Abstract

The study of the dynamics of chemical reactions, and in particular unusual phenomena such as oscillation has led to the development of mathematical strategies for understanding the equations governing their behavior. One feature of this development is the recognition that dynamical properties of a chemical reaction can be predicted from graph theoretical properties of a certain network, called a Chemical Reaction Network or CRN. It is a remarkable fact that much of the dynamics of these complicated systems of polynomial differential equations can, to a large extent, be understood by looking at an associated linear operator determined by an underlying chemical reaction network. In this paper, we use this perspective to drastically simplify the traditional treatment of the standard results pertaining to so-called deficiency zero systems of CRN theory. This also allows us to present novel proofs entirely in the more natural context of directed graph Laplacians, with minimal chemistry-specific language. In this way we provide an even more accessible introduction to the deficiency zero theory for the average mathematics student with little or no knowledge of chemistry.

1 Introduction

The first sporadic accounts of oscillating chemical reactions were published in the 19th century. At the time, they received very little attention, in part because known examples were difficult to reproduce and in part because of a belief among scientists that such behavior was impossible. When Bray published the first such detailed description of such a reaction in the 1920’s, the consensus among his peers was that the behavior must be the result of experimental error [3]. Indeed, 30 years later Belousov spent 8 years trying to publish a description of his famous reaction. His observations were eventually published in a non-peer reviewed journal. Belousov’s publication allowed other researchers to replicate his example, produce others, and eventually derive conditions needed for such reactions [29]. One feature of this latter development is the recognition that dynamical properties of a chemical reaction can be predicted from graph theoretical properties of a certain network, called a Chemical
Reaction Network or CRN. It is a remarkable fact that much of the dynamics of these complicated systems of polynomial differential equations can, to a large extent, be understood by looking at an associated linear operator determined by an underlying chemical reaction network. We will see that linear operator is, in fact, the weighted (out-degree) Laplacian matrix (defined in Section 2) associated to a directed graph (see Section 2).

The mathematical theory of chemical reaction networks began in the 1950’s with the work of Aris and achieved prominence in the 1970’s with the work of Horn, Jackson, Feinberg, and others. [14, 13, 11]. Since reaction rates are difficult to measure experimentally, this theory was in part motivated by the need to understand exotic behaviors of chemical reactions in a way that does not require knowing precise reaction rates. Examples of such behavior are as oscillation and bi-stability. The landmark 1987 Feinberg paper [9] combines much of this early work into two theorems: the deficiency zero theorem which we discuss below, and a generalization called the deficiency one theorem. In each case, the deficiency (see Definition 4.1) of a reaction network is used to eliminate the possibility of periodic orbits or bi-stability, regardless of rate coefficients. An important tool in this theory is the so-called stoichiometric compatibility class, which is essentially a class of systems where the number of atoms of each element present is preserved (as in the case of a chemical reaction). These are closely related to the invariant sets we define in Definition 3.3. Thus the deficiency zero theorem provides conditions under which the existence and uniqueness of an equilibrium in each stoichiometric compatibility class can be shown.

It is natural to view a traditional chemical reaction diagram, consisting of chemical compounds connected by arrows, as a directed graph. Probably the first paper in which this was done was [22, 23]. It turns out that many notions in the theory of chemical reaction networks have direct parallels in the language of directed networks. Indeed, strictly from the perspective of dynamics, there is independent mathematical interest in the notion that the behavior of the highly non-linear system can be at least partly understood by the analysis of directed graphs. There are many recent papers [20, 8, 17] that make use of this interplay to derive new results. However, much of the study of the Laplacian matrix in algebraic graph theory applies only to undirected graphs. Recent study of the directed graph Laplacian, in particular an effort to standardize the treatment of dynamical processes related to this matrix [27, 28, 6, 18], allow for a new perspective on the foundations of chemical reaction network theory.

In this paper, we use this perspective to drastically simplify the traditional treatment of the standard results pertaining to so-called deficiency zero systems of CRN theory. This also allows us to present the proofs with minimal chemistry-specific language, thereby providing an even more accessible introduction to the deficiency zero theory for the average mathematics student with little or no knowledge of chemistry. We cast our theory entirely in the standardized language of Laplacians and thereby entirely avoid the mention of stoichiometry, complex balance, and reversibility. We obtain all the classical results of the zero deficiency theory, and in some cases stronger versions, but with much less effort.

This is an area of active on-going research. One main focus of research is the Global Attractor conjecture, one of the open problems in the field, which asks whether the equilibrium within each invariant class (see Corollaries 5.4 and 6.3) is in fact a global attractor. This conjecture appears as early as [14], where it was mistakenly believed to be proved, and has been shown in certain cases as in [1]. We hope that our approach can provide new insight into this intriguing problem. The analysis of higher deficiency reaction networks is another active area of study [15, 19, 16]. Some results can be extended fairly easily to the deficiency 1 case as discussed in [10], but in general the behavior of
higher deficiency networks is not well understood. Another important open question that is related to the Global Attractor conjecture is that of “persistence”. In general, a persistent reaction network is one in which all chemical concentrations eventually have a positive lower bound. Informally, this means that the concentration of each species does not come close to dying out [4, 10]. One famous and, so far, unproved conjecture is that this is holds for every network whose associated directed graph is componentwise strongly connected (see 2.7) [21].

The original emphasis in reaction networks was biased towards controlling chemical reactions and therefore trying to ensure that exotic behavior does not arise. However, in recent years the promise of applying CRN theory to complex biological systems has shifted that interest towards seeking out and analyzing these behaviors [12]. For instance, for high deficiency case, it possible that reactions take place even though the the associated linear system of reaction equations is at an equilibrium. For a collection of examples, we refer the reader to the recently published [10].

The outline of this paper is as follows. In Section 2, we summarize the theory of graph Laplacians and its conclusions. The next section describes the mathematical definition of chemical reaction networks with mass action and subsequently we define the abstract Laplacian system on which we base our mathematical analysis. Section 4 states and proves the zero deficiency theorem. In Sections 5 and 6 it is proved that in zero deficient systems satisfying a certain connectedness property, each invariant subspace has a unique asymptotically stable equilibrium. Then we present some examples to illustrate the theory. In Section 7, we present a short dictionary between our results and their classical counterparts. Finally, in Section 8, we list some elementary results mainly from calculus and linear algebra, that are used in the main text.

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2 Laplacians

It is important to bear in mind that working using directed graphs to model certain phenomena can be confusing. Different authors may choose different orientation of the edges. And it does not stop there. For some applications authors tend to use the in-degree Laplacian as their go-to Laplacian (this is common in control theory) and in other cases (such as CRN) the out-degree Laplacian is used more often. Finally, since the Laplacians are not symmetric, the Laplacian in one paper might be the transpose of the Laplacian in another paper. In this work, we use the conventions of [5, 27, 28].

We now give a few of the basic facts of Laplacian dynamics in a directed graph G. From now on, we will assume that G has \( v \) vertices and \( e \) directed edges. The graph obtained by reversing the orientation of all edges will be called \( G^\ast \). The \( v \times e \) matrix \( B \) is the begin matrix [26] such \( B_{ij} = 1 \) if vertex \( i \) starts edge \( j \) and 0 otherwise. Similarly, the \( v \times e \) end matrix [26] \( E \) is defined by \( E_{ij} = 1 \) if vertex \( i \) ends edge \( j \) and 0 otherwise. We use these matrices to define the boundary operator (or incidence matrix in graph theory texts) \( \partial \):

\[
\partial = E - B.
\]

The weight matrix \( W \) is diagonal with (strictly) positive weights on the diagonal. The weights are equal to 1 in the unweighted case.

**Definition 2.1** [26] The undirected weighted Laplacian \( L \) is given by:

\[
L \equiv \partial W \partial^T = (E - B)W(E - B)^T.
\]
It is the sum of the in-degree Laplacian $L_{in}$ and the out-degree Laplacian $L_{out}$.

\[ L_{in} = EW(E - B)^T \quad \text{and} \quad L_{out} = -BW(E - B)^T. \]

Note that the out-degree Laplacian of $G$ is the same as the in-degree Laplacian of $G^\circ$.

**Remarks:** In general, a Laplacian is a square matrix with non-negative diagonal and non-positive off-diagonal elements whose row-sums all give zero. It is easy to see that any such matrix can be written in the form stipulated by Definition 2.1. We will not consider undirected graphs.

**Definition 2.2** [5, 27, 28] Given a directed graph $G$. A vertex $j$ is in the set reachable from the vertex $i$ if there is a directed path from $i$ to $j$. The set reachable from $i$ is called $R(i)$. A reach $R$ is a maximal reachable set. A cabal is the maximal set of vertices from which all of $R$ is reachable. A co-reach is a reach in $G^\circ$ and a co-cabal is a cabal in $G^\circ$. We assume that the reaches of a graph are labeled and ordered and denote the $m$th reach by $R_m$. The cabal of $R_m$ is denoted $B_m$. Similarly, $H_m$ is the set of vertices contained in $R_m$, but no other reach, and $C_m = R_m - H_m$.

We note that a cabal consisting of a single vertex is usually called a leader.

**Theorem 2.3** [5, 27, 28] Let $G$ be a digraph with $k \geq 1$ reaches. The eigenvalue 0 of $L_{in}$ has geometric and algebraic multiplicity $k$. All other eigenvalues have negative real part.

**Theorem 2.4** [5, 27, 28] Let $G$ be a digraph with $k \geq 1$ reaches. The right kernel of a Laplacian $L_{in}$ consists of the column vectors $\{\gamma_1, \cdots, \gamma_k\}$, where:

\[
\begin{align*}
\gamma_{m,j} &= 1 \quad \text{if} \quad j \in H_m \quad \text{(exclusive)} \\
\gamma_{m,j} &\in (0,1) \quad \text{if} \quad j \in C_m \quad \text{(common)} \\
\gamma_{m,j} &= 0 \quad \text{if} \quad j \notin R_m \quad \text{(not in reach)} \\
\sum_{m=1}^{k} \gamma_{m,j} &= 1
\end{align*}
\]

**Theorem 2.5** [27, 28] Let $G$ be a digraph with $k \geq 1$ reaches. The left kernel of a Laplacian $L_{in}$ consists of the row vectors $\{\tilde{\gamma}_1, \cdots, \tilde{\gamma}_k\}$, where:

\[
\begin{align*}
\tilde{\gamma}_{m,j} &> 0 \quad \text{if} \quad j \in B_m \quad \text{(cabal)} \\
\tilde{\gamma}_{m,j} &= 0 \quad \text{if} \quad j \notin B_m \quad \text{(not in cabal)} \\
\sum_{j=1}^{k} \tilde{\gamma}_{m,j} &= 1 \\
\{\tilde{\gamma}_m\}_{m=1}^{k} \text{ are orthogonal}
\end{align*}
\]

Later on it will be of considerable importance that the vectors $\{\tilde{\gamma}_1, \cdots, \tilde{\gamma}_k\}$ have disjoint support (as opposed to the vectors $\{\gamma_1, \cdots, \gamma_k\}$) and so form an orthogonal basis of the left kernel. We note in passing that these null vectors form a basis for the space of stationary distributions in Markov chains [27, 28] and are related to the maximal spanning forests [7].

**Definition 2.6** For directed graphs, we distinguish weakly connected components – a maximal group of vertices for which there is an undirected path between every pair of vertices – from strongly connected components (SC’s) – a maximal group of vertices for which there a directed path between every pair of vertices.
Definition 2.7 A graph $G$ is componentwise strongly connected (abbreviated to CSC) if every weak component is a strong component. Equivalently, every vertex is in a cabal.

We remark here that the following statements are equivalent:

- $G$ is a CSC,
- $G^\circ$ is a CSC, and
- every reach of $G$ (or $G^\circ$) is an SC.

Lemma 2.8 For any $G$, $\dim \text{Im} \partial$ equals the number of vertices minus the number of weak components. Furthermore, $\dim \text{Im} \partial^T$ equals the number weak components.

Proof. It is sufficient to prove this if $G$ consists of one weak component. Suppose $G$ is a weak component with $v$ vertices and $k$ reaches $\{R_i\}_1^k$. Note that $\partial^T 1 = 0$. Lemma 8.2 now implies that $\dim \text{Ker} \partial + \dim \text{Im} \partial = v$. Thus $\dim \text{Im} \partial \leq v - 1$.

Choose an arbitrary vertex $b$ as basepoint and let $r \neq b$ be any other vertex. By definition 2.2, there is an undirected path $\gamma$ from $b$ to $r$. Consider the directed edges $e_i$ of $\gamma$. When $\gamma$ traverses $e_i$ in the positive direction, multiply $e_i$ by $w_i = +1$, and in the other case by $w_i = -1$. The image under $\partial$ of $\sum w_i e_i = r - b$. This shows that $\dim \text{Im} \partial \geq v - 1$. The second statement follows from the first, because Lemma 8.2 implies that the sum of the two dimensions must be $v$.

Remark: This lemma is standard fare for students of algebraic graph theory [2] and, in fact, algebraic topology. In a nutshell, it is how the zeroth homology and cohomology groups are computed. To illustrate the procedure in the second paragraph of the proof, we turn to Figure 2.1. In that figure, denote the vertices marked with $i$ by $v_i$ and the edges marked with $k_j$ by $e_j$. Choose, for example, basepoint $e_1$ and endpoint $r = v_7$. A path $\gamma$ from $b$ to $r$ is given by $-e_2 + e_8$. Apply the boundary operator to get $\partial \gamma = -(v_6 - v_1) + (v_7 - v_0) = v_7 - v_1$. 

Figure 2.1: An example of a directed network.
3 Chemical Reaction Networks with Mass Action

The basic ingredients of a CRN are:

\[
\begin{aligned}
& c \text{ “concentrations of molecules or similar chemical substances”, each denoted by } x_i \\
& v \text{ vertices or “reacting mixtures”, each denoted by } v_i \\
& e \text{ directed edges or “reactions”, each denoted by } e_i.
\end{aligned}
\]

We then associate a linear vector space to each of these. The column vectors \((x_1, \ldots, x_c)^T\) form the space \(\mathbb{R}^c\); to each \(e_i\) we associate the \(i\)th standard basis vector in \(\mathbb{R}^e\); and in the same way the \(v_i\) give rise to \(\mathbb{R}^v\). To illustrate these notions, we note that the begin and end matrices \(B\) and \(E\) defined in Section 2 correspond to linear transformations \(B\) and \(E\) from \(\mathbb{R}^e\) to \(\mathbb{R}^v\), whereas their transpose acts in the opposite direction.

Next, we describe the relationship between the reacting mixtures and the molecules. (Note that we are dropping the quotation marks.) The count of \(j\)-molecules in the \(i\)th vertex – or reacting mixture – equals \(S_{ji}\). This defines a matrix \(S\) all of whose entries are non-negative integers. Given \(v \in \mathbb{R}^v\), a reacting mixture vector whose \(i\)th component is the number of reacting mixtures of type \(i\), the count of each type of molecule is

\[
x = Sv \quad \text{or} \quad x_j = \sum_{n} S_{ji}v_i. \tag{3.1}
\]

Note that if the \(j\)th row is of \(S\) is zero, then \(x_j\) is not defined. So \(S\) has no zero rows.

The physical intuition behind a reaction \(v_i \overset{e_\ell}{\rightarrow} v_j\) in a solution of chemicals is that the reaction rate is proportional to the probability that all the necessary molecules in \(v_i\), the tail of the arrow \(e_\ell\), “meet” in some small volume (this is called the mass action principle). The probability that molecule \(r\) is present in some small volume is proportional to \(x_r\), its concentration in the chemical mix. Assuming these probabilities are independent of one another, we see that the probability that all the right molecules of \(v_i\) are present in the small volume equals the product of all the concentrations of the the molecules in \(v_i\). With the above definition of \(S\), we see that this product is proportional to \(\prod_j x_j^{S_{ji}}\). We thus define a vector in vertex space \(\mathbb{R}^v\) (using the convention that \(0^0 := 1\)):

\[
\psi_i(x) \equiv \prod_j x_j^{S_{ji}} \quad \text{abbreviated to} \quad \psi(x) = \prod x^{S^T} \in \mathbb{R}^v. \tag{3.2}
\]

Next, we transform \(\psi \in \mathbb{R}^v\) to the vector in the edge space \(\mathbb{R}^e\) whose \(\ell\)th component is the reaction rate of the \(\ell\)th reaction \(v_i \overset{e_\ell}{\rightarrow} v_j\). From the previous paragraph, we conclude that the rate of the \(\ell\)th reaction is proportional to \(\psi_i(x)\), where the \(i\)th vertex is the tail of the \(\ell\)th directed edge. Thus using the begin matrix \(B\) of Section 2, we see that the reaction rates are proportional to

\[
B^T \psi(x) \in \mathbb{R}^e.
\]

In the chemical literature, this proportionality is (nearly) always expressed by a constant called \(k\). It is important to note that this constant is associated with the \(\ell\)th reaction – or edge – and not with the reacting mixture – or begin vertex – of that reaction. Thus we weight the edges using an \(e \times e\) diagonal matrix \(W\) whose \(\ell\)th diagonal element equals a (strictly) positive constant \(k_\ell\). The reaction rates are therefore given by

\[
WB^T \psi(x) \in \mathbb{R}^e.
\]
The reaction $\ell \rightarrow j$ adds to the mixture $j$ and subtracts from the mixture $\ell$, both at the rate $k_\ell \psi_\ell$. Again, with the definitions of $E$ and $B$ of Section 2, we compute the rates of change of the reacting mixtures $v \in \mathbb{R}^v$ as:

$$\dot{v} = (E - B)WB^T \psi(x) = \partial WB^T \psi(x) = -L^T_{\text{out}} \psi(x).$$

Finally, in chemical situations we can’t necessarily measure or observe directly the concentrations of reacting mixtures. Rather, we observe the concentrations of the various molecules $x_i$. That gives us the final form of the dynamical system associated to chemical reaction networks

$$\dot{x} = -SL^T_{\text{out}} \psi(x) \in \mathbb{R}^c. \quad (3.3)$$

Solutions of this system can also be derived from the solutions of the following system:

$$\dot{v} = -L^T_{\text{out}} \psi(Sv) \in \mathbb{R}^v, \quad (3.4)$$

where we used (3.1). Interestingly, the reverse is not necessarily true. A solution of (3.3) does not always determine a unique solution of (3.4). In fact, one of the problems that comes up in this type of system, is whether non-trivial reactions can take place even though $\dot{x} = 0$. From the above equations one can see that could happen if during these reactions $\dot{v} \in \text{Ker} S$. This is of course impossible if $\text{Ker} S \cap \text{Im} L^T_{\text{out}} = 0$, as we will see in Section 4.

To summarize the whole framework schematically, here is a diagram of the transformations involved in (3.6).

$$\mathbb{R}^c \leftarrow S \mathbb{R}^v \leftarrow \partial \mathbb{R}^e \leftarrow W \mathbb{R}^e \leftarrow B^T \mathbb{R}^e \leftarrow \psi \mathbb{R}^v \leftarrow \mathbb{R}^c. \quad (3.5)$$

Our next result is a reality check. Since concentrations cannot be negative, we want to make sure that the set $\mathbb{R}^c_+ = \{ x \in \mathbb{R}^c \mid \forall i : x_i \geq 0 \}$, also called the positive orthant, is forward invariant.

**Proposition 3.1** The positive orthant is forward invariant under the flow of (3.3).

**Proof.** It is sufficient to show that if $x_j = 0$, then $\dot{x}_j \geq 0$, because by the existence and uniqueness for ODE [25], solutions cannot cross each other.

So suppose $x_j = 0$. Since $S$ has no zero rows, there must be a $i$ such that $S_{ji}$ is a positive integer. From (3.2) we see that then $\psi_i = 0$. The off-diagonal elements of $-L^T_{\text{out}}$ are non-negative, and so for that same $i$

$$(-L^T_{\text{out}} \psi)_i = \sum_j (-L^T_{\text{out}})_{ij} \psi_j \geq 0.$$  

Using again that $S_{ji}$ is non-negative, we have

$$\dot{x}_j = -(SL^T_{\text{out}} \psi)_j = \sum_i S_{ji} (-L^T_{\text{out}} \psi)_i \geq 0.$$  

This proves the proposition.  

7
The preceding development shows that an out-degree Laplacian arises naturally in the analysis of CRNs. We will see that the algebraic results in Section 2 are of great use in this analysis. However to make use of them, we will need to adapt them to the out-degree Laplacian. Fortunately, this is extremely simple thanks to the dual relationship between the two, namely $L_{\text{out}}(G) = L_{\text{in}}(G^\circ)$ noted in definition 2.1. Theorems 2.3, 2.4, and 2.5 hold for $L_{\text{out}}$ if we replace each instance of reach and cabal with the dual notions of co-reach and co-cabal.

For the further mathematical development of the theory, there are a few facts that we will not use. The most important ones are the fact that $S$ is an integer matrix and the fact that the Laplacian is out-degree. Hence in the next few sections, we consider the following slightly more general problem. We will only return to considerations specific to actual chemical networks in Section 7.

**Definition 3.2** From now on, the matrix $S$ is a non-negative matrix with no zero rows, $\psi : \mathbb{R}^c_+ \rightarrow \mathbb{R}^v_+$ is defined in (3.2) and $L$ (the Laplacian) is $v \times v$ matrix with non-negative diagonal and non-positive off-diagonal elements whose row-sums all give zero. We consider the following system

$$\dot{x} = -SL^T \psi(x) \in \mathbb{R}^c. \quad (3.6)$$

Equation (3.6) implies that $\dot{x} \in \text{Im } SL^T$. Thus the orthogonal projection of $x$ to $(\text{Im } SL^T)^\perp = \text{Ker } LS^T$ is in fact a constant of the motion. Thus we have the following.

**Definition 3.3** Let $P : \mathbb{R}^c_+ \rightarrow \text{Ker } LS^T$ be the orthogonal projection. The sets $X_z$ are defined as $\{x \in \mathbb{R}^c_+ | P(x) = z\}$ and will be called invariant sets since they are invariant under the flow of (3.3).

### 4 The Laplacian Zero Deficiency Theorem

**Definition 4.1** The Laplacian deficiency of a chemical reaction network is given by

$$\delta_L \equiv \dim [\text{Ker } S \cap \text{Im } L^T] = \dim \text{Ker } SL^T - \dim \text{Ker } L^T.$$

**Theorem 4.2 (Zero Laplacian Deficiency)** Suppose a chemical reaction network (or CRN) has $\delta_L = 0$. Then the CRN has a (strictly) positive equilibrium if and only if $G$ is CSC.

**Proof.** We first prove $\implies$. From equation (3.6) we see that the existence of a positive equilibrium together with $\delta_L = 0$ implies that there is a positive vector $\psi^* = \psi(x^*)$ such that $L^T \psi^* = 0$. From Theorem 2.5, we conclude that (recalling that $k$ is the number of reaches)

$$\psi(x^*)^T = \sum_{m=1}^{k} a_m \tilde{\gamma}_m \quad \text{or} \quad \psi(x^*) = \sum_{m=1}^{k} a_m \tilde{\gamma}_m^T, \quad \forall a_m > 0. \quad (4.1)$$

Furthermore, since $x^* > 0$, we have $\psi^* > 0$ and so from the form of the $\tilde{\gamma}_m$, one notes that each reach must be a cabal, and thus a strong component. Thus $G$ is CSC.
Now we prove $\Leftarrow$. Suppose that every reach is a strong component, then using $\delta_L = 0$ we must show that (4.1) has a positive solution $\psi^*$ with $x^* > 0$. By positivity, we can take the componentwise logarithm of both sides. We note that $\ln \psi(x^*) = S^T \ln x^*$. The logarithm of the right hand side of (4.1) can be written as

$$\ln \sum_{m=1}^{k} a_m \bar{\gamma}_m^T = \sum_{m=1}^{k} (\ln a_m) 1_{R_m} + \ln \sum_{m=1}^{k} \bar{\gamma}_m^T,$$

where $1_{R_m}$ is the characteristic vector of the $m$th reach or (in this case) component. Note that $\sum_{m=1}^{k} \bar{\gamma}_m$ has all components positive by assumption. Thus from (4.1) we see that we need to solve

$$S^T \ln x^* = \sum_{m=1}^{k} (\ln a_m) 1_{R_m} + \ln \sum_{m=1}^{k} \bar{\gamma}_m^T.$$  \hfill (4.2)

In turn, this can be re-arranged as

$$\ln \sum_{m=1}^{k} \bar{\gamma}_m^T = S^T \ln x^* - \sum_{m=1}^{k} (\ln a_m) 1_{R_m}.$$  \hfill (4.3)

We observe that the first term of the right hand side ranges over $\text{Im} S^T$ and the second over $\text{Ker} L$. This has a solution if $\text{Im} S^T + \text{Ker} L = \mathbb{R}^v$. However, this is guaranteed by applying Proposition 8.3 to the zero deficiency condition.

One direction in this theorem can be significantly strengthened.

**Corollary 4.3** Suppose a chemical reaction network (or CRN) has $\delta_L = 0$. If the CRN has an orbit $x(t)$ such that for all $i$, $\ln x_i(t)$ is bounded, then $G$ is CSC.

**Proof.** We compute

$$\frac{x(\tau) - x(0)}{\tau} = \frac{1}{\tau} \int_0^\tau \dot{x} \, dt = -\frac{1}{\tau} \int_0^\tau S L^T \psi(x) \, dt = -S L^T \frac{1}{\tau} \int_0^\tau \psi(x) \, dt.$$

The left hand clearly converges to 0 as $\tau$ tends to infinity. The requirement on $x_i$ implies that it is bounded away from both 0 and infinity. Thus the term $\frac{1}{\tau} \int_0^\tau \psi(x) \, dt$ is a function $F : \mathbb{R}^+ \to [\epsilon, \epsilon^{-1}]^v$ for some $\epsilon > 0$. Since its range is compact, $F(n)$ must have a subsequence $F(n_i)$ convergent to some $F_\infty > 0$. For that subsequence, we get

$$0 = \lim_{i \to \infty} \frac{x(n_i) - x(0)}{n_0} = -S L^T F_\infty.$$

The remainder of the proof is as in the first part of Theorem 4.2 with $F_\infty$ replacing $\psi^*$.  \hfill $\blacksquare$
5 Existence and Uniqueness of Fixed Points

From now on, we will frequently use the Hadamard product ($\circ$) and its division counterpart (/). The definitions can be found in the appendix.

We will show that a CRN whose associated graph is CSC with zero Laplacian deficiency has exactly one positive equilibrium in each invariant set $X_z$ (see Definition 3.3). Informally speaking, then, the set of equilibria forms a graph (as in: is a function of) over Ker $LS^T$. The precise formulation is given below in Corollary 5.4.

**Lemma 5.1** Given a CSC system with $\delta_L = 0$. Suppose $x_1 > 0$ is an equilibrium. Then $x_2 > 0$ is an equilibrium iff $\ln \left[ \frac{\psi(x_2)}{\psi(x_1)} \right] \in \text{Ker } L$, which in turn is equivalent to $\ln \left[ \frac{x_2}{x_1} \right] \in \text{Ker } LS^T$.

**Proof.** By our hypotheses, $x_1 > 0$ is an equilibrium iff $\psi(x_1) = \sum_{i=1}^{k} a_i \gamma_i^T$, with all $a_i > 0$. Similarly, the fact that $x_2 > 0$ is an equilibrium is equivalent to $\psi(x_2) = \sum_{i=1}^{k} b_i \gamma_i^T$, with all $b_i > 0$. Thus, given that $x_1 > 0$ is an equilibrium, the same holds for $x_2$ iff

$$\psi(x_2)/\psi(x_1) = \sum_{i=1}^{k} \frac{b_i}{a_i} \mathbf{1}_{R_i} \iff \ln \left[ \frac{\psi(x_2)}{\psi(x_1)} \right] = \sum_{i=1}^{k} \ln \left[ \frac{b_i}{a_i} \right] \mathbf{1}_{R_i} \iff \ln \left[ \frac{x_2}{x_1} \right] \in \text{Ker } LS^T,$$

where we used that $\ln \psi = S^T \ln x$.

**Proposition 5.2** Given a CSC system with $\delta_L = 0$. For every $z \in \text{Ker } LS^T$, there exists $y \in \text{Im } SL^T$ such that $z + y$ is a positive equilibrium.

**Proof.** By Theorem 4.2, we may fix a positive equilibrium $x^*$. We also fix $z \in \text{Ker } LS^T$. By Lemma 5.1, any positive equilibrium $x$ can now be written as $x = x^* \circ \text{Exp } \mu$ with $\mu \in \text{Ker } LS^T$. It is now sufficient to show that there is a $\mu^* \in \mathbb{R}^c$ so that $x^* \circ \text{Exp } \mu^* - z$ is orthogonal to Ker $LS^T$ (i.e. is in $\text{Im } SL^T$), for then $z + y$ is a positive equilibrium. Thus we wish to prove

$$\exists \mu^* \in \text{Ker } LS^T \text{ such that } \forall v \in \text{Ker } LS^T : (x^* \circ \text{Exp } \mu^* - z, v) = 0,$$

where ($,$) stands for the usual inner product. We settle this by defining a smooth function $g(\mu)$ with a minimum at $\mu^*$ and with derivative $x^* \circ \text{Exp } \mu - z$.

To accomplish this, define $g : \mathbb{R}^c \to \mathbb{R}$ by setting

$$g(\mu) = (x^*, \text{Exp } \mu) - (z, \mu).$$

This function is a sum of $c$ 1-dimensional functions described in Lemma 8.6. Let $r_-$ be the minimum of the $c$ values for $x_-$ in that lemma and $r_+$ the maximum of the $x_+$. The lemma implies that

$$\forall \mu \notin [r_-, r_+]^c : g(\mu) \geq \sum_{i=1}^{c} x_i^* = g(0).$$

Therefore the set $C$ defined by

$$C \equiv \{ x \in \text{Ker } LS^T \mid g(x) \leq g(0) \}$$

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is non-empty (as it contains 0), closed (by continuity of \( g \)), and bounded.

Now we restrict \( g \) to \( \text{Ker} \, LS^T \). Since \( 0 \in \text{Ker} \, LS^T \), the continuous function \( g \) assumes its minimum in \( \text{Ker} \, LS^T \) at a point \( \mu^* \). Since \( g \) is also differentiable, at \( \mu = \mu^* \), we must have

\[
\forall v \in \text{Ker} \, LS^T : 0 = (Dg(\mu^*),v) = \lim_{\epsilon \to 0} \frac{g(\mu^* + \epsilon v) - g(\mu^*)}{\epsilon} = (x^* \odot \text{Exp} \mu^* - z, v),
\]

which establishes equation (5.1), thereby proving the proposition.

**Proposition 5.3** Given a CSC system with \( \delta_L = 0 \). For every \( z \in \text{Ker} \, LS^T \), there exists at most one \( y \in \text{Im} \, SL^T \) such that \( y + z \) is a positive equilibrium.

**Proof.** Suppose that the proposition is false and we have \( y_1 \) and \( y_2 \) both satisfying the requirements. Then by Lemma 5.1

\[
\text{Ln} \, (z + y_2) - \text{Ln} \, (z + y_1) \in \text{Ker} \, LS^T,
\]

and by hypothesis

\[
(z + y_2) - (z + y_1) \in \text{Im} \, SL^T.
\]

By Lemma 8.2, the two are orthogonal. Taking the inner product of the two differences gives

\[
((z + y_2) - (z + y_1), \text{Ln} \, (z + y_2) - \text{Ln} \, (z + y_1)) = 0.
\]

Lemma 8.5 now gives the result.

Putting the last two propositions together immediately gives the main result of this section. (We used Lemma 8.2 in the formulation of this result.)

**Corollary 5.4** For a CSC system with \( \delta_L = 0 \) we have the following. For every \( z \in \text{Ker} \, LS^T \), there is a unique \( y \in (\text{Ker} \, LS^T)^\perp = \text{Im} \, SL^T \) such that \( y + z \) is a positive equilibrium.

### 6 Convergence to Equilibria

For the definition of Lyapunov functions and the result concerning that we will need, we refer the reader to the appendix (Definition 8.7 and Theorem 8.8).

The existence of Lyapunov functions depends crucially on the following remarkable result.

**Proposition 6.1** Let \( \psi \) be a arbitrary (strictly) positive vectors and \( L \) an arbitrary in-degree or out-degree Laplacian. Suppose that \( \psi^* > 0 \) and \( \psi^* L = 0 \), then the associated graph is CSC and for all \( \psi > 0 \)

\[
\psi^T L (\text{Ln} \, \psi - \text{Ln} \, \psi^*) = (\psi - \psi^*)^T L (\text{Ln} \, \psi - \text{Ln} \, \psi^*) \geq 0.
\]

Equality holds if and only if on every strong component \( C_i \) there is a constant \( c_i > 0 \) such that

\[
\psi|_{C_i} = c_i \psi^*|_{C_i}.
\]
Proof. Let $\psi^* > 0$ and $\psi^T L = 0$. We start by observing that Theorem 2.5 says that then every vertex is in a cabal. This implies that the associated graph is CSC. Now we write

$$\psi^T L (\ln \psi - \ln \psi^*) = \psi^T L \ln (\psi/\psi^*)$$

in terms of a sum over its edges. For every directed edge, let $w_{ij}$ be the weight of the edge $j \to i$ (if $L$ is in-degree) and $i \to j$ (if $L$ is out-degree). Denote by $\sum_{\text{edges}}$ the sum over all directed edges. We obtain that $\psi^T L \ln (\psi/\psi^*)$ equals

$$\sum_{\text{edges}} w_{ij} \psi_i (\ln \psi_i/\psi^*_i - \ln \psi_j/\psi^*_j) = \sum_{\text{edges}} \psi^*_i w_{ij} \psi_i/\psi^*_i (\ln \psi_i/\psi^*_i - \ln \psi_j/\psi^*_j) \geq \sum_{\text{edges}} \psi^*_i w_{ij} (\psi_i/\psi^*_i - \psi_j/\psi^*_j) = \psi^T L (\psi/\psi^*).$$

The only inequality follows from Lemma 8.4 (plus the fact that all weights are positive). By assumption, $\psi^T$ is in the left kernel of $L$, and so the last expression gives zero.

Lemma 8.4 also implies the necessary and sufficient condition for equality. To be precise, that lemma asserts that the condition for equality in the above formula is that on each edge the value of $(\psi/\psi^*)$ at the head equals its value at the tail. Therefore $(\psi/\psi^*)$ is constant (and positive) on every reachable and co-reachable set.

Proposition 6.2 Given a Laplacian $L$ with $\delta_L = 0$ that has a strictly positive null vector $x^*$. The $\omega$-limit set of a point $x$ is bounded and is contained in the union of the boundary of $\mathbb{R}^c_+$ and the set of positive fixed points.

Proof. We will first show that $V : \mathbb{R}^c_+ \to \mathbb{R}$ in (6.1) defined by

$$V(x) \equiv \sum_{i=1}^c \int_{x_i}^{x_i^*} \ln(s/x^*_i) \, ds. \quad (6.1)$$

is a Lyapunov function (Definition 8.7) for (3.6). $V$ is clearly continuously differentiable. To show that $\dot{V} \leq 0$, we observe

$$\dot{V} = \dot{x}^T \ln(x/x^*) = - (S L^T \psi(x))^T \ln(x/x^*) = - \psi^T L S^T \ln(x/x^*) = - \psi^T L \ln(x/x^*).$$

Note from (3.2) that $x > 0$ implies $\psi(x) > 0$. It now follows from the first part of Proposition 6.1 that $\dot{V}(x(t)) \leq 0$. The second part of Proposition 6.1 says that $\dot{V}(x) = 0$ iff $\ln [\psi/\psi^*]$ is constant on strong components. Theorem 2.4 implies that then $\ln [\psi/\psi^*]$ is a right null vector of $L$. From Lemma 5.1 we conclude that then $\dot{V}(x) = 0$ implies that $x$ is an equilibrium.

Thus by Theorem 8.8, the $\omega$-limit set of an initial condition may be unbounded, may contain boundary points of the orthant, and may contain equilibrium points. We rule out the first possibility (unbounded) by showing that trajectories are bounded. Each integral in the sum of (6.1) has the form $I_b(a) = \int_b^a \ln s - \ln b \, ds$, we have

$$I_b(a) = \int_b^a \ln s - \ln b \, ds = [s \ln s - s - s \ln b]_b^a = a(\ln a - \ln b) - (a - b) \geq 0 \quad (6.2)$$
The final inequality here follows from Lemma 8.4. Thus each of the integrals in (6.1) is non-negative. Furthermore, on the one hand, \( V \leq 0 \) and so \( V(x(t)) \leq V(x(0)) \), and on the other,

\[
\int_{b}^{a} \ln s - \ln b \, ds = a(\ln a - \ln b - 1) + b
\]

tends to infinity if \( a \to \infty \). This proves that orbits are bounded.

**Remark:** We have required that system satisfies \( \delta_L = 0 \). This is used to ensure that for any positive equilibrium \( x^* \), we have \( \psi(x^*) = \sum_{i=1}^{k} a_i x_i^T \). If we start with the assumption that there is an equilibrium of that form, the hypothesis \( \delta_L = 0 \) is not necessary.

**Corollary 6.3** Suppose \( G \) is CSC with \( \delta_L = 0 \). The flow of (3.6) restricted to the invariant sets \( X_z \) (see Definition 3.3) has a unique positive equilibrium \( p_z \). Furthermore, that equilibrium is asymptotically stable in \( X_z \). The \( \omega \)-limit set of any initial condition either equals that equilibrium or is a bounded set contained in the boundary of the positive orthant.

**Proof.** Existence and uniqueness of \( p_z \) in \( X_z \) follow from Corollary 5.4. Given any positive equilibrium \( x^* \) and consider the function \( V \) in (6.1). Thus \( V \) is a sum of integrals as exhibited in (6.2):

\[
V(x) = \sum_{i=1}^{c} I_{x_i^*}(x_i).
\]

Now \( I_{x_i^*}(x_i) \) has a minimum 0 achieved at \( x_i = x_i^* \) and \( I_{x_i^*}(0) = x_i^* \). On the boundary \( \partial X_z \) of \( X_z \), at least one of the \( x_i \) must be zero. Therefore, \( V \) restricted to \( \partial X_z \) is greater than or equal to \( \min_i x_i^* \). So if we choose an initial condition \( x(0) \) such that \( V(x(0)) = V_0 < \min_i x_i^* \). From (6.2), we conclude that on the boundary of \( X_z \), we must have \( V \geq \min_i x_i^* \). Since \( \dot{V} \leq 0 \), the boundary cannot be reached from this initial condition. Thus by Proposition 6.2, the omega limit set is contained in the set of fixed points. But by Corollary 5.4, the fixed point is unique. Thus it is asymptotically stable.

**Remark:** This proof gives us a way of estimating the size of the basin of attraction of the fixed provided we know the coordinates of any positive fixed point of the system.

7 Comparison with Classical Results

We briefly compare our formulation of the main results – Theorem 4.2 and Corollaries 5.4 and 6.3 – with their formulation in the literature. For this we briefly return to the context of actual chemical reactions. Recall the equation (3.3), governing this type of system

\[
\dot{x} = -SL_{\text{out}}^T \psi(x) = S\partial WB^T \psi(x).
\]

The only nonlinear term is the function \( \psi \). So the split in treatment between it and the remaining – linear – terms seems very reasonable. However, since the revolutionary work done in the 70’s, the traditional split in treatment has been between \( S\partial \) on the one hand and \( WB^T \psi \) on the other. Thus
where we noted that $\mathbb{R}^c$ is stratified by invariant affine spaces $X_z$ (Definition 3.3), the traditional stratification is by the so-called *stoichiometry classes*. These are the sets where the projection to \((\text{Im} \, S \partial)^T = \text{Ker} \, \partial^T S^T\) is constant. Naturally, both statements are true.

Summarizing, the classical results in the literature are the same as Theorem 4.2 and Corollaries 5.4 and 6.3 if we make the following replacements:

\[
\delta_L = \dim \text{Ker} \, SL_{out}^T - \dim \text{Ker} \, L_{out}^T \quad \text{becomes} \quad \delta = \dim \text{Ker} \, S \partial - \dim \text{Ker} \, \partial \\
\text{Ker} \, L_{out}^T S^T \quad \text{and} \quad \text{Im} \, SL_{out}^T \quad \text{become} \quad \text{Ker} \, \partial^T S^T \quad \text{and} \quad \text{Im} \, S \partial \\
X_z \quad \text{becomes} \quad \text{stoichiometry class}
\]

The following proposition shows that if $\delta = 0$, then $\delta_L = 0$. However, in the case of CSC graphs, the two are equivalent. Thus Theorem 4.2 is equivalent to the traditional zero deficiency theorem for these graphs.

**Proposition 7.1** $\delta_L \leq \delta$ with equality if $G$ is CSC.

**Proof.** According to Proposition 8.3, we have

\[
[\text{Ker} \, S \cap \text{Im} \, \partial] = \text{Im} \, S^T + \text{Ker} \, \partial^T.
\]

This evidently implies that

\[
\delta = \dim [\text{Ker} \, S \cap \text{Im} \, \partial] = v - \dim [\text{Im} \, S^T + \text{Ker} \, \partial^T],
\]

where $v$ is the dimension of the vertex space (see Section 3). Similarly, we obtain that

\[
\delta_L = v - \dim [\text{Im} \, S^T + \text{Ker} \, BW \partial^T],
\]

where we have used that $L_{out} = -BW \partial^T$. The inequality follows from $\text{Ker} \, \partial^T \subseteq \text{Ker} \, BW \partial^T$.

When $G$ is CSC, Lemma 2.8 and Theorem 2.4 imply that in addition the dimensions of $\text{Ker} \, \partial^T$ and $\text{Ker} \, BW \partial^T = \text{Ker} \, L_{out}$ are equal. Thus the two sets must be equal. \hfill \blacksquare

Similarly, one proves of course that for CSC graphs, the dimensions of $\text{Ker} \, L_{out}^T S^T$ and $\text{Im} \, SL_{out}^T$ are the same as those of $\text{Ker} \, \partial^T S^T$ and $\text{Im} \, S \partial$ and so on.

It is interesting to note that for non-CSC graphs the situation is different as the following simple example shows. Consider the stargraph with 3 outgoing edges from the central vertex. It is easy to see that

\[
L_{out}^T = \begin{pmatrix} 3 & 0 & 0 & 0 \\ -1 & 0 & 0 & 0 \\ -1 & 0 & 0 & 0 \\ -1 & 0 & 0 & 0 \end{pmatrix} \quad \partial = \begin{pmatrix} -1 & -1 & -1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}.
\]

The values on the diagonal of the edge weighting matrix $W$ do not matter, so we can take them to be 1. Suppose further that

\[
S = (2 \ 1 \ 1 \ 1).
\]

Since we have

\[
SL_{out}^T = (3 \ 0 \ 0 \ 0) \quad \text{and} \quad S \partial = (2 \ 1 \ 1 \ 1),
\]

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it follows that in this example $\delta_L = 0$, while $\delta = 2$. The obvious generalization to the star graph with $k$ outgoing edges will give $\delta_L = 0$, while $\delta = k - 1$. This shows that the traditional deficiency can be made arbitrarily larger than the Laplacian one.

We finish by expressing a few mathematical expressions in terms of language commonly used in the study of chemical reaction networks:

- componentwise strongly connected becomes weakly reversible
- weakly connected component becomes linkage (class)
- reacting mixture or vertex becomes complex
- in-degree equals out-degree becomes balanced
- reversible (as Markov Chain) becomes detailed balanced

Here are some further observations on terminology. In graph theory the condition that in-degree equals out-degree is called balanced. For a connected graph, this condition is equivalent to having an Eulerian tour (a closed walk that uses each edge exactly once). Also $\mathrm{Im} \, \partial$ is called the bond space and $\ker \partial$ is called the cycle space [24].

Also, there is a notion called complex balanced. The meaning of this notion is that the system of equation 3.6 admits a positive equilibrium $x^*$ such that $\psi(x^*)$ in in $\ker L_{\text{out}}^T$. Note that an equilibrium $x^*$ could also be such that $L_{\text{out}}^T \psi(x^*)$ is not 0 but is in $\ker S$. Clearly, the last is impossible if $\delta_L = 0$. Vice versa, assume a system is complex balanced. Since $x^* > 0$, we have $\psi(x^*) > 0$. In turn, Theorem 2.5 then implies that all vertices are in a cabal. And so the graph is CSC (see Definition 2.7).

### 8 Appendix

We begin by introducing some notation. This concerns componentwise operations on vectors. Given vectors $x$ and $y$ in $\mathbb{R}^n$, we define $x \odot y$ as the vector whose components are $x_i y_i$. (This is also called the Hadamard product.) We write $x/y$ for the vector whose components are $x_i/y_i$ ($y_i \neq 0$ for all $i$). The componentwise logarithm of $x$ ($x_i > 0$ for all $i$) is denoted by $\ln x$, while the componentwise exponential of $x$ will be written as $\exp x$. From now on, will also write $x > 0$ for $x_i > 0$ for all $i$.

The first two lemmas are standard results of linear algebra. Let $A : \mathbb{R}^n \to \mathbb{R}^m$ and $B : \mathbb{R}^n \to \mathbb{R}^e$ be linear maps and $V$ and $W$ (linear) subspaces of $\mathbb{R}^n$.

**Lemma 8.1** For linear subspaces $V$ and $W$: $V^\perp \cap W^\perp = (V + W)^\perp$.

**Lemma 8.2** For any matrix $A$ we have: $\ker A^T = (\im A)^\perp$, where the complement is in the codomain of $A$.

Putting the previous lemmas together, we immediately see the following.

**Proposition 8.3** For any two matrices $A$ and $B$: $[\ker A \cap \im B^T]^\perp = \im A^T + \ker B$.

We will also need a few simple calculus lemmas.
Lemma 8.4  For any $a > 0$ and $b > 0$, we have: $a(\ln a - \ln b) \geq a - b$. Equality iff $a = b$.

Proof.  The tangent line to $\ln x$ at $x = 1$ is above the graph of that function for all $x \neq 1$, and so $x - 1 \geq \ln x$. Substituting $x = b/a$ yields the result.  

Lemma 8.5  For any $a > 0$ and $b > 0$, we have: $(a - b)(\ln a - \ln b) \geq 0$. Equality iff $a = b$.

Proof.  Lemma 8.4 implies $-b(\ln a - \ln b) \geq b - a$. Adding that inequality to the one in Lemma 8.4 proves the result.

Lemma 8.6  For any $a > 0$ and $b > 0$, there are $x_\pm \in \mathbb{R}$ such that $\forall x \notin [x_-, x_+] : ae^x - bx > a$.

Proof.  Taking the derivative of $f(x) \equiv ae^x - bx$ shows that this function has a global minimum at $x^*$ satisfying $x^* = \ln b - \ln a$. Lemma 8.4 implies that $f(x^*) \leq a$. Finally, $\lim_{x \to \pm \infty} f(x) = +\infty$.  

We will also need a result from the theory of dynamical systems.

Definition 8.7  A function $V : \mathcal{O} \subseteq \mathbb{R}^n \to \mathbb{R}$ where $\mathcal{O}$ is open, is called a Lyapunov function for the system $\dot{x} = f(x)$ in $\mathbb{R}^n$ if it is a continuously differentiable and satisfies that along a trajectory $V(x(t)) \leq 0$.

Theorem 8.8 [25]  Let $V : \mathcal{O} \to \mathbb{R}$ be a Lyapunov for the system $\dot{x} = f(x)$. The intersection of the $\omega$-limit set of a point $x$ and the set $\mathcal{O}$ is contained in the set where $\dot{V} = 0$.

References


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