly reversible decomposition (i.e., the subnetworks are weakly reversible). Analogous to the Feinberg Decomposition Theorem, Farinas et al. [8] showed that the set of complex balanced equilibria is equal to the finite intersection of the subnetwork's set of complex balanced equilibria if the network decomposition is incidence-independent.

A decomposition $\mathcal{N} = \mathcal{N}_1 \cup \dots \cup \mathcal{N}_k$ with $\mathcal{N}_i = (\mathcal{S}_i, \mathcal{C}_i, \mathcal{R}_i)$ is a \mathcal{C} -decomposition if $\mathcal{C}_i \cap \mathcal{C}_j = \emptyset$ for $i \neq j$. Note that a linkage class decomposition is also \mathcal{C} -decomposition. A striking property of \mathcal{C} -decomposition is cycle terminal-preserving, that is, given a \mathcal{C} -decomposition, the decomposition is cycle terminal if and only if \mathcal{N} is cycle terminal [8].

Farinas et al. [8] showed that any \mathcal{C} -decomposition is incidence-independent, and in terms of the set of complex balanced equilibria, they obtained the following result.

Theorem 7. . *Let $\mathcal{N} = \mathcal{N}_1 \cup \mathcal{N}_2 \cup \dots \cup \mathcal{N}_k$ be a weakly reversible \mathcal{C} -decomposition of a chemical kinetic system (\mathcal{N}, K) . If $Z_+(\mathcal{N}_i, K_i) \neq \emptyset$ for each subnetwork, then $Z_+(\mathcal{N}, K) \neq \emptyset$.*

Lastly, a deficiency-based decomposition is also introduced in [8]. A decomposition is a zero deficiency decomposition (*ZDD*) if each subnetwork in the decomposition has zero deficiency. In this study, we will show the importance of this decomposition class to determine the existence of ACB systems under the mass action assumption.

3 Results and discussion

3.1 PL-TIK decomposition of MAK systems

In this subsection, we define MA-TIK and MA-NTIK systems and their relevance to the relationship between a network deficiency and a kinetic reactant deficiency. At the end of the subsection, we introduce the concept of PL-TIK decomposition, which can be applied to MAK systems.

Definition 6. A MAK system with a \hat{T} -matrix that is column-rank maximal is called mass action, \hat{T} -independent kinetic system, or MA-TIK system. On the other hand, if the associated \hat{T} -matrix is not column-rank maximal, we call it a mass action, non- \hat{T} -independent kinetic system, or MA-NTIK system.

Remark. It can be deduced from the definition of a PL-TIK system that under MAK assumption, a weakly reversible network implies $\dim \ker \hat{Y} = \dim \ker \hat{T}$. Thus, it follows from Proposition 5 that a weakly reversible, deficiency-zero MAK system is PL-TIK. Also, it follows from Proposition 6 that for each linkage class \mathcal{L}_i , $0 = \delta_i = \hat{\delta}_i$. Additionally, $\delta > 0$ indicates that the system is non-PL-TIK.

Remark. From Remark 3.1, it follows from Definition 6 that any weakly reversible, zero deficiency MAK system is MA-TIK. Also, each of its linkage classes is MA-TIK. Furthermore, $\delta > 0$ implies that the system is MA-NTIK.

Remark. In general, any zero deficiency MAK system is MA-TIK. Since Boros [3] established \hat{Y} such that $\dim \text{Im } \hat{Y} = n \geq n_r = \dim \text{Im } \hat{T}$, it follows from Proposition 5 that $0 = \delta = \dim \ker \hat{Y} \geq \dim \ker \hat{T} = \hat{\delta}$ implies $\hat{\delta} = 0$. In other words, if the set of n columns in \hat{Y} is linearly independent, it must be the case that the set of n_r columns in \hat{T} is also linearly independent.

Tiongson et al. [24] introduced the notion of a PL-TIK decomposition of any power law kinetic system. A PL-TIK decomposition is a kinetics-based decomposition class where, for each subnetwork, the column vectors of each induced matrix \hat{T}_i are partitioned based on the kinetic orders of

\hat{T} . By investigating the equilibria properties of MA-TIK and MA-NTIK systems via their PL-TIK decomposition, we formalize the concept of a PL-TIK decomposition.

Definition 7. [24] A decomposition $\mathcal{N} = \mathcal{N}_1 \cup \dots \cup \mathcal{N}_k$ of a PLK system is called a PL-TIK decomposition if and only if each subnetwork \mathcal{N}_i has an associated column-rank maximal \hat{T}_i -matrix, or equivalently, $\hat{\delta}_i = 0$. Otherwise, the decomposition is said to be non-PL-TIK.

Remark. We can also refer to a PL-TIK decomposition as a Zero Kinetic Reactant Deficiency Decomposition (ZKRDD), as an analogous decomposition class to Zero Deficiency Decomposition (ZDD) introduced in [8]. Moreover, a non-PL-TIK decomposition is non-ZKRDD.

Given below is a result in [24] regarding the decomposition of a PL-TIK system. We modified the previous version of the proof to avoid ambiguity in the notations used.

Proposition 8. *Every decomposition of a PL-TIK system is also PL-TIK.*

Proof. Since (\mathcal{N}, K) is PL-TIK, it follows from Proposition 3 that

$$\text{Im } \hat{T} = \text{Im } \hat{T}^1 \oplus \text{Im } \hat{T}^2 \oplus \dots \oplus \text{Im } \hat{T}^l$$

Since an element of $\text{Im } \hat{T}$ can be expressed uniquely as a linear combination of elements of $\text{Im } \hat{T}^1, \text{Im } \hat{T}^2, \dots, \text{Im } \hat{T}^l$, it follows that it can also be expressed as a linear combination of the elements of $\text{Im } \hat{T}_{n_1}, \text{Im } \hat{T}_{n_2}, \dots, \text{Im } \hat{T}_{n_r}$.

From Remark 2.2, a PL-TIK system is a PLK system whose reactions with the same reactant complexes have the same corresponding columns of kinetic orders of \hat{T} , which are linearly independent per linkage class. If $\mathcal{N} = \mathcal{N}_1 \cup \mathcal{N}_2 \cup \dots \cup \mathcal{N}_k$ is a decomposition of (\mathcal{N}, K) , we will consider two cases here:

- i. If the two reactions r_i, r_j with the same reactant complex, say y , are in the same subnetwork, then

$$\text{Im } \hat{T} = \text{Im } \hat{T}_{n_r,1} \oplus \text{Im } \hat{T}_{n_r,2} \oplus \dots \oplus \text{Im } \hat{T}_{n_r,k}$$

where $\text{Im } \hat{T}_{n_{r,i}}$ is the image of \hat{T} generated by the reactant complexes of the i^{th} -subnetwork. Hence, $\hat{q} = \hat{q}_1 + \dots + \hat{q}_k$ and $n_r = \sum_{i=1}^k n_{r,i}$. It follows that

$$0 = n_r - \hat{q} = \sum_{i=1}^k n_{r,i} - \sum_{i=1}^k \hat{q}_i = \sum_{i=1}^k (n_{r,i} - \hat{q}_i).$$

Thus, $n_{r,i} - \hat{q}_i = 0$ for each subnetwork. Therefore, the decomposition is PL-TIK.

- ii. If the two reactions r_i, r_j with the same reactant complex y are not in the same subnetwork, it follows from Remark 2.2 that the columns of \hat{T} generated by y are identical and are also linearly independent to the other columns in \hat{T}_i and \hat{T}_j , respectively. Therefore, the columns of \hat{T}_i for each subnetwork \mathcal{N}_i are linearly independent per linkage class, that is, the decomposition is PL-TIK. ■

The following result follows from the fact that a MA-TIK system is also PL-TIK.

Corollary. *The \mathcal{C} -decomposition, linkage class decomposition, independent decomposition, incidence-independent decomposition, and zero deficiency decomposition of a MA-TIK system are also PL-TIK.*

Proof. This is a direct consequence of Proposition 8 and Definition 6. ■

Remark. From the above corollary, in a MA-TIK system, ZDD coincides with its PL-TIK decomposition. Hence, to characterize the existence of $E_+(\mathcal{N}_i, K_i)$, we can apply Theorem 4 or DZT.

3.2 PL-TIK decomposition of MA-NTIK systems

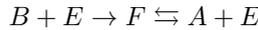
The next class of PL-RDK systems, where we applied the PL-TIK decomposition, is the counterpart of MA-TIK systems, called MA-NTIK systems. Unlike MA-TIK systems, only the linkage class decomposition and zero deficiency decomposition will ensure the existence of PL-TIK decomposition in MA-NTIK systems. In relation to this, we give examples that will show

that the other surveyed decomposition classes do not guarantee a PL-TIK decomposition.

Proposition 9. *Let (\mathcal{N}, K) be a non-zero deficiency MA-NTIK system. If $\mathcal{N} = \mathcal{N}_1 \cup \mathcal{N}_2 \cup \dots \cup \mathcal{N}_k$ is ZDD, then the decomposition is PL-TIK.*

Proof. Since the decomposition is ZDD, it follows directly from Remark 3.1 that each subnetwork is PL-TIK. Therefore, the decomposition is PL-TIK. ■

Example 2. Reidl et al. in [21] carefully studied the model of olfactory cilia dynamics. Using this model, we will show that the other decomposition classes of a non-zero deficiency MA-NTIK system are non-PL-TIK. The CRN representation of the said model was cited from the supplementary material of Talabis et al. in [22].



Note that $\delta = 10 - 4 - 4 = 2 > 0$, and so it is a non-zero deficiency MAK system. Under MAK assumption, the associated \hat{T} -matrix is

$$\hat{T} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}.$$

Observe that

$$\begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

It follows that the \hat{T} -matrix is not column-rank maximal, that is, (\mathcal{N}, K) is a non-zero deficiency MA-NTIK system.

Now, for an independent decomposition, consider this decomposition.

$$\mathcal{N}_1 : A \rightleftharpoons B \quad B + E \rightarrow F \rightleftharpoons A + E$$

$$\mathcal{N}_2 : B \rightarrow B + D \quad C + 4D \rightleftharpoons E \quad D \rightarrow 0$$

For \mathcal{N}_1 , $s_1 = 2$ since $S = \text{span} \{F - B - E, F - A - E\}$. Also, $s_2 = 2$ since $S = \text{span} \{D, E - C - 4D\}$. Note that $s = 4$. So, $s = 4 = 2 + 2 = s_1 + s_2$ and thus, the decomposition is independent. However for \mathcal{N}_1 , the associated \hat{T} -matrix under MAK assumption is given by

$$\hat{T} = \begin{bmatrix} 1 & 0 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Since

$$\begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix},$$

it follows that \mathcal{N}_1 is non-PL-TIK and thus, we have a non-PL-TIK decomposition.

Remark. Observe that the independent decomposition above is coincidentally an incidence-independent decomposition as well. Moreover, we have a similar result for \mathcal{C} -decomposition since it is also incidence-independent.

3.3 Zero deficiency decomposition algorithm

In any MAK system, zero deficiency decomposition is guaranteed, as presented in the main result below.

Theorem 10. *Let (\mathcal{N}, K) be a MAK system. Then there exists a zero deficiency decomposition (ZDD) $\mathcal{N}_1 \cup \mathcal{N}_2 \cup \dots \cup \mathcal{N}_k$ in \mathcal{N} .*

Proof. Let (\mathcal{N}, K) be a MAK system. Consider the given algorithm below, which we will call the Zero Deficiency Decomposition Algorithm.

Given a MAK system (\mathcal{N}, K) , get its matrix of complexes Y .

Step 1. Form the associated \hat{Y} -matrix by augmenting the column vectors c_1, c_2, \dots, c_n . Denote the augmented column vectors by $\hat{c}_1, \hat{c}_2, \dots, \hat{c}_n$.

Step 2. If $\hat{c}_1, \hat{c}_2, \dots, \hat{c}_n$ are linearly independent, then we are done. Otherwise, isolate from this set the first \hat{c}_j , which is a linear combination of its predecessors $\hat{c}_1, \hat{c}_2, \dots, \hat{c}_{j-1}$, and collect the reactions associated with these vectors to form \mathcal{N}_1 .

Step 3. If the remaining column vectors $\hat{c}_j, \hat{c}_{j+1}, \dots, \hat{c}_n$ are linearly independent, then collect the reactions associated with these vectors to form \mathcal{N}_2 and we are done. Otherwise, isolate from this set the second linearly dependent column vector $\hat{c}_m, j < m \leq n$, and collect the reactions formed by the predecessors $\hat{c}_j, \hat{c}_{j+1}, \dots, \hat{c}_{m-1}$ to form \mathcal{N}_2 .

Step 4. Continue the isolation process on the remaining column vectors until there is no column vector that is a linear combination of its predecessors. The subnetworks that were formed will comprise a zero deficiency decomposition for the given MAK system.

Note that if we suppose the augmented column vectors $\hat{c}_1, \hat{c}_2, \dots, \hat{c}_n$ as a set of vectors, then the last three steps of the algorithm are a direct consequence of the steps adapted in [16], to ensure a linearly independent set of column vectors for each subnetwork. By Proposition 5, each subnetwork implies $\delta_i = 0$. Therefore, for any MAK system, we can obtain a Zero Deficiency Decomposition from the above algorithm. ■

Example 3. By applying the ZDD algorithm, we have the following steps to obtain the corresponding zero deficiency decomposition of the MAK system induced by the Olfactory Cilia Dynamics model.

$$Y = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \end{bmatrix}.$$

Step 1. The associated \hat{Y} -matrix is given by

$$\hat{Y} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 4 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 1 & 1 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}.$$

Step 2. From Example 2, note that

$$(\hat{c}_1) \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} + (\hat{c}_5) \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix} - (\hat{c}_2) \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix} = (\hat{c}_7) \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}.$$

Thus, $\mathcal{N}_1 = \{\hat{c}_1, \hat{c}_2, \hat{c}_3, \hat{c}_4, \hat{c}_5, \hat{c}_6\}$.

Step 3. Hence, the remaining column vectors will comprise the second subnetwork, that is, $\mathcal{N}_2 = \{\hat{c}_7, \hat{c}_8\}$.

Step 4. Therefore, the ZDD of the above model is given by

$$\mathcal{N}_1 : A \rightleftharpoons B \rightarrow B + D \quad C + 4D \rightleftharpoons E \quad B + E \rightarrow F \rightarrow A + E$$

$$\mathcal{N}_2 : A + E \rightarrow F \quad D \rightarrow 0$$

3.4 Positive equilibria of MAK systems via zero deficiency decomposition

In this subsection, we discuss the characterization of the set of positive equilibria of MAK systems via zero deficiency decomposition, that is, the nonemptiness of $E_+(\mathcal{N}, K)$ for both MA-TIK and MA-NTIK systems.

Since any decomposition of a PL-TIK is also PL-TIK (Proposition 8), the following proposition appears to be a special case of ZKRDT established by Talabis et al. [19].

Proposition 11. *Let (\mathcal{N}, K) be a MA-TIK system. Let $\mathcal{N} = \mathcal{N}_1 \cup \mathcal{N}_2 \cup \dots \cup \mathcal{N}_k$ be any decomposition.*

1. *If $\delta = 0$, then $Z_+(\mathcal{N}, K) \neq \emptyset$ if and only if (\mathcal{N}, K) has a weakly reversible decomposition.*
2. *If $\delta > 0$, then $Z_+(\mathcal{N}, K) = \emptyset$.*

Proof. Let $\mathcal{N} = \mathcal{N}_1 \cup \mathcal{N}_2 \cup \cdots \cup \mathcal{N}_k$ be any decomposition.

1. Suppose $\delta = 0$. It follows from Remark 3.1 that (\mathcal{N}, K) is MA-TIK, and so, its decomposition is PL-TIK from Corollary 3.1. Hence, the conclusion follows from ZKRDT since a weakly reversible decomposition implies a weakly reversible parent network.
2. Suppose $\delta > 0$. From Corollary 3.1, it follows that any decomposition of a MA-TIK system is PL-TIK. Now, from Remark 3.1, a weakly reversible, non-zero deficiency MAK system is MA-NTIK. Thus, it follows that a non-zero deficiency MA-TIK system is necessarily non-weakly reversible. Therefore, from ZKRDT, $Z_+(\mathcal{N}, K) = \emptyset$. ■

Remark. In relation to the work of Horn and Jackson [18], in terms of MA-TIK systems, the above proposition shows that only weakly reversible, zero deficiency MAK systems are ACB systems.

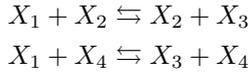
The main result in this subsection is an extension of ZKRDT, since it also covers non-PL-TIK systems, that is, MA-NTIK systems. The result is mainly applied to non-zero deficiency MA-NTIK systems.

Theorem 12. *Let (\mathcal{N}, K) be a non-zero deficiency MA-NTIK system. Let $\mathcal{N} = \mathcal{N}_1 \cup \mathcal{N}_2 \cup \cdots \cup \mathcal{N}_k$ be a zero deficiency, \mathcal{C} -decomposition. Then, $Z_+(\mathcal{N}, K) \neq \emptyset$ if and only if the decomposition is weakly reversible.*

Proof. From Proposition 9, ZDD implies PL-TIK decomposition. Suppose $Z_+(\mathcal{N}, K) \neq \emptyset$. It follows from Proposition 1 that the underlying network is weakly reversible. Thus, the PL-TIK decomposition is also weakly reversible. Suppose the decomposition is weakly reversible. Since the decomposition is PL-TIK, it follows from ZKRDT that $Z_+(\mathcal{N}_i, K_i) \neq \emptyset$. Thus, it follows from Theorem 7 that $Z_+(\mathcal{N}, K) \neq \emptyset$. ■

Remark. The main result above states that a weakly reversible, non-zero deficiency MA-NTIK system with zero deficiency \mathcal{C} -decomposition is an absolutely complex balanced (ACB) system.

Example 4. To illustrate Theorem 12, consider this deficiency-one MAK system below. Feinberg utilized this network in [11], and Boros cited this particular CRN in his PhD dissertation [3].



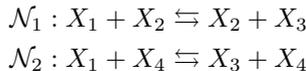
Note that $\delta = 4 - 2 - 1 = 1 > 0$, and so, it is a non-zero deficiency MAK system. Under MAK assumption, the associated \hat{T} -matrix is

$$\hat{T} = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 1 & 1 & 0 & 0 \\ 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 \\ 1 & 1 & 0 & 0 \\ 0 & 0 & 1 & 1 \end{bmatrix}.$$

Observe that

$$\begin{bmatrix} 0 \\ 1 \\ 1 \\ 0 \\ 1 \\ 0 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \\ 1 \\ 0 \\ 1 \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 1 \end{bmatrix} = \begin{bmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix}.$$

It follows that the \hat{T} -matrix is not column-rank maximal; that is, (\mathcal{N}, K) is a nondeficiency-zero MA-NTIK system. Now, consider its linkage class decomposition (and hence, a \mathcal{C} -decomposition) given below.

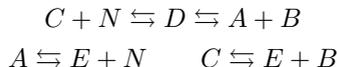


Observe that each subnetwork is weakly reversible and has zero deficiency. Hence, the network has a weakly reversible and deficiency-zero \mathcal{C} -decomposition. It follows from Remark 3.4 that the CRN under MAK assumption is an ACB system.

3.5 Application to human dihydrofolate reductase (DHFR) catalysis

To end this section, we applied our results to the mechanism for Human Dihydrofolate Reductase (DHFR) catalysis. In the paper “Understanding bistability in complex enzyme-driven reaction networks”, Craciun et al. (2006) explained the mechanism underlying the operation of a classical

anti-cancer target (the enzyme Dihydrofolate Reductase (DHFR)) through the three groups of reaction in this catalytic process [6]. Among the three groups of reactions, we chose the second group of reactions which showed the unbinding of the products from the enzyme. In his book “Foundations of Chemical Reaction Network Theory” [10], Feinberg cited the corresponding reaction network of the second group of reactions, which we simplified below.



where E is the enzyme DHFR, N is NADP^+ (the oxidized form of nicotinamide adenine dinucleotide phosphate (NADP)), A is the product of E and N , B is H4F (tetrahydrofolate), C is the product of E and B , and D is the product of E , N , and B .

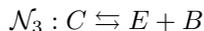
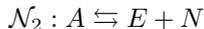
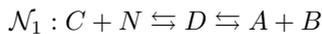
Note that $\delta = 7 - 3 - 3 = 1 > 0$, and so, it is a non-zero deficiency MAK system. Under MAK assumption, the associated \hat{T} -matrix is

$$\hat{T} = \begin{bmatrix} 0 & 0 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 1 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 1 \end{bmatrix}.$$

Observe that

$$\begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ 0 \end{bmatrix} - \begin{bmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix} - \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{bmatrix}.$$

It follows that the \hat{T} -matrix is not column-rank maximal; that is, (\mathcal{N}, K) is a non-zero deficiency MA-NTIK system. Now, consider its linkage class decomposition (and hence, a \mathcal{C} -decomposition) given below.



Observe that each subnetwork is weakly reversible and has zero deficiency. Hence, the network has a weakly reversible and deficiency-zero \mathcal{C} -decomposition. It follows from Remark 3.4 that, under MAK assumption, the Human DHFR catalysis model is an ACB system.

4 Conclusion and outlook

The results of this paper, as well as some research problems for recommendations, are summarized as follows:

1. We introduced the concept of MA-TIK and MA-NTIK systems for MAK systems. We plan to extend their properties, that is, their capacity for multi-stationarity via zero deficiency decomposition.
2. We developed an algorithm that obtains a zero deficiency decomposition from any MAK system and applied it to the Olfactory Cilia Dynamics. We also plan to improve the algorithm to generate a weakly reversible decomposition.
3. We proposed and proved our main result, which involves the characterization of a Mass Action system as an ACB system via zero deficiency, \mathcal{C} -decomposition. In addition, we applied this result to the Human DHFR catalysis model and showed that it is an ACB system. We plan to modify this result (that is, by requiring zero deficiency decomposition only and discarding the \mathcal{C} -decomposition criterion) to emphasize the importance of the algorithm given above.

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