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Absolute Concentration Robustness in Power Law Kinetic Systems

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Abstract

Absolute concentration robustness (ACR) is a condition wherein a species in a chemical kinetic system possesses the same value for any positive steady state the network may admit regardless of initial conditions. Thus far, results on ACR center on chemical kinetic systems with deficiency one. In this contribution, we use the idea of dynamic equivalence of chemical reaction networks to derive novel results that guarantee ACR for some classes of power law kinetic systems with deficiency zero. Furthermore, using network decomposition, we identify ACR in higher deficiency networks (i.e. deficiency ≥ 2) by considering the presence of a low deficiency subnetwork with ACR. Network decomposition also enabled us to recognize and define a weaker form of concentration robustness than ACR, which we named as 'balanced concentration robustness'. Finally, we discuss and emphasize our view of ACR as a primarily kinetic character rather than a condition that arises from structural sources.

1 Introduction

A network is said to exhibit robustness if it maintains its function despite changes in environmental or structural conditions [20, 21]. As it is required for homeostasis and

adaptive responses to environmental disruptions, robustness becomes fundamental and ubiquitous in many biological processes [3, 4, 20, 25]. A class of robust behavior known as "concentration robustness" concerns the invariance of some quantity involving the concentrations of the different species in a network for any steady state [7].

Of particular interest is the concentration robustness property called *absolute concentration robustness* (ACR), which was first introduced by Shinar and Feinberg in their influential paper published in *Science* [25]. A system possesses this feature if it admits at least one positive steady state and the concentration of a particular species in the system has the same value in every positive steady state set by parameters. The work of Shinar and Feinberg centered on a mathematical theorem that specifies a large class of mass action systems that are absolute concentration robust. Interestingly, this theorem provides sufficient conditions that are apparently structural in nature.

Specifically, they stated their by means of a structural index called the *deficiency* (denoted by δ) of a network, which measures the amount of 'linear independence' among the reactions of the network [26]. The theorem is stated as follows: Consider a mass action system that admits a positive steady state. Suppose that (i) the deficiency of the network is one, and (ii) there are nonterminal complexes which differ only in the species X. Then the system has ACR in species X.

In our previous work [14], we showed that this result easily extends to kinetic systems more general than mass action systems, namely *power law kinetic systems with reactant-determined interactions* (denoted by "PL-RDK"). For PL-RDK systems, the kinetic order vectors of reactions with the same reactant complexes are identical. The *Shinar-Feinberg Theorem on ACR for PL-RDK systems* retains the deficiency one condition but replaces the last criterion by considering the kinetic order differences of the species. Our result specifies that under the same deficiency one assumption, and the criterion that there are nonterminal complexes whose kinetic order of its species differ only in X, the PL-RDK system that admits a positive equilibrium exhibits ACR in X.

In this contribution, we explore ACR as a dynamical property that is conserved under *dynamic equivalence*. Two different chemical reaction networks with the same set of kinetics are dynamically equivalent if they generate the same set of ordinary differential equations. This approach has led us to derive novel results on ACR for deficiency zero PL-RDK systems and for a class of power law kinetic systems that are non-PL-RDK

(denoted as "PL-NDK").

In addition to dynamic equivalence, this contribution applies useful techniques in network decomposition to establish ACR. This is particularly relevant in detecting ACR in systems where the underlying chemical reaction networks have higher deficiency (i.e. $\delta \geq 2$). The concept of independent decompositions [11] has enabled us to identify ACR in larger networks through the presence of a low deficiency ($\delta \leq 1$) subnetwork with ACR as a "building block." The key argument used is a result of Feinberg (Remark 5.4, [11]) that relates independent decomposition with the set of positive equilibria of a system.

In an analogous approach, incidence independent decompositions of larger networks with low deficiency subnetwork exhibiting ACR are also investigated. This effort has led us to identify another type of concentration robustness that is weaker than ACR. We call this property as *balanced concentration robustness* (BCR). A system displays BCR in a species X if it has complex balanced steady states and the value of X is the same for any set of complex balanced steady states the system may admit. Using a theorem that relates incidence independent decompositions with the set of complex balanced equilibria of a system (Theorem 5), this work generates a new result that guarantees the presence of BCR for larger networks.

Finally, this work provides a discussion that emphasizes the primarily kinetic property of ACR. This perspective is a shift from our usual view that ACR, as a system property, is induced by "structural sources".

The rest of the paper is structured as follows. Section 2 reviews and assembles fundamental ideas and results in chemical reaction network theory (CRNT) that are relevant for later sections. Section 3 presents the ACR theorem for deficiency zero PL-RDK systems and for a class of PL-NDK systems. In Section 4, we employ decomposition theory to identify large classes of PLK systems, including such with higher deficiency, that possess ACR or BCR. Section 5 discusses our view that ACR is a primarily kinetic property of a chemical kinetic system. Section 6 summarizes our results and outlines perspectives for future work. Lastly, the discussion in Appendix provides the adaptation of the proof presented in [14] for deficiency zero PL-RDK networks.

2 Fundamentals of chemical reaction network theory

We review some basic notions involving chemical reaction networks. The reader may refer to [12, 29] for more details.

Notation: We denote the real numbers by $\mathbb{R}$, the non-negative real numbers by $\mathbb{R}_{\geq 0}$, and the positive real numbers by $\mathbb{R}_{>0}$. Suppose $\mathscr{I}$ is a finite index set. By $\mathbb{R}^{\mathscr{I}}$, we mean the usual vector space of real-valued functions with domain $\mathscr{I}$. For $x \in \mathbb{R}^{\mathscr{I}}$, the i^{th} coordinate of x is denoted by x_i, where $i \in \mathscr{I}$. The sets $\mathbb{R}^{\mathscr{I}}_{\geq 0}$ and $\mathbb{R}^{\mathscr{I}}_{>0}$ are called the *non-negative* and *positive orthants* of $\mathbb{R}^{\mathscr{I}}$, respectively. Addition, subtraction, and scalar multiplication in $\mathbb{R}^{\mathscr{I}}$are defined in the usual way. If $x \in \mathbb{R}^{\mathscr{I}}_{>0}$ and $y \in \mathbb{R}^{\mathscr{I}}$, we define $x^y \in \mathbb{R}_{>0}$ by $x^y = \prod_{i \in \mathscr{I}} x_i^{y_i}$. Finally, for integers a and b, let $\overline{a, b} = \{j \in \mathbb{Z} | a \leq j \leq b\}$.

A chemical reaction network (CRN) is a system of interdependent chemical reactions. Each reaction is represented as an ordered pair of vectors, called complexes, of chemical species.

Definition 1. A **chemical reaction network** (CRN) $\mathscr{N}$ is a triple $(\mathscr{S}, \mathscr{C}, \mathscr{R})$ of three finite sets: (1) a set $\mathscr{S} = \{X_1, X_2, \ldots, X_m\}$ of **species**, (2) a set $\mathscr{C} \subset \mathbb{R}^{\mathscr{S}}_{\geq 0}$ of **complexes**, consisting of nonnegative linear combinations of the species such that $\bigcup_{y \in \mathscr{C}} \operatorname{supp} y = \mathscr{S}$, and (3) a set $\mathscr{R} = \{R_1, R_2, \ldots, R_r\} \subset \mathscr{C} \times \mathscr{C}$ of **reactions** such that $(y, y) \notin \mathscr{R}$ for any $y \in \mathscr{C}$, and for each $y \in \mathscr{C}$, there exists $y' \in \mathscr{C}$ such that either $(y, y') \in \mathscr{R}$ or $(y', y) \in \mathscr{R}$. We denote the number of species with m, the number of complexes with n and the number of reactions with r.

We use the convention that an element $R_j = (y_j, y'_j) \in \mathscr{R}$ is denoted by $R_j : y_j \to y'_j$. In this reaction, we say that y_j is the **reactant** complex and y'_j is the **product** complex. Connected components of a CRN are called **linkage classes**, strongly connected components are called **strong linkage classes**, and strongly connected components without outgoing arrows are called **terminal strong linkage classes**. We denote the number of linkage classes with ℓ, that of the strong linkage classes with $s\ell$, and that of terminal strong linkage classes with t. A CRN is **weakly reversible** if every linkage class is a strong linkage class. A complex is called **terminal** if it belongs to a terminal strong linkage class; otherwise, the complex is called **nonterminal**.

With each reaction $y \to y'$, we associate a **reaction vector** obtained by subtracting

the reactant complex y from the product complex y'. The **stoichiometric subspace** S of a CRN is the linear subspace of $\mathbb{R}^{\mathscr{S}}$ defined by $S := \text{span}\,\{y' - y \in \mathbb{R}^{\mathscr{S}} | y \to y' \in \mathscr{R}\}$. The **rank** of the CRN is defined as $s := \dim S$. The **deficiency** of a CRN, denoted by δ, is the integer defined by $\delta = n - \ell - s$.

We recall four maps relevant in the study of CRNs: map of complexes, incidence map, stoichiometric map and Laplacian map.

Definition 2. Let $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a CRN. The **map of complexes** $Y : \mathbb{R}^{\mathscr{C}} \to \mathbb{R}^{\mathscr{S}}_{\geq 0}$ maps the basis vector ω_y to the complex $y \in \mathscr{C}$. The **incidence map** $I_a : \mathbb{R}^{\mathscr{R}} \to \mathbb{R}^{\mathscr{C}}$ is the linear map defined by mapping for each reaction $R_j : y_j \to y'_j \in \mathscr{R}$, the basis vector ω_j to the vector $\omega_{y'_j} - \omega_{y_j} \in \mathscr{C}$. The **stoichiometric map** $N : \mathbb{R}^{\mathscr{R}} \to \mathbb{R}^{\mathscr{S}}$ is defined as $N = Y \circ I_a$. For each $k \in \mathbb{R}^{\mathscr{R}}_{>0}$, the linear transformation $A_k : \mathbb{R}^{\mathscr{C}} \to \mathbb{R}^{\mathscr{C}}$ called **Laplacian map** is the mapping defined by $A_k x := \sum_{y \to y' \in \mathscr{R}} k_{y \to y'} x_y (\omega_{y'} - \omega_y)$, where x_y refers to the y^{th} component of $x \in \mathbb{R}^{\mathscr{C}}$ relative to the standard basis.

By *kinetics* of a CRN, we mean the assignment of a rate function to each reaction in the CRN. We shall denote a kinetics for a network $\mathscr{N}$ by K. The pair $(\mathscr{N}, K)$ denotes the chemical kinetic system. Specifically, this paper tackles its results in the context of power law kinetic systems. Here, power law kinetics is defined by an $r \times m$ matrix $F = [F_{ij}]$, called the **kinetic order matrix**, and vector $k \in \mathbb{R}^{\mathscr{R}}_{>0}$, called the **rate vector**.

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

$$K_i(x) = k_i x^{F_{i,\cdot}} \quad \text{for all } i \in \overline{1,r}.$$

with $k_i \in \mathbb{R}_{>0}$ and $F_{ij} \in \mathbb{R}$. A PLK system has **reactant-determined kinetics** (of type **PL-RDK**) if for any two reactions R_i, $R_j \in \mathscr{R}$ with identical reactant complexes, the corresponding rows of kinetic orders in F are identical, i.e. $F_{ih} = F_{jh}$ for $h \in \overline{1,m}$. Otherwise, a PLK system has **non-reactant-determined kinetics** (of type **PL-NDK**).

An example of PL-RDK is the well-known **mass action kinetics** (MAK), where $K_j(x) = k_j x^{Y_{\cdot,j}}$ for all reactions $R_j : y_j \to y'_j \in \mathscr{R}$ with $k_j \in \mathbb{R}_{>0}$, which are called rate constants. The vector $Y_{\cdot j}$ contains the stoichiometric coefficients of a reactant complex $y_j \in \mathscr{C}$.

Definition 4. The **species formation rate function** of a chemical kinetic system is the vector field

$$f(c) = NK(c) = \sum_{y_j \to y_j' \in \mathscr{R}} K_j(c)(y_j' - y_j), \text{ where } c \in \mathbb{R}^{\mathscr{S}}_{\geq 0}.$$

The equation $\mathrm{d}c/\mathrm{d}t = f(c(t))$ is the **ODE or dynamical system** of the chemical kinetic system. A **positive equilibrium or steady state** c^* is an element of $\mathbb{R}^{\mathscr{S}}_{>0}$ for which $f(c^*) = 0$. The set of positive equilibria of a chemical kinetic system is denoted by $E_+(\mathscr{N}, K)$.

Two distinct CRNs with the same set of kinetics may give rise to identical set of ordinary differential equations. Such systems are said to be **dynamically equivalent**. This idea had been tackled as early as 1970s. For instance, Horn and Jackson [18] studied dynamical equivalence (which they termed as *macro-equivalence)* for a class of weakly reversible MAK systems. An extensive study of the dynamical equivalence of MAK systems was done by Craciun and Pantea [6], with a supplementary note from Szederkényi [27].

The idea of dynamic equivalence is useful in understanding the qualitative behavior of chemical kinetic systems. If a kinetic system is found to be dynamically equivalent to another system that possesses desirable features about its dynamics (e.g., existence of positive steady state, capacity for multiple steady states, etc.) or network structure (e.g., weak reversibility, low deficiency, small number of linkage classes, mass conservation, etc.), then the dynamical property of the desirable system applies for the system that does not have the nice features. In this regard, the work of Craciun et al. [5], for instance, becomes helpful since it aims to find reaction networks (which they called *kinetic realizations*) inducing a given system of polynomial differential equations with as many good properties as possible.

Arceo et al. [2] identified two large sets of kinetic systems, namely the **complex factorizable** (CF) kinetics and its complement, the **non-complex factorizable** (NF) kinetics. Complex factorizable kinetics generalize the key structural property of MAK that the species formation rate function decomposes as $\mathrm{d}x/\mathrm{d}t = Y \circ A_k \circ \Psi_k$, where Y is the map of complexes, A_k is the Laplacian map, and $\Psi_k : \mathbb{R}^{\mathscr{S}}_{\geq 0} \to \mathbb{R}^{\mathscr{C}}_{\geq 0}$ such that $I_a \circ K(x) = A_k \circ \Psi_k(x)$ for all $x \in \mathbb{R}^{\mathscr{S}}_{\geq 0}$. In the set of power law kinetics, the complex-factorizable kinetic systems are precisely the PL-RDK systems.

The *complex formation rate function* is the analogue of the species formation rate

function for complexes.

Definition 5. The **complex formation rate function** $g : \mathbb{R}^{\mathscr{S}}_{>0} \to \mathbb{R}^{\mathscr{C}}$ of a chemical kinetic system is the given by

$$g(c) = I_a K(c) = \sum_{y_j \to y'_j \in \mathscr{R}} K_j(c)(\omega_{y'_j} - \omega_{y_j}),$$

where I_a is the incidence map.

Horn and Jackson [18] introduced the notion of *complex balancing* in chemical kinetics. A system is complex balanced at a composition $c \in \mathbb{R}^{\mathscr{S}}_{>0}$ if for each complex, formation and degradation are at equilibrium, i.e. when $g(c) = 0$. A chemical kinetic system $(\mathscr{N}, K)$ is called **complex balanced** if it has a complex balanced steady state. The set of positive complex balanced steady states of the system is denoted by $Z_+(\mathscr{N}, K)$. We recall the following well-known results related to existence of complex balanced equilibria:

Proposition 1 (Theorem 2B, Horn [17])**.** *If a chemical kinetic system has a complex balanced equilibrium, then the underlying CRN is weakly reversible.*

Proposition 2 (Corollary 4.8, Feinberg [10])**.** *If a chemical kinetic system has deficiency 0, then its steady states are all complex balanced.*

Finally, we recall some ideas about ACR in PL-RDK system.

Definition 6. A PL-RDK system $(\mathscr{N}, K)$ has **absolute concentration robustness** (ACR) 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 $c^{**}_X = c^*_X$.

Shinar and Feinberg [25] established simple sufficient conditions for an MAK system to exhibit ACR. In [14], it was shown that this result can be extended to deficiency one PL-RDK systems. The extension of the Shinar-Feinberg Theorem on ACR for PL-RDK systems is stated below.

Theorem 1 (Shinar-Feinberg Theorem on ACR for PL-RDK systems, [14])**.** *Let $(\mathscr{N}, K)$ be a deficiency one PL-RDK system which admits a positive equilibrium. If $y, y' \in \mathscr{C}$ are nonterminal complexes whose kinetic order vectors differ only in species X, then the system has ACR in X.*

To illustrate, we recall from [14] the following deficiency-one PL-RDK system representation for a power law approximation of the pre-industrial carbon cycle model of Anderies et al. [1]. We provide the CRN and its corresponding kinetic order matrix:

$$\begin{array}{c} A_1 + 2A_2 \xrightarrow{R_1} 2A_1 + A_2 \\ A_1 + A_2 \xrightarrow{R_2} 2A_2 \\ A_2 \underset{R_4}{\overset{R_3}{\rightleftarrows}} A_3 \end{array} \quad , \qquad F = \begin{array}{c} \\ R_1 \\ R_2 \\ R_3 \\ R_4 \end{array} \begin{array}{c} \begin{array}{ccc} A_1 & A_2 & A_3 \end{array} \\ \begin{bmatrix} p_1 & q_1 & 0 \\ p_2 & q_2 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \end{array}, \tag{2.1}$$

where $p_1 = p_2 = -68$ and $q_1 = 0.58$, and $q_2 = 0.91$. The uniqueness of a positive steady state (in a stoichiometric compatibility class) of the system can guaranteed by the Deficiency one algorithm for power-law systems [13] or the Multistationarity Algorithm for PLK systems of Hernandez et al. [16]. The conditions of the Shinar-Feinberg Theorem on ACR for PL-RDK systems are satisfied by a PL-RDK system where the kinetic order vectors of the nonterminal vertices $A_1 + 2A_2$ and $A_1 + A_2$ differ only in A_2. Hence, it exhibits ACR in A_2.

3 ACR in deficiency zero PL-RDK and minimally PL-NDK systems

For convenience, we introduce the following terminology to refer to a pair of reactions whose reactants' kinetic order vectors differ only in one species.

Definition 7. 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 subnetwork of the PLK system is of **SF-type** if it contains an SF-pair in X.

We present an ACR theorem for deficiency zero PL-RDK systems and for a class of deficiency zero PL-NDK systems. We denote the later as "minimally PL-NDK" because in terms of their NDK properties, they take minimal values: a single NDK node, two complex factorizable subsets (or CF-subsets) and in the special case of binary nodes, a single reaction in each CF-subset. For both PLK systems, the key property for ACR in a species X is the presence of an SF-reaction pair. We use the CF-RM$_+$ method introduced in [23] to show its dynamic equivalence with an appropriate deficiency one PL-RDK system.

Definition 8. A PL-NDK system is **minimally PL-NDK** if it contains a single NDK node which has two CF-subsets, at least one of which contains only one reaction. Such a node is called a **minimal NDK node**. If both CF-subsets have only one reaction, we call the node a **binary NDK node**.

The **CF-RM$_+$** method transforms a PL-NDK system to a dynamically equivalent PL-RDK system. The procedure is as follows: At each NDK node, except for a CF-subset with a maximal number of reactions, the reactions in a CF-subset are replaced by adding the same reactant multiple to reactant and product complexes, such that the new reactants and products do not coincide with any existing complexes. Suppose $(\mathscr{N}, K)$ is a PL-NDK system that is transformed into a PL-RDK system $(\mathscr{N}^*, K^*)$ via CF-RM$_+$ algorithm. The two key properties of $\mathscr{N}$ and $\mathscr{N}^*$ are the invariance of the stoichiometric subspaces and the kinetic order matrices. Details of the algorithm can be found in [23].

Theorem 2. *Let $(\mathscr{N}, K)$ be a deficiency zero PL-RDK or minimally PL-NDK system with a positive equilibrium. If the system is of SF-type in a species X, then it has ACR in X.*

Proof. We begin with the PL-NDK case. Let $y \to y'$ be single reaction in the hypothesized CF-subset of the minimal NDK node. Applying CF-RM$_+$ method to transform $(\mathscr{N}, K)$, we obtain as a transform of $\mathscr{N}$ the network $\mathscr{N}^*$ with $\mathscr{S}^* = \mathscr{S}$, $\mathscr{C}^* = \mathscr{C} \cup \{y+ay, y'+ay\}$ where a is an appropriate integral multiple of y and $\mathscr{R}^* = \mathscr{R} \cup \{y + ay \to y' + ay\}$. Since we assume that the network has a complex balanced equilibrium, by Proposition 1, it is weakly reversible, and hence each linkage class is weakly reversible. Since each reaction in the linkage class of the NDK node is in a cycle, the CF-RM$_+$ creates only one additional linkage class, namely $\{y + ay \to y' + ay\}$. Hence, the deficiency of $\mathscr{N}^*$ is $\delta^* = (n + 2) - (\ell + 1) - s = \delta + 1 = 1$. The kinetic order matrix remains the same, so the transform $\mathscr{N}^*$ is still of SF-type in X. As a dynamically equivalent PL-RDK system, $\mathscr{N}^*$ has a positive equilibrium and hence, fulfill the assumptions of the extension of the Shinar-Feinberg ACR Theorem for PL-RDK system (Theorem 1). Thus, $\mathscr{N}^*$ has ACR in X.

In the PL-RDK case, we can apply the CF-RM$_+$ method to any reaction and also obtain an appropriate dynamically equivalent deficiency one system as in the minimally PL-NDK case. ■

An adaptation of the direct proof in [14] to the deficiency zero PL-RDK system is provided in the Appendix. However, the argument yields only a restricted result.

Corollary 1. *Let $(\mathscr{N}, K)$ be a deficiency zero, minimally PL-NDK system with a complex balanced equilibrium. Suppose the reactant of the NDK node is monospecies, i.e. it is of the form nX for some positive integer n and species X. Then $(\mathscr{N}, K)$ has ACR in X.*

Proof. Since the node is monospecies, the kinetic order vectors of its branching reactions have non-zero values only in X. Since it is an NDK, those non-zero values must be different. Hence, a reaction from one CF-subset and one from the other form an SF-pair, and the claim follows from the previous proposition. ■

Example 1. For the PLK system in (2.1), we consider the following dynamically equivalent deficiency zero PL-RDK system with associated kinetic order matrix F:

$$\begin{array}{c} A_1 + 2A_2 \underset{R_2}{\overset{R_1}{\rightleftarrows}} 2A_1 + A_2 \\ A_2 \underset{R_4}{\overset{R_3}{\rightleftarrows}} A_3 \end{array} \qquad F = \begin{array}{c} \\ R_1 \\ R_2 \\ R_3 \\ R_4 \end{array} \begin{array}{c} \begin{array}{ccc} A_1 & A_2 & A_3 \end{array} \\ \begin{bmatrix} p_1 & q_1 & 0 \\ p_2 & q_2 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \end{array}, \tag{3.1}$$

where $p_1 = p_2 = -68$ and $q_1 = 0.58$, and $q_2 = 0.91$. Since $\{R_1, R_2\}$ is an SF-pair in A_2, it follows from Theorem 2 that there is ACR in A_2.

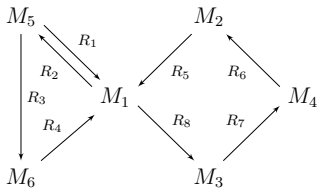
Example 2. The Shinar-Feinberg theorem on ACR for MAK systems [25] provided theoretical support to empirically observed concentration robustness in isocitrate dehydrogenase kinase-phosphatase-isocitrate dehydrogenase (IDHKP-IDH) glyoxylate bypass control system. Using the technique of network translation of Johnston [19], the MAK system of IDHKP-IDH glyoxylate bypass control system has the following dynamically equivalent weakly reversible deficiency zero PL-RDK system.

$$\begin{array}{ccc} EI_p + I + E & \underset{R_2}{\overset{R_1}{\rightleftarrows}} & EI_pI + E \\ {\scriptstyle R_6}\uparrow & & \downarrow{\scriptstyle R_3} \\ 2EI_p & \underset{R_4}{\overset{R_5}{\rightleftarrows}} & EI_p + I_p + E \end{array} \qquad F = \begin{array}{c} \\ R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \end{array} \begin{array}{c} \begin{array}{ccccc} EI_p & I & EI_pI & I_p & E \end{array} \\ \begin{bmatrix} 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 1 \\ 1 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 \end{bmatrix} \end{array} \tag{3.2}$$

The reaction pair $\{R_1, R_5\}$ forms an SF-pair in I and hence, it follows from Theorem 2 that the system has ACR in species I, which agrees with the result in [25].

Remark 1. Under mass action kinetics, any deficiency zero and conservative (i.e. the orthogonal complement of its stoichiometric subspace meets $\mathbb{R}^{\mathscr{S}}_{>0}$) CRN cannot exhibit ACR [26]. These properties that thwart ACR for MAK systems do not extend to power law kinetics as shown in Examples 1 and 2. These two deficiency zero and conservative PL-RDK systems display ACR.

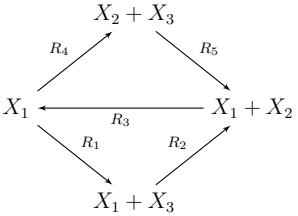
Example 3. A deficiency zero subnetwork of Schmitz's pre-industrial carbon cycle model [24] studied in Fortun et al. [15] is shown below. Its kinetic order matrix F is also provided.



$$F = \begin{array}{c} \\ R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \\ R_6 \\ R_7 \\ R_8 \end{array} \begin{array}{c} \begin{array}{cccccc} M_1 & M_2 & M_3 & M_4 & M_5 & M_6 \end{array} \\ \begin{bmatrix} 0 & 0 & 0 & 0 & 1 & 0 \\ 0.36 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 9.4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \end{array}. \tag{3.3}$$

The existence of a positive steady state of the system is established using the Deficiency Zero theorem for PL-NDK systems (Theorem 2, [15]). With $\delta = 0$, any positive steady state of the system must be complex balanced (Proposition 2). The reaction pair $\{R_2, R_8\}$ form an SF-pair in M_1. Since the reactant complex M_1 of the single binary NDK node is monospecies, it follows from Corollary 1 that it has ACR in M_1.

Example 4. Consider the following network with species set $\{X_1, X_2, X_3, X_4\}$ and power law kinetics given by the kinetic order matrix F.



$$F = \begin{array}{c} \\ R_1 \\ R_2 \\ R_3 \\ R_4 \\ R_5 \end{array} \begin{array}{c} \begin{array}{ccc} X_1 & X_2 & X_3 \end{array} \\ \begin{bmatrix} 1 & 0 & 0 \\ 0.5 & 0 & 0.5 \\ -1 & 0.5 & 0 \\ 0.5 & 0 & 0 \\ 0 & 1 & 1 \end{bmatrix} \end{array}. \tag{3.4}$$

X_1 is the only NDK node, and it is binary. The reaction pairs $\{R_1, R_4\}$ and $\{R_2, R_4\}$ are SF pairs in X_1 and X_3, respectively. The stoichiometric matrix N of the network is given by:

$$N = \begin{array}{c} \\ X_1 \\ X_2 \\ X_3 \end{array} \begin{array}{c} \begin{array}{ccccc} R_1 & R_2 & R_3 & R_4 & R_5 \end{array} \\ \begin{bmatrix} 0 & 0 & 0 & -1 & 1 \\ 0 & 1 & -1 & 1 & 0 \\ 1 & -1 & 0 & 1 & -1 \end{bmatrix} \end{array}.$$

Since the rows of N are linearly independent, $s = 3$, and hence there is only one stoichiometric class. The deficiency $\delta = 4 - 1 - 3 = 0$. The ODE system is the following:

$$\begin{aligned}
\frac{dX_1}{dt} &= k_5 X_2 X_3 - k_4 X_1^{0.5} \\
\frac{dX_2}{dt} &= k_2 X_1^{0.5} X_3^{0.5} + k_4 X_1^{0.5} - k_3 X_1^{-1} X_2^{0.5} \\
\frac{dX_3}{dt} &= k_1 X_1 + k_4 X_1^{0.5} - k_2 X_1^{0.5} X_3^{0.5} - k_5 X_2 X_3
\end{aligned}$$

Once again, by Theorem 2 of [15], there exist rate constants such that the system has a positive steady state. In particular, for the rate vector $k = (1, 1, 2, 1, 1)$, the system has the steady state $(1, 1, 1)$. Hence, the system has ACR in X_1 and X_3. In general, for rate vectors satisfying the equations $k_1 = k_2$ and $k_3 = (k_1 + k_4)(\frac{k_5}{k_4})^{0.5}$, the equilibrium is given by $(1, \frac{k_4}{k_5}, 1)$. That this equilibrium is complex balanced is due to $\delta = 0$ and Proposition 2.

4 Decomposition theory and ACR

In this section, we use decomposition theory to identify large classes of PLK systems, including such with higher deficiency, i.e. $\delta \geq 2$. These results suggest that ACR is essentially a "local" property of a low deficiency subnetwork, which serves as a "building block." We first review the required concepts and results from decomposition theory and then formulate the new results on ACR.

4.1 A review of decomposition theory

We refer to [8] for more details on the concepts and results in decomposition theory.

Definition 9. Let $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a CRN. A **covering** of $\mathscr{N}$ is a collection of subsets $\{\mathscr{R}_1, \mathscr{R}_2, \ldots, \mathscr{R}_p\}$ whose union is $\mathscr{R}$. A covering is called a **decomposition** of $\mathscr{N}$ if the sets $\mathscr{R}_i$ form a partition of $\mathscr{R}$.

Clearly, each $\mathscr{R}_i$ defines a subnetwork $\mathscr{N}_i$ of $\mathscr{N}$, namely $\mathscr{C}_i$ consisting of all complexes occurring in $\mathscr{R}_i$ and $\mathscr{S}_i$ consisting of all the species occurring in $\mathscr{C}_i$.

Proposition 3 (Prop. 3., [8])**.** *If $\{\mathscr{R}_1, \mathscr{R}_2, \ldots, \mathscr{R}_p\}$ is a network covering, then*

(i) $S = S_1 + S_2 + \cdots + S_p$;

(ii) $s \leq s_1 + s_2 + \cdots + s_p$, *where* $s = \dim S$ *and* $s_i = \dim S_i$ *for* $i \in \overline{1, p}$.

Feinberg [11] identified the important subclass of independent decomposition:

Definition 10. A decomposition is **independent** if S is the direct sum of the subnetworks' stoichiometric subspaces S_i or equivalently, $s = s_1 + s_2 + \cdots + s_p$.

Fortun et al. [15] derived a basic property of independent decompositions:

Proposition 4 (Lemma 1, [15]). *If $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$ is an independent decomposition, then $\delta \leq \delta_1 + \delta_2 + \cdots + \delta_p$, where δ_i represents the deficiency of the subnetwork $\mathscr{N}_i$.*

Feinberg [11] established the following relationship between the positive equilibria of the "parent network" and those of the subnetworks of an independent decomposition.

Theorem 3 (Rem. 5.4, [11]). *Let $(\mathscr{N}, K)$ be a chemical kinetic system with partition $\{\mathscr{R}_1, \mathscr{R}_2, \ldots, \mathscr{R}_p\}$. If $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$ is the network decomposition generated by the partition and $E_+(\mathscr{N}_i, K_i) = \{x \in \mathbb{R}^{\mathscr{S}}_{>0} | N_i K_i(x) = 0\}$, then*

(i) $\bigcap_{i \in \overline{1,p}} E_+(\mathscr{N}_i, K_i) \subseteq E_+(\mathscr{N}, K)$

(ii) If the network decomposition is independent, then equality holds.

Farinas et al. [8] introduced the concept of an *incidence independent decomposition*, which naturally complements the independence property. The starting point is the following basic observation:

Proposition 5 (Prop. 6, [8]). *If $\{\mathscr{R}_i\}$ is a network covering, then*

(i) $\operatorname{Im} I_a = \operatorname{Im} I_{a,1} + \operatorname{Im} I_{a,2} + \cdots + \operatorname{Im} I_{a,p}$, *where $I_{a,i}$ denotes the incidence map of the subnetwork $\mathscr{N}_i$.*

(ii) $n - \ell \leq (n_1 - \ell_1) + (n_2 - \ell_2) + \cdots + (n_p - \ell_p)$, *where $n - \ell = \dim I_a$ and $n_i - \ell_i = \dim I_{a,i}$ for $i \in \overline{1,p}$.*

The analogous concept to independent decomposition is the following:

Definition 11. A decomposition $\{\mathscr{N}_1, \mathscr{N}_2, \ldots, \mathscr{N}_p\}$ of a CRN is **incidence independent** if and only if the image of the incidence map I_a of $\mathscr{N}$ is the direct sum of the images of the incidence maps of the subnetworks.

It follows from this definition that $n - \ell = \sum(n_i - \ell_i)$. The linkage classes form the primary example of an incidence independent decomposition, since $n = \sum n_i$ and $\ell = \sum \ell_i$. In fact, the linkage class decompositions belong to the important subclass of $\mathscr{C}$-decompositions discussed Definition 12.

The following result is the analogue of Proposition 4 for incidence independent decomposition.

Proposition 6 (Prop. 7, [8]). *Let $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$ be an incidence independent decomposition. Then $\delta \geq \delta_1 + \delta_2 + \cdots + \delta_p$.*

A decomposition is **bi-independent** if it is both independent and incidence independent. Independent linkage class decomposition is the best known example of bi-independent decomposition.

Proposition 7 (Prop. 9, [8]). *A decomposition $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$ is independent or incidence independent and $\sum_{i=1}^{p} \delta_i = \delta$ if and only if $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$ is bi-independent.*

$\mathscr{C}$-decompositions form an important class of incidence independent decompositions:

Definition 12. A decomposition $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$ with $\mathscr{N}_i = (\mathscr{S}_i, \mathscr{C}_i, \mathscr{R}_i)$ is a **$\mathscr{C}$-decomposition** if $\mathscr{C}_i \cap \mathscr{C}_j = \emptyset$ for $i \neq j$.

A $\mathscr{C}$-decomposition partitions not only the set of reactions but also the set of complexes. The primary examples of $\mathscr{C}$-decomposition are the linkage classes. Linkage classes, in fact, essentially determine the structure of a $\mathscr{C}$-decomposition.

Theorem 4 (Structure Theorem for $\mathscr{C}$-decomposition, Th. 1 [8]). *Let $\mathscr{L}_1, \mathscr{L}_2, \ldots, \mathscr{L}_\ell$ be the linkage classes of a network $\mathscr{N}$. A decomposition $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N} \cup \cdots \cup \mathscr{N}_p$ is a $\mathscr{C}$-decomposition if and only if each $\mathscr{N}_i$ is the union of linkage classes and each linkage class is contained in only one $\mathscr{N}_i$.*

The following result shows the relationship between the set of incidence independent decompositions and the set of complex balanced equilibria of any kinetic system. It is the precise analogue of Theorem 3.

Theorem 5 (Theorem 4, [8]). *Let $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a CRN and $\mathscr{N}_i = (\mathscr{S}_i, \mathscr{C}_i, \mathscr{R}_i)$ for $i \in \overline{1,p}$ be the subnetworks of a decomposition. Let K be any kinetics, and $Z_+(\mathscr{N}, K)$ and $Z_+(\mathscr{N}_i, K_i)$ be the set of complex balanced equilibria of $\mathscr{N}$ and $\mathscr{N}_i$, respectively. Then*

(i) $\bigcap_{i\in\overline{1,p}} Z_+(\mathscr{N}_i, K_i) \subseteq Z_+(\mathscr{N}, K)$

If the decomposition is incidence independent, then

(ii) $Z_+(\mathscr{N}, K) = \bigcap_{i\in\overline{1,p}} Z_+(\mathscr{N}_i, K_i)$

(iii) $Z_+(\mathscr{N}, K) \neq \emptyset$ *implies* $Z_+(\mathscr{N}_i, K_i) \neq \emptyset$ *for each* $i \in \overline{1,p}$.

4.2 ACR in PLK systems with a positive equilibrium

We can now demonstrate ACR in classes of PL-NDK and higher deficiency PLK systems.

Proposition 8. *Let* $(\mathscr{N}, K)$ *be a PLK system with a positive equilibrium and an independent decomposition* $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$. *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 $(\mathscr{N}, K)$ *has ACR in* X.

Proof. Since $E_+(\mathscr{N}, K) \neq \emptyset$ and the decomposition is independent, $E_+(\mathscr{N}, K_i) \neq \emptyset$ for each $i \in \overline{1,p}$. We denote the PL-RDK or minimally subnetwork with $\mathscr{N}_{\text{ACR}}$ and associated kinetics K_{ACR}. The subnetwork $\mathscr{N}_{\text{ACR}}$ fulfills the conditions for Theorem 1 or Theorem 2 and hence, it has ACR in X for all equilibria in $E_+(\mathscr{N}_{\text{ACR}}, K_{\text{ACR}})$. Since the latter set contains $E_+(\mathscr{N}, K)$, the PLK system $(\mathscr{N}, K)$ has ACR in X. ■

To ensure that higher deficiency network occur, we have the next result:

Corollary 2. *If the decomposition in the previous proposition is bi-independent and at least one more subnetwork* $\mathscr{N}_j$ *has* $\delta_j > 1$, *then the network* $\mathscr{N}$ *has higher deficiency.*

Proof. For a bi-independent decomposition, we have $\delta = \delta_1 + \delta_2 + \cdots + \delta_p$. ■

4.3 BCR for classes of PLK systems with complex balanced equilibrium

Incidence independent decompositions of CRNs are more common than independent ones. For instance, all linkage class decompositions are incidence independent, but few are independent. This motivates the introduction of a weaker form of concentration robustness than ACR:

Definition 13. A complex balanced chemical kinetic system $(\mathscr{N}, K)$ has **balanced concentration robustness (BCR)** in a species $X \in \mathscr{S}$ if X has the same value for all $c \in Z_+(\mathscr{N}, K)$.

Clearly, a system that has ACR in a species implies that it also exhibits BCR for that species. A class of systems for which the converse holds (justifying the notation) is given by the following definition.

Definition 14. A complex balanced system is **absolutely complex balanced (ACB)** if $Z_+(\mathscr{N}, K) = E_+(\mathscr{N}, K)$.

Examples of absolutely complex balanced systems are deficiency zero networks with positive equilibrium (for any kinetics) and complex balanced mass action systems (for any deficiency).

We have an analogous result of Proposition 8 for complex balanced systems and BCR:

Proposition 9. *Let $(\mathscr{N}, K)$ be a PLK system with a complex balanced equilibrium and an incidence independent decomposition $\mathscr{N} = \mathscr{N}_1 \cup \mathscr{N}_2 \cup \cdots \cup \mathscr{N}_p$. 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 $(\mathscr{N}, K)$ has BCR in X.

Proof. Since $Z_+(\mathscr{N}, K) \neq \emptyset$ and the decomposition is independent, Theorem 5 guarantees that $Z_+(\mathscr{N}, K_i) \neq \emptyset$ for each $i \in \overline{1,p}$. Denote the PL-RDK or minimally subnetwork with $\mathscr{N}_{\text{ACR}}$ and associated kinetics K_{ACR}. This subnetwork satisfies the conditions for Theorem 1 or Theorem 2 and hence, it has ACR in X for all equilibria in $E_+(\mathscr{N}_{\text{ACR}}, K_{\text{ACR}})$. Since the latter set contains $Z_+(\mathscr{N}, K)$, the PLK system $(\mathscr{N}, K)$ has BCR in X. ■

5 Discussion: the primarily kinetic character of ACR

In this section, we describe the evolution of the assessment of ACR as a system property – from the emphasis on its "structural sources" in the original papers of Shinar and Feinberg [25, 26] to our current view of its primarily kinetic character.

Shinar and Feinberg entitled their groundbreaking paper [25] *Structural sources of robustness in biochemical reaction networks* in which "structural" referred to the hypotheses (i) of the network's deficiency being equal to one, and (ii) of the presence of two reactant complexes which differed only in a species X. The kinetic assumptions were the use of MAK and the existence of a positive equilibrium. In a further paper [26], they emphasized these structural aspects by speaking of "design principles" for networks in order to achieve robustness.

The extension of the Shinar-Feinberg ACR Theorem for PL-RDK systems (Theorem 1), maintained the first structural property but transformed the second to the kinetic property of a pair of reactions whose kinetic order vectors differed only in the coordinate for species X. In the special case of MAK systems, the kinetic order values coincide with the stoichiometric coefficients of the reactant complexes, thus "hiding" its kinetic character. Nevertheless, even in this extension, some structural aspects should be noted, as expressed in the following proposition:

Proposition 10. *Let $\{R, R'\}$ be an SF-pair in the species X of a PLK system $(\mathscr{N}, K)$ and y, y' their reactant complexes. Then*

(i) For any species $Y \neq X$, $Y \in$ supp y if and only if $Y \in$ supp y'.

(ii) $X \in$ supp $y \cup$ supp y'.

(iii) If the stoichiometric coefficients of complexes in $\mathscr{N}$ are only 0 or 1, then y and y' differ only in X.

In this paper, we highlighted the importance of the invariance of ACR under dynamic equivalence by identifying deficiency zero PLK systems through the use of the CF-RM$_+$ method. In our view, the usefulness of this invariance property further emphasizes the primarily kinetic character of ACR. A comparison with the property of a system of having a complex balanced equilibrium yields the complementary insight that the latter is often lost under dynamic equivalence, so that one could say, that the existence of a complex balanced equilibrium is a primarily structural property.

With low deficiency subnetworks as "building blocks", results on decomposition help overcome the structural restriction initially suggested by the deficiency one requirement. Nevertheless, one should not forget that that special case is the starting point of the broader identification of ACR in PLK systems.

To conclude our discussion of this topic, we introduce the concept of a *Birch system*.

Definition 15. A **Birch system** is a kinetic system with only one positive equilibrium (in the whole species space).

Being a Birch system is a purely kinetic property. The name is derived from Birch's Theorem for weakly reversible deficiency zero MAK systems. If the system is open (i.e., non-mass conserving), there is only one stoichiometric class and the positive (in this case, complex balanced) equilibrium is unique in species space.

Example 5. The independent realization or any open (or non-mass conserving) subnetwork realization of a regular S-system.

The following (straightforward) proposition makes the connection between Birch systems and ACR explicit, revealing in our view its primarily kinetic character further:

Proposition 11. *A chemical kinetic system is a Birch system if and only if it has ACR in every species.*

6 Summary and outlook

In conclusion, we summarize our results and outline some perspectives for further research.

1. We used the idea that ACR is a condition that is invariant under dynamic equivalence of CRNs to formulate new results that indicate ACR in deficiency zero PL-RDK system and minimally PL-NDK systems. The key concept needed in deriving these results involved the CF-RM_+ transformation of a system into a dynamically equivalent PLK system that fulfills the assumptions of the Shinar-Feinberg ACR Theorem for PL-RDK systems (Theorem 1). Examples were also provided to illustrate these results.

2. Using independent decomposition, we presented a result that identifies ACR in higher deficiency networks. This result indicated that ACR is a "local" property of a low deficiency subnetwork that serves as a "building block" of a larger ACR-possessing network.

3. In a similar approach, we used incidence independent decomposition to investigate the dynamics of larger networks with low deficiency subnetworks that ACR in a

species. This led us to identify a weaker concentration robustness than ACR, which we called 'balanced concentration robustness' (BCR). Our result suggests that if a PLK system has complex balanced equilibrium, incidence independent decomposition, and a subnetwork that has ACR for a species, then the system has BCR for that species.

4. In previous literature, much attention is given to the view that ACR is a property that is conferred from structural sources. Here, however, we provided a discussion that emphasized the primarily kinetic character of ACR.
5. As future prospect, we plan to work on computational approaches and tools for identification of ACR and BCR using the results presented in this paper.
6. The results presented in this paper may also be expanded to systems that are bigger than power law kinetic systems such as poly-PL systems, introduced in [28].

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A Appendix: ACR in a deficiency zero PL-RDK systems

We provide an adaptation of the direct proof [14] of Theorem 1 to the deficiency zero case. Unlike Theorem 2, however, this result leads only to a restricted result: SF-pairs belong to the same linkage class.

Theorem 6. *Let $\mathscr{N}$ be deficiency zero PL-RDK system that has a positive equilibrium. If a pair of reactions in a linkage class forms an SF-pair in species X, then the system has ACR in X.*

The following result is crucial in proving the Theorem 6.

Proposition 12 (Prop. 4.1, [10])**.** *Let $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a CRN with terminal strong linkage classes $\mathscr{C}^1, \mathscr{C}^2, \ldots, \mathscr{C}^t$. Let $k \in \mathbb{R}^{\mathscr{R}}_{>0}$ and A_k its associated Laplacian. Then Ker A_k has a basis $b^1, b^2, \ldots, b^t$ such that supp $b^i = \mathscr{C}^i$ for all $i \in \overline{1,t}$.*

Feinberg [10] provided a geometric interpretation of deficiency: $\delta = \dim(\text{Ker } Y \cap \text{Im } I_a)$. From this fact and Proposition 12, the following result follows.

Proposition 13 (Cor. 4.12, [10])**.** *Let $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ be a CRN with deficiency δ and t terminal strong linkage classes. If every linkage class of the CRN is a terminal strong linkage class, then for each $k \in \mathbb{R}^{\mathscr{R}}_{>0}$, $\dim(Ker\, Y A_k) = \delta + t$.*

Throughout the proof, the vector $\log x \in \mathbb{R}^{\mathscr{I}}$,where $x \in \mathbb{R}^{\mathscr{I}}_{>0}$, is given by $(\log x)_i = \log x_i$, for all $i \in \mathscr{I}$. If $x, y \in \mathbb{R}^{\mathscr{I}}$, the standard scalar product $x \cdot y \in \mathbb{R}$ is defined by $x \cdot y = \sum_{i \in \mathscr{I}} x_i y_i$.

Proof of Theorem 6

Let c^* is a positive steady state of the PL-RDK system. That is, there exists $k \in \mathbb{R}^{\mathscr{R}}_{>0}$ such that

$$\sum_{y \to y' \in \mathscr{R}} k_{y \to y'} (c^*)^{\widetilde{y}} (y' - y) = 0. \tag{A.1}$$

Here, we write $\widetilde{y}$ for $\widetilde{Y}_{,y}$, where $\widetilde{Y}$ is the $m \times n$ matrix defined by Müller and Regensburger in [22] and is constructed as follows: For each reactant complex, the associated column of $\widetilde{Y}$ is the transpose of the kinetic order matrix row of the complex's reaction, otherwise (i.e., for non-reactant complexes), the column is 0. In other words, $\widetilde{y} = \widetilde{Y}_{,y}$ refers to the kinetic order vector of the reactant complex y.

For each $y \to y' \in \mathscr{R}$, define the positive number $\kappa_{y \to y'}$ by

$$\kappa_{y \to y'} := k_{y \to y'} (c^*)^{\widetilde{y}}. \tag{A.2}$$

Thus, we obtain

$$\sum_{y \to y' \in \mathscr{R}} \kappa_{y \to y'} (y' - y) = 0. \tag{A.3}$$

Suppose that c^{**} is also a positive equilibrium of the system. Hence,

$$\sum_{y \to y' \in \mathscr{R}} k_{y \to y'} (c^{**})^{\widetilde{y}} (y' - y) = 0. \tag{A.4}$$

Define

$$\mu := \log c^{**} - \log c^*. \tag{A.5}$$

With $\kappa \in \mathbb{R}^{\mathscr{R}}_{>0}$ given by Equation (A.2) and μ given by Equation (A.5), it follows from Equation (A.4) that

$$\sum_{y \to y' \in \mathscr{R}} \kappa_{y \to y'} e^{\widetilde{y} \cdot \mu} (y' - y) = 0. \tag{A.6}$$

Let $\mathbf{1}^{\mathscr{C}} \in \mathbb{R}^{\mathscr{C}}$ such that

$$\mathbf{1}^{\mathscr{C}} = \sum_{y \in \mathscr{C}} \omega_y.$$

Observe that Equations (A.3) and (A.6) can be respectively written as

$$Y A_\kappa \mathbf{1}^{\mathscr{C}} = 0, \text{ and } Y A_\kappa \left(\sum_{y \in \mathscr{C}} e^{\widetilde{y} \cdot \mu} \omega_y \right) = 0.$$

Equivalently,

$$\mathbf{1}^{\mathscr{C}} \in \text{Ker } Y A_\kappa, \text{ and} \tag{A.7}$$

$$\sum_{y\in\mathscr{C}} e^{\widetilde{y}\cdot\mu}\omega_y \in \text{Ker } YA_\kappa. \tag{A.8}$$

Therefore, c^* and c^{**} are positive equilibria of the PL-RDK system $(\mathscr{N}, K)$ if and only if (A.7) and (A.8) hold.

Since the network is deficiency zero, by Proposition 2, its steady states are all complex balanced. It follows from Proposition 1 that the underlying network is necessarily weakly reversible. Consequently, every linkage class of the CRN is a terminal strong linkage class. Moreover, since $\delta = 0$, it follows from Proposition 13 that

$$\dim(\text{Ker } YA_\kappa) = t. \tag{A.9}$$

Note that Ker $A_\kappa \subseteq$ Ker YA_κ. But because of Equation (A.9), we have Ker $A_\kappa =$ Ker YA_κ.

Let $\{b^1, b^2, \ldots, b^t\} \subset \mathbb{R}^{\mathscr{C}}_{\geq 0}$ be a basis for Ker A_κ as in Proposition 12. Because Ker $A_\kappa =$ Ker YA_κ and $\mathbf{1}^{\mathscr{C}} \in$ Ker YA_κ, it must be that

$$\mathbf{1}^{\mathscr{C}} \in \text{span } \{b^1, b^2, \ldots, b^t\}. \tag{A.10}$$

We consider a new basis for Ker YA_κ that includes $\mathbf{1}^{\mathscr{C}}$. Consider removing the vector in $\{b^1, b^2, \ldots, b^t\}$ whose support are precisely those reactant complexes, y and y', with interactions differing only in one species. For convenience, assume that this vector is b^1. Hence, $\{\mathbf{1}^{\mathscr{C}}, b^2, \ldots, b^t\}$ forms a basis for Ker YA_κ.

Since $\sum_{y\in\mathscr{C}} e^{\widetilde{y}\cdot\mu}\omega_y \in$ Ker YA_κ, there exist $\lambda_1, \lambda_2, \ldots, \lambda_t$ such that

$$\sum_{y\in\mathscr{C}} e^{\widetilde{y}\cdot\mu}\omega_y = \lambda_1\mathbf{1}^{\mathscr{C}} + \sum_{i=2}^{t}\lambda_i b^i. \tag{A.11}$$

Observe that each vector b^i, $i = 2, \ldots, t$, has its support entirely on terminal complexes except for the complexes y and y'. This observation, along with Equation (A.11), implies that for reactant complexes $y \in \mathscr{C}$ and $y' \in \mathscr{C}$, we have

$$\widetilde{y}\cdot\mu = \widetilde{y'}\cdot\mu. \tag{A.12}$$

Or equivalently, we have

$$(\widetilde{y} - \widetilde{y'})\cdot(\log c^{**} - \log c^*) = 0. \tag{A.13}$$

Now, since $y, y' \in \mathscr{C}$ are reactant complexes whose interactions differ only in species X, we have

$$\widetilde{y} - \widetilde{y'} = mX$$

for some nonzero $m \in \mathbb{R}$. Thus, Equation (A.13) reduces to $m(\log c_X^* - \log c_X^{**}) = 0$. It follows that $c_X^* = c_X^{**}$. That is, the system has ACR in species X. ■