Complex-Balanced Steady States of Chemical Reaction Networks that Contain an Eulerian Cycle

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Abstract

This work pertains to chemical reaction networks and their equilibria, called steady-states. Our main result states that for a cyclic chemical reaction network, there is a straightforward characterization for when a complex balancing steady state exists. We then extend our results to chemical reaction networks consisting of a closed path traversing each directed edge exactly once.
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1 Introduction

Chemical reaction network theory (CRNT) models the behavior of a network of chemical reactions based on mass-action dynamics. One aim of the study of such networks is to identify steady states (equilibria) of the mass-action ordinary differential equations that govern the chemical concentrations of a chemical reaction network (CRN); this means that we may come to useful conclusions about graphs without physical experimentation. CRNT’s applications are most pertinent to chemical engineering, where controlled reactions are plentiful and varied in nature. We first introduce some terminology to allow for a more precise investigation, following the presentation in [5] and [8]. We then provide motivation and historical background in Section 1.3.

1.1 Chemical Reaction Networks

We here provide some preliminary definitions before formally introducing a CRN.

Definition 1.1 (Species). A chemical species refers to a physical element or chemical compound. We denote a species labeled $i$ as $A_i$ throughout this paper.

Definition 1.2 (Complex). A chemical complex is a positive integer linear combination of species. We denote a complex labelled $i$ as $y_i$ throughout this paper.

Example 1.3 (Complex). The complex consisting of 1 molecule of $A_1$ and 2 molecules of $A_2$ is written $A_1 + 2A_2$.

Definition 1.4 (Reaction). A chemical reaction is a process that converts one complex (the source complex) into another complex (the target complex).

Example 1.5 (Reaction). Given species $A_1$, $A_2$ and $A_3$, the directed graph

$$A_1 + 2A_2 \rightarrow A_3$$

denotes a reaction that converts the source complex $A_1 + 2A_2$ to the target $A_3$.

Definition 1.6 (Reversible Reaction). A reversible reaction is a bidirectional reaction.

Definition 1.7 (CRN). A CRN is a finite directed graph $G = (V, E)$, where the set of vertices $V$ is labelled by complexes and the set of edges $E$ denote reactions between them.
Definition 1.8 (Weakly Reversible Network). A weakly reversible network is a CRN with the property that if there exists a directed path from some complex $y_i$ to $y_j$, then there also must exist a path from $y_j$ to $y_i$.

Convention 1.9. Throughout this paper, we work with a fixed network $G = (V, E)$ with species set $S = \{A_1, A_2, \ldots, A_k\}$ and $|S| = k$. We set the number of complexes $|V| = m$, and index them by $y_i$, $1 \leq i \leq m$.

Example 1.10 (CRN). The CRN

$$A_1 + 2A_2 \rightleftharpoons A_3 \rightarrow A_4$$

consists of 4 species, $A_i$, $1 \leq i \leq 4$, 3 complexes, and 3 reactions; each edge is a reaction. The first two reactions, from $A_1 + 2A_2$ to $A_3$ and from $A_3$ to $A_1 + 2A_2$, together form a reversible reaction. The third reaction, between $A_3$ and $A_4$, is not reversible. The leftmost complex has two species, $A_1$ and $A_2$. This network is not weakly reversible, because there is no directed path from the complex $A_4$ to any other complex. If there were a reaction from $A_4$ to $A_1 + 2A_2$, or from $A_4$ to $A_3$, then the network would be weakly reversible.

1.2 Chemical Reaction Systems and Steady States

Each CRN defines a system of ordinary differential equations called a chemical reaction system (CRS). This CRS is a dynamical system that describes the behavior of the concentrations of chemical species as the reactions in the network occur. Before formally defining a CRS, we first examine the elements of a CRN which affect its reaction rates. In this section, we use the fixed CRN $G$ as presented in Convention 1.9.

Definition 1.11. We define $\mathbb{Z}_S^{>0}$ as the positive orthant of the $k$-dimensional integer-valued vector space, with one basis vector for each species in $G$.

Definition 1.12 (Species Vector). We denote by $y_i \in \mathbb{Z}_S^{>0}$ the species vector of the $i^{th}$ complex in the network $G$. The species vector for the $i^{th}$ complex $y_i = n_1A_1 + n_2A_2 + \ldots + n_kA_k$ is the column vector

$$y_i = \begin{pmatrix} n_1 \\ n_2 \\ \vdots \\ n_k \end{pmatrix} \in \mathbb{Z}_S^{>0}.$$
Definition 1.13 (Species Space). For a CRN with \( k \) species, the species space, denoted \( \mathbb{R}^S_{>0} \), is the positive orthant of the \( k \)-dimensional real vector space, with one basis vector for each species. Note that species vectors and complexes are in bijective correspondence, so we may refer to either by \( y_i \) during the paper. A point \( \bar{c} \in \mathbb{R}^S_{>0} \) in the species space \( G \) is viewed as a concentration vector, where the \( i^{th} \) coordinate \( c_i \) denotes the concentration of species \( A_i \).

Definition 1.14 (Reaction Vector). The reaction vector for a reaction is the vector obtained by subtracting the source complex’s species vector from the target complex’s species vector (i.e., the reaction vector for \( y_j \rightarrow y_i \) is \( y_i - y_j \)). It encodes the net change in each species that occurs as a result of the reaction.

Definition 1.15 (Mass-Action Dynamics). Mass-action dynamics is a method of predicting the rate at which objects interact. In CRNT, the objects are the species in the source complex of a reaction. Mass-action dynamics assumes the rate of a reaction is proportional to the mathematical product of the concentrations of the reactants. The product of concentrations with the proportionality constant \( \kappa \) is referred to throughout the paper as ‘the rate of reaction.’

Convention 1.16. Let the species vector \( y_i \) act as the exponent vector for the concentration vector \( \bar{c} \). Then for the species vector \( y_i = (n_1, n_2, \ldots, n_k)^T \), the reaction \( y_i \rightarrow y_j \) has the rate of reaction \( \kappa_{y_i \rightarrow y_j} c^{y_i} y_j \). Note that \( \kappa \) is indexed by reactions in \( E(G) \). When referring to the collection of these rate constants, we write it \( \bar{\kappa} \).

Definition 1.17 (CRS). A CRS \( (G, \bar{\kappa}) \) is the system of differential equations associated with a CRN \( G \) that describes the rates at which the species’ concentrations change. These rates are determined by mass-action dynamics, yielding the differential equations:

\[
\frac{d\bar{c}}{dt} = \sum_{y \rightarrow y'} (\kappa_{y \rightarrow y'}) c^y (y' - y). \tag{1.18}
\]

Note that while a CRN is defined simply by the graph \( G \), a CRS is a system of ODEs determined by both \( G \) and \( \bar{\kappa} \), where \( \bar{\kappa} \) denotes the set of reaction rate constants.

Definition 1.19 (Steady State). Consider a CRS. A vector \( \bar{c} \in \mathbb{R}^S_{>0} \) is called a positive steady state if \( \frac{d\bar{c}}{dt} = 0 \). We denote steady states as \( \bar{c}^* \).

Example 1.20 (CRS). We return to Example 1.10, explicitly stating its CRS. In order to do this, we must identify each summand in (1.18).
1. The reaction $A_1 + 2A_2 \rightarrow A_3$ has the source complex $A_1 + 2A_2$, so if we assign this reaction the constant $\kappa_1$, mass-action dynamics gives us a rate of reaction $\kappa_1 c_1 c_2^2$. Therefore this reaction contributes the following rates of change to the entire system:

$$\frac{dc_1}{dt} = -\kappa_1 c_1 c_2^2, \quad \frac{dc_2}{dt} = -2\kappa_1 c_1 c_2^2, \quad \frac{dc_3}{dt} = \kappa_1 c_1 c_2^2, \quad \frac{dc_4}{dt} = 0.$$ 

The integer coefficients above reflect the fact that, with each occurrence of the reaction, one unit of $A_1$ is consumed, two units of $A_2$ are consumed, and one unit of $A_3$ is produced. That is, the coefficients correspond the net number of units involved in the reaction.

2. Similarly, the reaction $A_3 \rightarrow A_1 + 2A_2$ has the source complex $A_3$ and assigning the rate constant $\kappa_2$ gives the rate of reaction $\kappa_2 c_3$. For this reaction,

$$\frac{dc_1}{dt} = \kappa_2 c_3, \quad \frac{dc_2}{dt} = 2\kappa_2 c_3, \quad \frac{dc_3}{dt} = -\kappa_2 c_3, \quad \frac{dc_4}{dt} = 0.$$ 

3. Finally, the reaction $A_3 \rightarrow A_4$ is analyzed in kind. Assigning constant $\kappa_3$, we have a rate of $\kappa_3 c_3$, and the system

$$\frac{dc_1}{dt} = 0, \quad \frac{dc_2}{dt} = 0, \quad \frac{dc_3}{dt} = -\kappa_3 c_3, \quad \frac{dc_4}{dt} = \kappa_3 c_3.$$ 

Taken together, these three reactions characterize the rate of change of concentrations of the species in the CRN. We obtain the CRS below:

$$\frac{dc_1}{dt} = -\kappa_1 c_1 c_2^2 + \kappa_2 c_3$$
$$\frac{dc_2}{dt} = -2\kappa_1 c_1 c_2^2 + 2\kappa_2 c_3$$
$$\frac{dc_3}{dt} = \kappa_1 c_1 c_2^2 - \kappa_2 c_3 - \kappa_3 c_3$$
$$\frac{dc_4}{dt} = \kappa_3 c_3$$

We may identify a steady state $\bar{c}$ without much trouble because $\frac{dc_4}{dt}$ is linear. In particular, $\bar{c}$ is only equal to 0 when $c_3 = 0$. This implies $c_1 c_2^2 = 0$, which in turn implies that at least one of $c_1$ and $c_2$ is equal to 0. This is not surprising since this reaction is not weakly reversible; the complex $A_4$ serves as a sink for the network.
Thus, all zeroes of the CRS occur when all non-$A_4$ species concentrations are zero. Since steady states $\bar{c}^*$ correspond to positive vectors, this network has no steady states.

We have derived our CRS by examining each reaction and assigning to it a rate $\kappa_{y \rightarrow y'}\bar{c}^y$. We now express (1.18) through a matrix product, as it will be useful in later computations. In particular, this places us in a setting where linear algebra is readily applied.

**Convention 1.21 (Matrix Product Notation).** For the CRN $G$, let

$$Y := \begin{pmatrix} y_1 & y_2 & \cdots & y_m \end{pmatrix} \in \mathbb{Z}^{k \times m},$$

be the matrix whose columns are the species vectors of the $m$ complexes in the network and rows correspond to species.

We now encode the reactions in the CRN with a matrix $A_\kappa$. For a fixed $i$, $1 \leq i \leq m$, we define the off-diagonal entries

$$A_{\kappa(i,j)} = \begin{cases} \kappa_{y_j \rightarrow y_i} : y_j \rightarrow y_i \in E(G) \\ 0 : else \end{cases}.$$

We define the diagonal entry $i,i$ as the negative sum of the entries in the $i^{th}$ column. This appropriately associates rate constants with their source reactions in $Y$.

The expression $\Psi(\bar{c})$ is the column vector which contains concentration monomials for the $i^{th}$ complex in the $i^{th}$ coordinate, i.e.,

$$\Psi(\bar{c}) := \begin{pmatrix} \bar{c}^{y_1} \\ \bar{c}^{y_2} \\ \vdots \\ \bar{c}^{y_m} \end{pmatrix}.

(1.22)$$

It is straightforward now to rewrite the (1.18) as

$$\frac{d\bar{c}}{dt} = Y A_\kappa \Psi(\bar{c}),

(1.23)$$

**Example 1.24.** We express the associated CRS in Example 1.10 as in (1.23) with matrices

$$Y = \begin{pmatrix} 1 & 0 & 0 \\ 2 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad A_\kappa = \begin{pmatrix} -\kappa_1 & \kappa_2 & 0 \\ \kappa_1 & -\kappa_2 - \kappa_3 & 0 \\ 0 & \kappa_3 & 0 \end{pmatrix}, \quad \text{and} \quad \Psi(c) = \begin{pmatrix} c_1 c_2^2 \\ c_3 \end{pmatrix}. $$

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**Definition 1.25** (Stoichiometric Subspace). The span of the reaction vectors of a CRN is called the *stoichiometric space* $S \subset \mathbb{R}^S$ of the network. That is, $S := \text{span}\{y_i - y_j | y_j \rightarrow y_i \in E(G)\}$, and we set $s := \dim(\text{span}(S))$.

Given an initial concentration vector $\bar{c}_0 := \bar{c}(0) \in \mathbb{R}^S_{>0}$, we may define the cosets $P$ as stoichiometric compatibility classes:

$$P := (\bar{c}_0 + S) \cap \mathbb{R}^S_{\geq 0}.$$ 

These structures are special in that the trajectory of $\bar{c}(t)$ is always in $\bar{c}_0 + S$. One goal of CRNT is to identify the positive steady state $\bar{c}^* \in \mathbb{R}^S_{>0}$ such that $(\bar{c}^* - \bar{c}_0) \in S$; (that is, a steady state in each $P$). CRNT aims to identify solutions in all $P$: if we have solutions for every $P$, then we have identified a positive steady state every possible set of initial conditions.

### 1.3 Historical Background

CRNT is devoted to developing and analyzing a complete model of CRNs. Recall the definition of “steady state” from Definition 1.19. We now discuss two questions related to these steady states.

**Question 1.26.** Do all weakly reversible CRNs admit positive steady states (for all choices of rate constants)?

**Question 1.27.** Do all weakly reversible CRNs admit positive steady states in each stoichiometric compatibility class (for all choices of rate constants)?

Fortunately, the answer to both questions is “yes.” Later in this paper, we will explore how our work provides a new perspective on these answers. Historically, Horn and Jackson are responsible for the advent of chemical reaction network theory. By using mass-action dynamics, they enabled mathematicians to identify and analyze invariant algebraic structures underlying intricate networks (as in [7]). One condition that depends on such structures is known as complex-balancing (introduced in [7]).

**Definition 1.28** (Complex-Balancing). Consider the CRS $(G, \bar{\kappa})$. A steady state is *complex-balancing* if, for all complexes $x$, the rate at which $x$ is produced is equal to the rate at which it is consumed; i.e., the sum of the rates of all reactions whose target is $x$ are equivalent to the sum of all rates of reactions whose source is $x$:

$$\sum_{y \rightarrow x} \kappa_{y \rightarrow x} c^y = \sum_{x \rightarrow y'} \kappa_{x \rightarrow y'} c^x.$$
Significantly, $A_{\kappa} \Psi(\bar{c}^*) = 0$ if and only if $\bar{c}^*$ is a complex balancing steady state. The proof of this follows directly from the definition of $A_{\kappa}$: each row $i$ of $A_{\kappa}$ multiplied by $\Psi(\bar{c})$ expresses the change at any given moment in the net amount of reactants at a given node $y_i$. If this is zero, the rate of reactant consumption is equal to the rate of reactant arrival.

Another idea used to analyze networks is the idea of deficiency. Deficiency is a nonnegative integer that gives a measure of how far a CRN is from complex-balancing. For weakly reversible networks, deficiency is a function of the dimension of the stoichiometric subspace, the number of complexes, and the number of linkage classes (a measure of the connectedness of the network)[4]. The explicit deficiency formula is the number of complexes minus the number of linkage classes minus the dimension of the stoichiometric subspace.

This paper examines networks given by an Eulerian cycle and explores the relationship between their network structure and their rate constants.

Note that if $(G, \kappa)$ is complex-balancing, then $G$ is weakly reversible. Feinberg has shown that a network has deficiency zero if and only if all choices of $\kappa$ yield a complex-balancing solution [4]. Complex-balancing may also occur outside of deficiency zero cases. In fact, we show that, with the correct rate constants, unidirectional cycles may exhibit complex-balancing (and are of arbitrary deficiency), see Theorem 2.5.

**Definition 1.29 (Unidirectional Cycle Graph).** A unidirectional cycle graph is a directed graph such that

1. There are as many nodes as there are edges,
2. Each node is the target of exactly one edge, and
3. Each node is the source of exactly one edge.

**Example 1.30.** Given species $A_1, A_2, A_3,$ and $A_4$, a unidirectional 4-cycle network is depicted below:

\[
\begin{array}{c}
A_1 \\
\kappa_4 \uparrow \\
\kappa_4 \\
\end{array} \begin{array}{c}
\rightarrow \\
\downarrow \kappa_2 \\
\leftarrow \\
\end{array} \begin{array}{c}
A_2 \\
A_3 \\
A_4 \\
\end{array}
\]

Unidirectional cycle graphs provide the simplest possible instance of complex-balancing. Since there are other complex-balancing networks beyond the trivial ones, the following question arises:
**Question 1.31** ([6]). Fix a weakly-reversible CRN $G$. Denoting the set of rate constants for the rates of reaction as $\bar{\kappa}$, for which $\bar{\kappa}$ is the CRS $(G, \bar{\kappa})$ complex-balancing?

As an answer to Question 1.31, Horn enumerated some necessary and sufficient conditions for complex-balancing; Feinberg examined this condition in [3]; in [2], Craciun, et al., examined complex-balancing from a more modern algebraic viewpoint. In addition, in the pioneering paper [7], Horn and Jackson studied how some properties of the complex balanced reaction cycles have implications for all complex-balanced networks.

In this paper, we give a complete answer to Question 1.31 in the case of unidirectional, cyclic networks (Theorem 2.5). We then extend this result to the class of networks that contain an Eulerian cycle (see Definition 3.1). Finally, we give a straightforward method for identifying a steady state once we are certain that it exists. This differs from Horn and Jackson’s approach, whose main theorem states that if a system has one complex-balancing steady state, then all of its steady states are complex-balancing [7]. By combining [7, Lemma 5B] with Theorem 3.3 and the graph-theoretic properties used to identify Eulerian cycles, we show that if a graph has an equal number of incoming and outgoing reactions at any node, then there exist reaction rate constants such that all the steady states of $(G, \bar{\kappa})$ are complex-balancing and all rates of reaction are equal.

## 2 Complex-Balancing Steady States of Cyclic Networks

In this section, we will provide a criterion to determine when complex-balancing occurs, as in [7], restricting attention to cyclic networks.

**Example 2.1.** The unidirectional 4-cycle in Example 1.30 has a complex-balancing steady state for all $\bar{\kappa}$. It corresponds to equivalence among all rates of reaction $A_i \rightarrow A_{i+1}$, where $A_5 := A_1$. Given any $\bar{\kappa}$, there is a choice of $\bar{\kappa}^*$ which provides a steady state. Explicitly, this is $\kappa_1 c_1 = \kappa_2 c_2 = \kappa_3 c_3 = \kappa_4 c_4$.

To identify where the complex-balancing conditions lie in the matrix product (1.23), we examine its steady states:

$$0 = \frac{d\bar{\kappa}}{dt} = Y A_\kappa \Psi(\bar{\kappa}).$$
It is useful to further decompose the matrix product as 
\[ A \kappa := A \cdot \text{Diag}(\bar{\kappa}), \]
where \( \text{Diag}(\bar{\kappa}) \) is the diagonal matrix with \( \kappa_i \) on the \( i^{th} \) diagonal entry. This is possible because \( G \) is a unidirectional cycle.

**Example 2.2.** In Example 1.10, we had
\[
A \kappa = \begin{pmatrix}
-\kappa_1 & \kappa_2 & 0 \\
\kappa_1 & -\kappa_2 & -\kappa_3 \\
0 & 0 & \kappa_3
\end{pmatrix}.
\]

In order to decompose \( A \kappa \), note that the \( i^{th} \) column is multiplied by the scalar value \( \kappa_i \). Hence
\[
A \kappa = A \cdot \text{Diag}(\bar{\kappa}) = \begin{pmatrix}
-1 & 1 & 0 \\
1 & -1 & -1 \\
0 & 0 & 1
\end{pmatrix}
\begin{pmatrix}
\kappa_1 & 0 & 0 \\
0 & \kappa_2 & 0 \\
0 & 0 & \kappa_3
\end{pmatrix} = \begin{pmatrix}
-\kappa_1 & \kappa_2 & 0 \\
\kappa_1 & -\kappa_2 & -\kappa_3 \\
0 & 0 & \kappa_3
\end{pmatrix}.
\]

This decomposition proves useful: we define \( \rho \) to be some row reduction matrix which converts \( A \) to row echelon form by left multiplication. Using the fact that \( \frac{d\bar{c}}{dt} = YA_{\kappa} \Psi(\bar{c}) \), we obtain \( \frac{d\bar{c}}{dt} = YA \text{Diag}(\bar{\kappa}) \Psi(\bar{c}) \). Since \( \rho \) is a row reduction matrix, it is invertible. Combined with the commutativity of the matrix \( \text{Diag}(\bar{\kappa}) \), we have
\[ \frac{d\bar{c}}{dt} = (Y \text{Diag}(\bar{\kappa}) \rho^{-1}) (\rho A) \Psi(\bar{c}). \tag{2.3} \]

If we let \( \text{null}(B) \) denote the nullspace of a given matrix \( B \), then (2.3) implies that
\[ \text{null}(A) = \text{null}(\rho A) \subseteq \text{null}(YA_{\kappa}). \]

We now focus on steady states \( \bar{c}^* \) which result from the condition \( \bar{c} \in \mathbb{R}^S \) of the form \( \Psi(\bar{c}) \in \text{null}(A') \), where \( A' := \rho A \); that is, the reduced row echelon form of \( A \) is \( A' \). Cycle graphs always have matrices \( A \) of the following form (that reduce to \( A' \)):
\[
A := \begin{pmatrix}
-1 & 1 & 0 \\
1 & -1 & -1 \\
\vdots & \vdots & \ddots \\
1 & -1 & 1
\end{pmatrix} \quad \text{and} \quad A' := \begin{pmatrix}
1 & -1 & 0 & 0 \\
1 & -1 & 0 & 0 \\
\ddots & \ddots & \ddots & \vdots \\
1 & -1 & 0 & 0
\end{pmatrix},
\]

where the entries not displayed are zero. We define \( \tilde{A}' \) to be the \((m - 1) \times m\) matrix \( A' \) with the final row removed. With this in mind, we may now tie complex-balancing steady states of unidirectional cycles into the structure of the matrix \( A \).
Lemma 2.4. Let \( G \) be a unidirectional cyclic graph. Then for \( \bar{c} \in \mathbb{R}^S \), \((G, \bar{\kappa})\) has a complex-balancing steady state at \( \bar{c}^* \) if and only if \( \kappa_i \bar{c}^{y_i} = \kappa_j \bar{c}^{y_j} \) for all \( i, j \).

Proof. By definition, a complex-balancing steady state exists if and only if there exists \( \bar{c}^* \) such that \( \kappa_i \bar{c}^* y_i = \kappa_j \bar{c}^* y_j \) for all \( i, j \), by Proposition 2.4. Because all the terms are positive, taking logs of both sides yields the inner product \( \langle (y_i - y_m), \log(\bar{c}) \rangle = \log(\kappa_m) \) for all \( i, 1 \leq i < m \). By definition of \( \bar{A}'Y^T \), we have \( \bar{A}'Y^T \log(\bar{c}) = \omega(\bar{\kappa}) \). Finally, we see that this has a solution \( \bar{c} \) if and only if \( \omega(\bar{\kappa}) \in \text{Im}(\bar{A}'Y^T) \), by definition of the image.

Example 2.6. Consider the following network:

\[
\begin{align*}
2A_4 & \xleftarrow{\kappa_4} A_2 + A_3 + A_4 \\
A_2 + 2A_3 & \xleftarrow{\kappa_3} A_4 + 5A_1
\end{align*}
\]

To this network we associate the CRS by multiplying \( YA_\kappa \Psi(\bar{C}) \), which gives
\[
\begin{align*}
\frac{dc_1}{dt} &= 5\kappa_2 c_2 c_3 c_4 - 5\kappa_3 c_4 c_1^5 + \kappa_3 c_4 c_1 - 4\kappa_4 c_1^4 c_3^2 \\
\frac{dc_2}{dt} &= \kappa_1 c_4^2 - \kappa_2 c_2 c_3 c_4 \\
\frac{dc_3}{dt} &= \kappa_1 c_4^2 - \kappa_2 c_2 c_3 c_4 + 2\kappa_3 c_4 c_1^5 - 2\kappa_4 c_1^4 c_3^1 \\
\frac{dc_4}{dt} &= -2\kappa_1 c_4^2 + \kappa_1 c_4^2 - \kappa_3 c_4 c_1^5 + 2\kappa_4 c_1^4 c_3^2.
\end{align*}
\]

Let \( \bar{\kappa} = \{1, 2, 3, 1\}^T \) and \( \omega(\bar{\kappa}) = \{(1, -\log(2), -\log(3))\}^T \). We want to identify which \( \bar{c} \), if any, give us a steady state solution by the method of Theorem 2.5. In this case,

\[
\tilde{A} = \begin{pmatrix}
1 & 0 & 0 & -1 \\
0 & 1 & 0 & -1 \\
0 & 0 & 1 & -1
\end{pmatrix}
\quad \text{and} \quad
Y^T = \begin{pmatrix}
0 & 0 & 0 & 2 \\
0 & 1 & 1 & 1 \\
5 & 0 & 0 & 1 \\
4 & 0 & 2 & 0
\end{pmatrix}.
\]

Reducing \( \tilde{A}Y^T \log(\bar{c}) = \omega(\bar{\kappa}) \) gives the log linear system of equations

\[
\begin{align*}
\log(c_1) - \log(c_4) &= \frac{1}{5} \\
\log(c_2) - 2\log(c_4) &= \frac{9}{10} - \log(2) - \frac{2\log(3)}{5} \\
\log(c_3) - 3\log(c_4) &= \frac{1}{10} + 2\log(3) - \frac{2\log(3)}{5}.
\end{align*}
\]

Setting \( c_4 = 1 \), this last system yields

\[
\begin{align*}
c_1 &= \frac{2^2}{3^5} \\
c_2 &= \frac{1}{2^5 3^5} \\
c_3 &= \frac{2^6}{3^7}.
\end{align*}
\]

Hence, since this \( \bar{\kappa} \) was such that \( \omega(\bar{\kappa}) \in \text{Im}(\tilde{A}Y^T) \), we were able to explicitly identify \( \bar{c}^* \) such that \( \bar{c}^* \) is a steady state solution, using Theorem 2.5.

### 3 Networks Containing Eulerian Cycles

The aim of this section is to extend Theorem 2.5 to more general networks. This will provide a criterion to determine exactly when we may use this particular matrix decomposition to identify steady states. Namely, Theorem 2.5 extends to Eulerian cycles, which we now define.
**Definition 3.1.** A directed graph $G$ contains an **Eulerian cycle** if and only if there exists a closed directed path which includes all the edges in $G$ exactly once.

We arrived at Theorem 2.5 using the structure of $\tilde{A}'\text{Diag}(\tilde{\kappa})$ in the matrix decomposition (1.23). Graphs containing an Eulerian cycle allow for the same condition to be imposed.

**Proposition 3.2.** Let $G$ be a connected, weakly reversible CRN. Then $G$ contains an Eulerian cycle if and only if for each node of $G$ the number of incoming reactions is equal to the number of outgoing reactions. We let $\{\#\{\text{in}\} = \#\{\text{out}\}\}_G$ denote node-wise equality of incoming and outgoing quantities of reactions in $G$.

*Proof.* For a finite graph $G$, we first assume that the condition $\{\#\{\text{in}\} = \#\{\text{out}\}\}_G$ holds. We then choose some node $\alpha$ to be the beginning of a path $P_1$. We define the path such that it includes an edge in the set $E$ at most once. We may select any outgoing path we desire, and because the property $\{\#\{\text{in}\} = \#\{\text{out}\}\}_G$ holds, any node selected for the next step in the path must have an outgoing edge. Because the graph $G$ is finite, this process must terminate. We pursue the path $P_1$ until we have no other outgoing nodes to choose. Note that $P_1$ must actually be a cycle, since the only node which has fewer unvisited outgoing edges than incoming edges is $\alpha$, so $P_1$ must terminate at $\alpha$. In addition, $P_1$ is an Eulerian cycle.

Now consider the graph $G'$ which consists of $G$ minus any edges visited in $P_1$ minus any isolated nodes (i.e., nodes with no edges). Note that all of the assumptions on $G$ also hold for $G'$. Thus, we fix a node $\alpha'$ of $G$, and we use $\alpha'$ to begin defining a path $P_2$, just as we did with $\alpha$ for $P_1$. In fact, we may repeat this as many times as needed, say $n$ times, until we have included every edge of $G$. Writing $G = \bigcup_{i=1}^{n} P_i$, we see that $G$ is a union of cycles, including each edge only once. Since the union of cycles is cyclic, and each edge is included only once in $\bigcup_{i=1}^{n} P_i$, $G$ must be an Eulerian cycle.

We will prove the converse by contradiction. Assume for contradiction that $G$ is a graph for which $\{\#\{\text{in}\} = \#\{\text{out}\}\}_G$ does not hold and $G$ is an Eulerian cycle. Then there must be at least one node of $G$ which has an unequal number of incoming and outgoing reactions. Since an Eulerian path includes all edges exactly once, all edges with this node as an endpoint must be in this path. However, since the number of incoming and outgoing nodes is not equal, this means that the Eulerian cycle cannot both start and end at this node, as there would always be some excluded edge if it did so). Therefore $G$ is not Eulerian, a contradiction. \qed

We are now prepared to generalize Theorem 2.5.
Theorem 3.3. Let $G$ be a CRN. Then there exists $\bar{\kappa}$ such that there a complex-balancing steady state of the form $\kappa_i c^y_i = \kappa_j c^y_j$ for all $i, j$ if and only if $G$ is an Eulerian cycle.

Proof. Assume for contradiction that such a steady state exists but that $G$ is not an Eulerian cycle. Then by Proposition 3.2 there exists a node $\alpha$ with $r$ incoming reactions and $s$ outgoing reactions where $r \neq s$. Since our steady state is complex-balancing, we know that for all reactions coming toward $\alpha$ from a complex $y$ and all outgoing reactions from $\alpha$ to a complex $y'$ that $\sum_{y \rightarrow \alpha} \kappa_{y \rightarrow \alpha} c^y = \sum_{\alpha \rightarrow y'} \kappa_{\alpha \rightarrow y'} c^\alpha$. This is equivalent to saying $\sum_{y \rightarrow \alpha} \kappa_{y \rightarrow \alpha} c^y - \sum_{\alpha \rightarrow y'} \kappa_{\alpha \rightarrow y'} c^\alpha = 0$. However, since $\kappa_i c^y_i = \kappa_j c^y_j$ for all $i, j$, this implies that $r \kappa_{y \rightarrow \alpha} c^y - s \kappa_{\alpha \rightarrow y'} c^\alpha = 0$. We see that $r \kappa_{y \rightarrow \alpha} c^y - s \kappa_{\alpha \rightarrow y'} c^\alpha = 0$. Then $(r - s)(\kappa_{y \rightarrow x} c^y) = 0$, and $(r - s) = 0$, which is a contradiction.

For the converse, take $\kappa_i = c_i = 1$ for all $i$ to obtain a steady state. \hfill \Box

4 Appendix: Related Methods in CRNT

CRNT includes many different approaches to the problem of steady states. Since Eulerian cycles are a subset of networks which have complex-balancing solutions, we review here other techniques used to solve complex-balancing problems and show how they relate to our work in this paper.

4.1 Algebraic Geometry and Complex-Balancing

The method of linear algebra is effective in the context of the Eulerian cycle. However, in order to generalize this notion further, we need to incorporate more sophisticated algebra. This was achieved in [2] using toric varieties; we now review that method in the context of our results.

Convention 4.1. We denote the polynomial ring whose variables represent the rate constants $\kappa_i$ and chemical concentrations $c_j$ of a CRN $G(V, E)$ as $\mathbb{Q}[\kappa, c] = \mathbb{Q}[\kappa_1, \kappa_2, \ldots, \kappa_{|E|}, c_1, c_2, \ldots, c_k]$.

Definition 4.2 (Variety). For an ideal $I \in \mathbb{Q}[\kappa, c]$, the variety of $I$, $V(I) \subset \mathbb{C}^{|E| + k}$, is the set of all rate constants and chemical concentrations such that $f(\kappa_1, \kappa_2, \ldots, \kappa_{|E|}, c_1, c_2, \ldots, c_k) = 0$ for all $f \in I$.

In general, the larger the ideal, the smaller the variety. This is because adding a new polynomial to an ideal adds a new set of roots, which at most can contain the
set of all other shared roots. Note that, while we are interested in rational solutions, we work in \( \mathbb{C} \) because it is algebraically closed.

In CRNT, we are seeking out the zeroes of \( YA_\kappa \Psi(\bar{c}) \). Define \( \langle YA_\kappa \Psi(\bar{c}) \rangle \) to be the ideal generated by the entries of this matrix product. From an algebraic standpoint, the zeroes of \( YA_\kappa \Psi(\bar{c}) \) are precisely the elements of \( V(\langle YA_\kappa \Psi(\bar{c}) \rangle) \subset \mathbb{Q}^m \). This variety is not efficiently computable in general. As in [2], we limit our approach to \( V(\langle A_\kappa \Psi(\bar{c}) \rangle) \). We need two more structures in order to complete our review of [2]. These structures require the following definition.

**Definition 4.3** (Saturation). The saturation of an ideal \( I \) with respect to \( J \), written \( (I : J)^\infty \), is all the elements \( r \in R \) such that \( r \cdot J^N \in I \), where \( N \in \mathbb{N} \).

Over \( \mathbb{C} \), saturation augments an ideal \( I \) in such a way that \( V((I : J)^\infty) \) contains the irreducible components of \( V(I) \) that are not contained in \( V(J) \). In [2], the authors define the complex-balancing ideal \( C_G := \langle (A_\kappa \Psi(\bar{c})) : (c_1 \cdots c_k)^\infty \rangle \). The purpose of this is to remove all solutions requiring trivial concentrations. Now \( C_G \) has a toric subideal, \( T_G \), which is necessarily generated by binomial equations. The insight of [2] is that, in the positive orthant, these varieties have the property that \( V_{>0}(T_G) = V_{>0}(C_G) = V_{>0}(A_\kappa \Psi(\bar{c})) = V_{>0}(YA_\kappa \Psi(\bar{c})) \).

Thus in order to find complex-balancing solutions, one may reduce the problem to one of a system of binomials being equal to zero. This is exactly the situation covered in this paper, in the case of Eulerian cycle. As we have seen, such systems are log-linear and lend themselves to a myriad of computationally efficient methods for solving.

**Example 4.4.** The CRS

\[
\begin{align*}
\frac{dc_1}{dt} &= 5\kappa_2 c_2 c_3 c_4 - 5\kappa_3 c_4 c_5^5 + \kappa_3 c_4 c_1^5 - 4\kappa_4 c_4^1 c_3^2 \\
\frac{dc_2}{dt} &= \kappa_1 c_4^2 - \kappa_2 c_2 c_3 c_4 \\
\frac{dc_3}{dt} &= \kappa_1 c_4^2 - \kappa_2 c_2 c_3 c_4 + 2\kappa_3 c_4 c_1^5 - 2\kappa_4 c_4^1 c_3^1 \\
\frac{dc_4}{dt} &= -2\kappa_1 c_4^2 + \kappa_1 c_4^2 - \kappa_3 c_4 c_5^5 + 2\kappa_4 c_4^1 c_3^2
\end{align*}
\]

has the associated ideal

\[
\langle A_\kappa \Psi(\bar{c}) \rangle = \langle -\kappa_1 c_4^2 + \kappa_4 c_4^1 c_3^2, \kappa_1 c_4^2 - \kappa_2 c_2 c_3 c_4, \kappa_2 c_2 c_3 c_4 - \kappa_3 c_4 c_1^5, \kappa_3 c_4 c_1 - \kappa_4 c_4^1 c_3^2 \rangle.
\]

Because this ideal is toric, we need work no further to employ the more sophisticated methods of toric varieties, which may be found explicitly using programs such as Maple or Macaulay2.
In conclusion, what the algebro-geometric method of [2] allows a reduction in the complexity of the general question, “Given $G$, what are the complex-balancing solutions, if they exist?” When the CRN is an Eulerian cycle, $\langle A_\kappa \Psi(\bar{c}) \rangle$ is already a binomial ideal. Our approach using linear algebra sheds further light on complex-balancing solutions for these networks.

### 4.2 Convex Optimization and CRNT

Because CRNT is by nature applied mathematics, many physical and chemical constraints may be applied to CRN analysis. For example, the conservation of mass adds an additional linear equation which may be used to solve the CRN system. This also means that CRNT may be thought of in terms of optimization problems.

**Definition 4.5** (Optimization Problem). Given a set of functions indexed by $\{f_0, f_1, \ldots, f_k\}$, the associated optimization problem takes the form

$$
\begin{align*}
\text{minimize} & \quad f_0(x) \\
\text{subject to} & \quad f_i \leq b_i, \quad i = 1, \ldots, k,
\end{align*}
$$

where $\bar{x} = (x_1, \ldots, x_k)$ is a variable vector and $b \in \mathbb{R}^k$ is a constant vector.

In general, these problems cannot be easily solved. However, enforcing more structure on an optimization problem yields more accessible solutions.

**Definition 4.6** (Convex Optimization [1]). An optimization problem is *convex* if for all $x, y \in \mathbb{R}^k$

$$
\begin{align*}
f_i(\alpha x + \beta y) &\leq \alpha f_i(x) + \beta f_i(y) \quad \text{for all } \alpha + \beta = 1, \text{ with } \alpha \geq 0, \beta \geq 0.
\end{align*}
$$

**Example 4.7.** Consider the points $(-1, 2)$ and $(1, 2) \in \mathbb{R}^2$. An optimization problem is to minimize the distance between two points, each of which is respectively constrained in a disk of radius one about each of $(-1, 2)$ or $(1, 2)$. This is a convex optimization problem because the Euclidean distance between two points is a convex function, i.e.,

$$
\begin{align*}
d(\alpha x + \beta y, z) &= \sqrt{(\alpha x + \beta y)^2 + z^2} \\
&\leq \alpha \sqrt{x^2 + z^2} + \beta \sqrt{y^2 + z^2} \\
&= \alpha d(x, z) + \beta d(y, z).
\end{align*}
$$
Because convex optimization problems are well studied, it only remains to set up CRNs properly. This requires identifying precise optimization parameters, which is the achievement of [9]. By defining a parameter $b \in \mathbb{R}^m$ that describes external fluctuations in chemical concentrations, the authors are able to state that there are solutions for CRNs under specific circumstances. Specifically, the result of [9] is as follows: for a single terminal-linkage network $G$, and for any $b \in \text{Im}(YA_\kappa)$, there exists a positive steady state for the CRS associated to $G$. Eulerian cycles are single terminal-linkage networks with $b = 0$, which is always in the image of $YA_\kappa$. Thus, the result in [9, Section 2] states that there exists a solution $C^*$ for any Eulerian cycle, as well as a method to identify $\bar{c}^*$. The verification of this claim is what requires the convex optimization set up. The method in our paper adds simplicity: calculating the solution $\bar{c}^*$ Eulerian cycle may be reduced to matrix operations which are computationally more efficient than a general convex optimization problem.
References


