ON THE STEADY STATES OF WEAKLY REVERSIBLE CHEMICAL REACTION NETWORKS

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Abstract. A natural condition on the structure of the underlying chemical reaction network, namely weak reversibility, is shown to guarantee the existence of an equilibrium (steady state) in each positive stoichiometric compatibility class for the associated mass-action system. Furthermore, an index formula is given for the set of equilibria in a given stoichiometric compatibility class.

Key words. chemical reaction network, weak reversibility, equilibria.

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1. Introduction. The goal of chemical reaction network theory is to formulate conditions under which the dynamical fate of composition trajectories can be ascertained, even in complex reactions. Chemical reaction systems considered in practical applications are often very complicated. In principle, the number of species involved can be arbitrarily high. In practice, a full system can involve tens or hundreds of species. Although models with a handful of species are usually used, these systems are still “high” dimensional from the perspective of dynamical system. Moreover, the reactions between the complexes is often only known approximately, since the determination of rate constants is quite difficult, if not impossible. A natural approach is therefore to attempt to give a qualitative description of the behavior of the reaction system.

The modeling of chemical reactions can be achieved via the mass-action assumption. A typical chemical reaction network (CRN) obeying mass-action kinetics consists of three components: \( \{S, Y, K = (k_{ij})\} \), where

1. \( S = \{S_1, S_2, ..., S_n\} \) is the set of species involved in the chemical reaction.
2. \( Y = \{Y_1, Y_2, ..., Y_m\} \) is the set of complexes in the given CRN, with each \( Y_i \in \mathbb{R}^n, i = 1, 2, ..., m \).
3. If we have a reaction \( Y_i \rightarrow Y_j \), then \( k_{ij} = k_{Y_i \rightarrow Y_j} > 0 \) is the rate constant for the reaction \( Y_i \rightarrow Y_j \), assuming mass-action kinetics. If there is no reaction from \( Y_i \) to \( Y_j \), then we define \( k_{ij} = k_{Y_i \rightarrow Y_j} = 0 \).

In this framework, the equation governing the evolution of chemical concentrations is given by:

\[
\dot{x} = f(x) = \sum_{i,j=1}^{m} k_{ij} x^Y_i (Y_j - Y_i)
\]

where \( x \in \mathbb{R}_+^n = \{x = (x_1, ..., x_n) : x_i > 0, i = 1, 2, ..., n\} \), and each \( x_i \) is the concentration of species \( S_i \) in the chemical reaction network.

The system we obtain is an array of ordinary differential equations with polynomial vector fields determining the behavior of the concentration of each species in

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the reactor. This ODE could be quite complicated: the dimension of the equation could be dauntingly high, while the number of parameters (rate constants, for example) could be equally large. It is therefore quite surprising, but nevertheless true, that many systems exhibit relatively simple dynamics. In fact, based on considerable experience, chemical experimentalists have developed an “intuition” that a “normal” chemical experiment will quickly lead to some steady state.

So one of the primary concerns of chemical reaction network theory, up to now, has been to determine the capacity of a given reaction network system for multiple steady states. This theme emerged from the early work of chemical reaction network theory ([6], [8]), where chemical reaction networks were classified according to their deficiency. Horn, Jackson and Feinberg give a quite complete picture of the behavior of the deficiency-zero and deficiency-one mass-action systems ([4], [5]). Introductory material for chemical reaction network theory is given in ([2], [3]), and we will follow the notation and definitions in these papers as much as possible.

The capacity of a reaction network for multiple states depends heavily on the underlying algebraic structure of the reaction system, given by the “react to” relation between the complexes. Two complexes are linked together if there is a reaction between them, and we say two complexes are in the same linkage class if we can find a finite sequence of reactions between them. It is not hard to check that the linear subspace spanned by all the reaction vectors \( Y_j - Y_i \), for each reaction \( Y_i \rightarrow Y_j \), is invariant under the flow induced by (1.1). It is called the stoichiometric subspace. Each linear manifold parallel to it is called a stoichiometric compatibility class (SCC), which is also invariant under the flow.

The “react to” relation between the complexes also gives us various notions of reversibility, as alluded to above. If each reaction \( A \rightarrow B \) in the chemical reaction network is accompanied by the reverse reaction \( B \rightarrow A \), then this reaction network is called reversible. If for each reaction \( A \rightarrow B \) we have a reaction chain from \( B \) to \( A \), i.e., we can find a finite sequence of reactions \( B \rightarrow C_1, C_1 \rightarrow C_2, \ldots, C_{n-1} \rightarrow C_n, C_n \rightarrow A \), then this reaction system is called weakly reversible. We would consider solely weakly reversible chemical reaction networks in this paper.

In the early eighties, Nachman obtained the existence of steady states in each stoichiometric compatibility class if there is only one linkage class in the chemical reaction network ([10]). Using this result, Feinberg showed the existence of steady states in each SCC (personal communications) if the chemical reaction network is weakly reversible and the deficiency is equal to the summation of the deficiencies of each linkage class. So the next natural question is about the existence of steady states for general weakly reversible systems.

We are interested in the following two problems:
1. Does there exist a positive steady state for (1.1)?
2. Does there exist a steady state in each nonempty, positive stoichiometric compatibility class for (1.1)?

The main result in this paper gives an affirmative answer to the two questions above, under a natural condition.

**Theorem 1.1.** For each weakly reversible chemical reaction network obeying mass-action kinetics, the flow of (1.1) has finitely many (at least one) steady states in each nonempty, positive stoichiometric compatibility class.

Our result shows that the experimental chemists’ “intuition” is well grounded, at least for weakly reversible and mass-action chemical reaction networks. It shows that for such systems there will always be some steady state in each stoichiometric
compatibility class (SCC), and although the numbers of steady state may differ for different SCC, the summation of the indices for the steady states remains the same (see Corollary 5.2). Moreover, this does not depend on the specific values of the positive rate constants, as long as the system remains weakly reversible. This would be quite appealing to experimental chemists since the rate constants are difficult to measure.

**Remark 1.2.** The component of the complexes $Y_i$ is called the stoichiometric coefficients, and for typical chemical reactions, it should be a nonnegative integer. But our result holds when the stoichiometric coefficients are real, thus for example we allow the following reaction:

$$0 \rightarrow 2A + B, \quad 2.5B + C \rightarrow 0, \quad -2C + D = E$$

as long as the chemical reaction is weakly reversible. Therefore the case where there is “source” and “sink” for the chemical reaction system can still be described by our result.

**Plan of the paper.** In section 2, we define two matrices $C, R$ that determine the reaction network structure, discuss their properties and reformulate the existence problem as that of an intersection problem of two hypersurfaces. In section 3, we restrict ourselves to the case of one linkage class. A vector-valued function $G(z)$ is defined, and a priori estimate of $(G(z), z)$ is given and used to solve the intersection problem in a special case. In section 4, we discuss the case of $l$ linkage classes and construct a bounded, convex set so that the intersection problem is reduced to proving that a corresponding vector field is pointing in at each point of its boundary. Thus we give the proof of the existence of steady states in the whole $R^n$ space. In section 5, we utilize the remark given at the end of section 4 to prove the existence of a steady state in each stoichiometric compatibility class, and then we use a homotopy argument to give the proof of the index formula.

**2. Reaction network structure and reformulation of the equation.** It has long been known that the existence of steady states depends heavily on the algebraic structure of the chemical reaction network. For example, when the reaction network is reversible, forest-like and the deficiency of the network is 0, one can show the existence of steady states in $R^n_+$ (the reader is referred to [9] concerning the precise exposition). But it is not obvious how to extend the result to the weakly reversible reaction networks of arbitrary deficiency.

The information about a weakly reversible reaction network can essentially be decomposed into two parts: one about the configuration of the complexes in the $R^n$ space, offered by the set $\mathcal{Y} = \{Y_1, Y_2, \ldots, Y_m\}$; the other one about the reaction information between the complexes, given by the rate constants $k_{ij}, i, j = 1, 2, \ldots, m$. We give the following

**Definition 2.1.** For each weakly reversible chemical reaction network $\{S, \mathcal{Y}, K\}$, the configuration matrix $C$ is given by

$$C = \begin{pmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_m \end{pmatrix}_{m \times n} = \begin{pmatrix} y_{11} & y_{12} & \cdots & y_{1n} \\ y_{21} & y_{22} & \cdots & y_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ y_{m1} & y_{m2} & \cdots & y_{mn} \end{pmatrix}.$$
while the relation matrix \( \mathbf{R} \) is given by

\[
\mathbf{R} = (r_{ij})_{m \times m}, \quad \text{with } r_{ij} = \begin{cases} k_{ij}, & \text{if } i \neq j, \\ -\sum_{k \neq i} k_{ik}, & \text{if } i = j. \end{cases}
\]

Therefore the reaction network structure is completely determined by the two matrices \( \{ \mathbf{C}, \mathbf{R} \} \). Notice that the property of weak reversibility is uniquely determined by the relation matrix \( \mathbf{R} \). They will both play a role in the existence of the positive equilibrium, but it will turn out that the specific structure of \( \mathbf{R} \) will be crucial in the following development.

System (1.1) can be rewritten in terms of \( \{ \mathbf{C}, \mathbf{R} \} \):

\[
\dot{x} = (x Y_1 \quad x Y_2 \quad \ldots \quad x Y_m)_{1 \times m} \mathbf{R}_{m \times m} \begin{pmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_m \end{pmatrix}_{m \times 1} = (e^{\ln x \cdot Y_1} \quad e^{\ln x \cdot Y_2} \quad \ldots \quad e^{\ln x \cdot Y_m})_{1 \times m} \cdot \mathbf{R} \cdot \mathbf{C}
\]

where \( \{ \mathbf{C}, \mathbf{R} \} \) are given as above.

We list some basic properties of the relation matrix \( \mathbf{R} \).

1. \( \mathbf{R} = (r_{ij})_{m \times m} \) satisfies:
   - \( \sum_{j=1}^{m} r_{ij} = 0 \), for \( i = 1, 2, \ldots, m \)
   - \( r_{ij} \geq 0 \), for \( i \neq j \)
   - \( r_{ii} < 0 \), for \( i = 1, 2, \ldots, m \)

2. Every two complexes in the same linkage class are linked by “reaction chains”.
   Mathematically, this means for each pair \( Y_i, Y_j \) in a certain linkage class, there exist \( Y_i_1, Y_i_2, \ldots, Y_i_s \) such that \( Y_i_1 = Y_i, Y_i_s = Y_j \) and \( r_{i_k - i_k^'} > 0 \) for \( k = 2, 3, \ldots, s \).

3. If the CRN has \( l \) linkage classes, \( l > 1 \), then by relabeling \( Y_1, Y_2, \ldots, Y_m \) we can write \( \mathbf{R} \) as the following diagonal block form

\[
\mathbf{R} = \begin{pmatrix} \mathbf{R}_1 \\ \mathbf{R}_2 \\ \vdots \\ \mathbf{R}_l \end{pmatrix}
\]

where each \( \mathbf{R}_i \) being the relation matrix for a linkage class.

The only thing in item 1 which needs explanation is \( r_{ii} < 0 \). If \( r_{ii} = 0 \) for some \( i \), then \( r_{ij} = 0 \) for \( j \neq i \). Thus the complex \( Y_i \) does not react to any other complexes. By weak reversibility of the chemical reaction network, no other complex will react to \( Y_i \) either. Thus \( Y_i \) can safely be discarded and we only need to consider the subnetwork without \( Y_i \). Therefore we will always assume that each complex \( Y_i \) appears at least once in the chemical reaction network.

Remark 2.2. It is interesting to observe that the classical Perron-Frobenius theory for matrices with positive entries can be used to get information about the eigenvalue distribution of the relation matrix \( \mathbf{R} \). For example, we can prove that \( \mathbf{R} \) has only nonpositive eigenvalues, and the algebraic multiplicity of the zero eigenvalue of \( \mathbf{R} \) is exactly the number of linkage classes within the CRN. Also, the eigenvector
corresponding to the zero eigenvalue is nonnegative. This spectral information seems to have decisive influence on the stability property of the phase portrait of the flow. The interested reader is referred to ([7]).

**Notation 1.** For each CRN we define the norm of its relation matrix \( R \) to be \(|R| = \max_{i=1,2,\ldots,m} |r_{ii}|\). Also, we define \( \tau(R) = \min_{i \neq j, i,j \in \{1,2,\ldots,m\}} \{ r_{ij} : r_{ij} > 0 \} \).

Our next task in this section is to transfer the existence problem to one of intersection of two hypersurfaces. The idea is to see that \( x \in \mathbb{R}^n_+ \) is an equilibrium point for system (2.1) if and only if

\[
\left( e^{\ln x \cdot Y_1} e^{\ln x \cdot Y_2} \ldots e^{\ln x \cdot Y_m} \right)_{1 \times m} \cdot R \in \{ z \in \mathbb{R}^m : z \cdot C = 0 \},
\]

So it is natural to consider the intersection

\[
(2.3) \quad \left( \left( e^{\ln x \cdot Y_1} e^{\ln x \cdot Y_2} \ldots e^{\ln x \cdot Y_m} \right) \cdot R : x \in \mathbb{R}^n_+ \right) \cap \{ z \in \mathbb{R}^m : z \cdot C = 0 \}
\]

if we want to find positive steady states for (2.1).

**Notation 2.** \( N = \{ z \in \mathbb{R}^m : z \cdot C = 0 \} \), \( K = \{ z \in \mathbb{R}^m : z = x \cdot C^t \ \text{for some} \ x \in \mathbb{R}^n \} \).

Note that \( K = N^\perp \), \( K^\perp = N \) where \( N^\perp \) and \( K^\perp \) mean the orthogonal subspaces of \( N \) and \( K \) in \( \mathbb{R}^m \) respectively.

**Definition 2.3.** We define the relation function \( G(z) : \mathbb{R}^m \to \mathbb{R}^m \) as

\[
(2.4) \quad G(z) \overset{\text{def}}{=} e^z \cdot R = (e^{z_1} e^{z_2} \ldots e^{z_m}) R.
\]

Then we have the following

**Proposition 2.4.** There exists a positive equilibrium point for (2.1) in \( \mathbb{R}^n_+ \) if and only if

\[
(2.5) \quad G(K) \cap K^\perp \neq \emptyset.
\]

**Proof.** It suffices to notice that

\[
G(K) = \left\{ \left( e^{\ln x \cdot Y_1} e^{\ln x \cdot Y_2} \ldots e^{\ln x \cdot Y_m} \right)_{1 \times m} \cdot R : x \in \mathbb{R}^n_+ \right\}
\]

and

\[
K^\perp = N = \{ z \in \mathbb{R}^m : z \cdot C = 0 \}
\]

then from equation (2.3) and the preceding discussion, we obtain the result \( \square \)

**Remark 2.5.** The idea of using the intersection of two hypersurfaces to prove an existence result can be traced to Felix E. Browder in ([1]). Although it turns out that the relation function \( G(z) : \mathbb{R}^m \to \mathbb{R}^m \) is not monotone, the fact that we are dealing with a finite dimensional ODE still pulls us through.
3. The case of one linkage class. In this section we will solve the intersection problem, assuming that the CRN has only one linkage class. The general strategy is as follows: to prove that \( G(K) \cap K^\perp \neq \emptyset \), it is equivalent to showing that

\[
0 \in \Pi_K \circ G(K), \tag{*}
\]

where \( \Pi_K : \mathbb{R}^m \to K \) is the standard projection operator. One sufficient condition for (*) to hold is that there exists a large ball \( B(r) = \{ z \in K : |z| < r \} \) in \( K \) such that

\[
(\Pi_K \circ G(z), z) < 0
\]

for \( z \in \partial B(r) = \{ z \in K : |z| = r \} \). Then by the Brouwer Fixed Point theorem we obtain (*)

So basically, we need to estimate

\[
(\Pi_K \circ G(z), z) = (G(z), z)
\]

for \( z \in K \) and try to show that we can find a ball \( B(r) \) such that

\[
(G(z), z) < 0
\]

for \( z \in \partial B(r) \). But here we encounter some technical difficulties: one quickly finds that \( (G(z), z) \) will be identically zero if \( z \) lies in the \( 1 - d \) subspace \( D = \{ z = a \cdot (1, 1, \ldots, 1) \in \mathbb{R}^m : a \in \mathbb{R} \} \). Thus we will have to avoid this degenerate subspace \( D \).

Definition 3.1. We set \( \mathbb{1}^m = (1, 1, 1, \ldots, 1)_{1 \times m} \), \( P_m = \{ z \in \mathbb{R}^m : \mathbb{1}^m \cdot z = 0 \} \), and we define the norm on \( \mathbb{R}^m \) as \( |z|_2 = \sum_{i=1}^m z_i^2 \). If \( z \in P_m \), we define another equivalent norm \( |z| = \max_{i=1, 2, \ldots, m} z_i \).

We start from the following

Lemma 3.2. Let \( s \geq 1 \) be fixed. Then

\[
\max_{-L \leq y_i \leq 0, i=1,2,\ldots,s} y_1 + e^{y_1}y_2 + \ldots + e^{y_{s-1}}y_s + e^{y_s}(-L) \to -\infty \quad (3.1)
\]

as \( L \to +\infty \).

Proof. We will show (3.1) by induction on \( s \).

Step 1: If \( s = 1 \), then

\[
\max_{-L \leq y \leq 0} y_1 + e^{y}(-L) = \max \{-L, -L + e^{-L}(-L), -1 - \ln L\} \to -\infty
\]

as \( L \to +\infty \).

Thus the lemma is true for \( s = 1 \).

Step 2: Now suppose that the lemma is true for \( s < k \). Define

\[
A_{k,L} = \max_{-L \leq y_i \leq 0, i=1,2,\ldots,k} \{ y_1 + e^{y_1}y_2 + \ldots + e^{y_k}(-L) \}
\]
then by assumption we know that $A_{k,L} \to -\infty$ as $L \to +\infty$.
For $s = k + 1$, let $-L \leq y_1, y_2, \ldots, y_k \leq 0$ be fixed, then

$$\Psi(y_{k+1}; y_1, y_2, \ldots, y_k) = y_1 + e^{y_1}y_2 + \ldots + e^{y_k}y_{k+1} + e^{y_{k+1}}(-L)$$

will achieve its maximum at $y_{k+1} = 0, -L$ or $y_k - \ln L$. So we have

$$(3.2)_{k+1,L} = \max_{-L \leq y_i \leq 0, i = 1, 2, \ldots, k+1} \Psi(y_{k+1}; y_1, y_2, \ldots, y_k) \leq \max \{-L, A_{k,L}, A_{k,ln L}\},$$

therefore $A_{k+1,L} \to -\infty$ as $L \to +\infty$. Thus the lemma is true for $s = k + 1$.

Step 3: Combining Steps 1 and 2 we see that the lemma is true for all $s \geq 1$. \(\square\)

The fundamental lemma is the following

**Lemma 3.3.** If the CRN has exactly one linkage class, then there exists a function $c(r)$ on $R^1$ with $c(r) \to +\infty$ as $r \to +\infty$ such that

$$(3.3) \quad (G(z), z) \leq -c(|z|)e^{|z|}$$

for all $z \in P_m$.

*Proof.* For all $z \in P_m$, we have

$$(3.4) \quad \begin{cases} \frac{(G(z), z)}{e^{|z|}} = \frac{e^{|z|}R_y}{e^{|z|}L} = e^{-|z|L}R_y \leq e^{-|z|L}R(z^t - |z|1_m^t) = e^yRy^t \end{cases}$$

where $y = z - |z|1_m$.  

**Notation 3.** $B_L = \{y \in R^m : -L \leq y_i \leq 0, \forall i = 1, 2, \ldots, m; \min_i y_i = -L, \max_i y_i = 0\}$.

Then lemma 3.3 is equivalent to the following

**Claim:** Define $F : B_L \to R$ as $F(y) = e^yRy^t, y \in B_L$, then

$$C_L = \max_{y \in B_L} F(y) \to -\infty$$

as $L \to +\infty$.

Proof of Claim: Given $y \in B_L$, by relabeling $Y_1, Y_2, \ldots, Y_m$ we can write $y$ as

$$y = (\hat{y}_1, \hat{y}_2, -L1_3)$$

where

$$\begin{cases} -L < \hat{y}_i < 0, \forall 1 \leq i \leq t_2 \\
t_1 + t_2 + t_3 = m, t_1 \geq 1, t_3 \geq 1 \end{cases}.$$

So we have

$$(3.5) \quad F(y) = e^yRy^t = \left( \begin{array}{c} \hat{y}_1 \\ e^{-L1_3} \end{array} \right) \left( \begin{array}{ccc} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{array} \right) \left( \begin{array}{c} 0^t_1 \\ \hat{y}^t_2 \\ -L1_{t_3} \end{array} \right)$$

\begin{align*}
&= e^0R_{12}\hat{y}^t_1 + e^{0L1_3}\left( -L1^t_{t_3} \right) + \underbrace{e^{-L1_3}}_{(1)} + e^{0L1_3}(-L1^t_{t_3}) + e^{-L1_3}R_{13}\left( -L1^t_{t_3} \right) + e^{0L1_3}R_{23}\left( -L1^t_{t_3} \right) + e^{-L1_3}R_{33}\left( -L1^t_{t_3} \right) + e^{0L1_3}R_{22}\left( -L1^t_{t_3} \right)
\end{align*}
Estimate of term (3): we have

\[
\begin{align*}
term(3) &= e^{-L} (-L)_{ii} R_{i3} \sum_{i,j} + e^{2R_{i2} t} \leq t_3 |R| L e^{-L} + t_2 |R| (\max_{-\infty < s \leq 0} |e^s|) \\
& \leq (t_2 + t_3) |R| e^{-1} \leq \frac{e}{e} |R|
\end{align*}
\]

(3.6)

To estimate terms (1) and (2) we need to consider two cases:

- **R**_{13} \neq 0, by which we mean there is at least one element a_{ij} \in R_{13} which is larger than 0, then

\[
term(2) \leq (-L) a_{ij} \leq -L \cdot \tau(R).
\]

Notice that term (1) will always be nonpositive since each element in R_{12}, R_{23} is nonnegative, and each element in \( \frac{R}{2} \) and \(-L\frac{R}{3}\) is strictly negative.

So we have

\[
(3.7) \quad term(1) + (2) + (3) \leq \frac{m}{e} |R| - L \cdot \tau(R)
\]

- If R_{13} = 0, notice that

\[
R = \begin{pmatrix} R_{11} & R_{12} & R_{13} \\ R_{21} & R_{22} & R_{23} \\ R_{31} & R_{32} & R_{33} \end{pmatrix}
\]

corresponds to the decomposition of the CRN to three subnetworks \( N_1 = \{Y_1, Y_2, \ldots, Y_t\}, N_2 = \{Y_{t+1}, Y_{t+2}, \ldots, Y_{t+t_2}\}, N_3 = \{Y_{t+t_2+1}, Y_{t+t_2+2}, \ldots, Y_m\}. \) \( R_{ii} \) corresponds to the relation matrix for \( N_i, i = 1, 2, 3. \) (Although \( N_i \) together with \( R_{ii} \) may not correspond to a weakly reversible chemical reaction network) while \( R_{ij}, i \neq j \in \{1, 2, 3\} \) gives the information about reaction vectors from \( N_i \) to \( N_j. \)

Now \( R_{13} = 0 \) means that each \( Y_i \) belonging to \( N_1 \) must pass \( N_2 \) to get to \( Y_j \) which belongs to \( N_3. \) So we can always find a “reaction chain”

\[
Y_{i_1} \rightarrow Y_{i_2} \rightarrow \ldots \rightarrow Y_{i_s}, s \geq 3
\]

such that \( Y_{i_1} \in N_1, Y_{i_s} \in N_3, \) and \( Y_{i_k} \in N_2 \) for \( k \in \{2, \ldots, s-1\}, \) which means that \( a_{i_1 i_2}, a_{i_2 i_3}, \ldots, a_{i_{s-1} i_s} > 0 \) with

\[
a_{i_1 i_2} \in R_{12}, a_{i_2 i_3}, a_{i_3 i_4}, \ldots, a_{i_{s-2} i_{s-1}} \in R_{22}, a_{i_{s-1} i_s} \in R_{23}.
\]

So now we have

\[
\begin{align*}
term(1) + (2) + (3) \leq & a_{i_1 i_2} y_{i_2} + e^{y_{i_2}} a_{i_2 i_3} y_{i_3} + \ldots + e^{y_{i_{s-1}}} a_{i_{s-1} i_s} (-L) + \frac{e}{e} |R| \\
& \leq \tau(R) |y_{i_2} + e^{y_{i_2}} y_{i_3} + \ldots + e^{y_{i_{s-2}}} y_{i_{s-1}} + e^{y_{i_{s-1}}} (-L)| + \frac{e}{e} |R| \\
& \leq \tau(R) \cdot A_{s-2, L} + \frac{e}{e} |R|,
\end{align*}
\]

(3.8)

where in the last inequality of (3.8) we have used lemma 3.2.

Combining (3.7), (3.8) we see that
\[ \max_{y \in B_L} F(y) \leq \max \left\{ \frac{m}{e} |R| - L \cdot \tau(R), \tau(R) \cdot A_{s-2,L} + \frac{m}{e} |R| \right\}, \]

thus \( C_L = \max_{y \in B_L} F(y) \rightarrow -\infty \) as \( L \rightarrow +\infty \). The proof of the Claim is now complete, and the proof of Lemma 3.3 follows from that of the Claim.

\[ \blacksquare \]

Remark 3.4. This lemma was obtained by Adrian Nachman, around 1983. Using this lemma, Nachman was able to show the existence of positive equilibrium points for weakly reversible chemical reaction networks with one linkage class. After this Feinberg showed the existence of equilibrium points when the CRN is weakly reversible and has the property that the deficiency of the CRN is equal to the sum of the deficiencies of each linkage class subnetwork.

Corollary 3.5. If \( G(z) = e^z \cdot R \) where \( R \) is the relation matrix for some CRN of only one linkage class, then for all \( \tilde{C} > 0 \), there exists \( r(\tilde{C}, R) > 0 \) such that for all \( w \in P_m, |w|_2 \leq \tilde{C} \), we have

\[ (G(z + w), z) < 0, \quad z \in P_m, |z|_2 > r(\tilde{C}, R). \]

\[ \text{Proof.} \] First observe that

\[ (G(z + w), z) = e^{z+w} \cdot R \cdot z^t = e^z \cdot R(w) \cdot z^t \]

where \( \tilde{R}(w) = \text{Diag}(e^{w_1}, e^{w_2}, \ldots, e^{w_m}) \cdot R \), with \( \text{Diag}(e^{w_1}, e^{w_2}, \ldots, e^{w_m}) \) being the \( m \times m \) diagonal matrix. Thus \( \tilde{R}(w) \) is still a relation matrix of some CRN.

Think about \( \tilde{R}(w) = \text{Diag}(e^{w_1}, e^{w_2}, \ldots, e^{w_m}) \cdot R \) as a perturbation of \( R \), in the class of relation matrix. Fix \( \tilde{C} > 0 \), then for \( w \in \{ w \in P_m, |w|_2 \leq \tilde{C} \} \), the proof of Lemma 3.3 still holds for \( \tilde{R}(w) \), specifically the estimate (3.9) holds for \( w \in P_m, |w|_2 \leq \tilde{C} \), with \( R \) replaced by \( \tilde{R}(w) \). Now observe that

\[ \min_{|w|_2 \leq \tilde{C}} \tau(\tilde{R}(w)) > 0, \]

then due to the compactness of \( \{ w \in P_m, |w|_2 \leq \tilde{C} \} \) we can choose \( r(\tilde{C}, R) > 0 \) large enough such that

\[ (G(z + w), z) = (e^z \cdot \tilde{R}(w), z) < 0 \]

holds for \( w \in \{ w \in P_m, |w|_2 \leq \tilde{C} \} \) uniformly, where \( z \in P_m, |z|_2 > r(\tilde{C}, R) \). \[ \blacksquare \]

Corollary 3.6. If \( G(z) = e^z \cdot R \) where \( R \) is the relation matrix for some CRN of only one linkage class, then there exists constant \( t_0(R) > 0 \) such that

\[ (G(z), z) < t_0(R), \quad z \in P_m \]

\[ \text{Proof.} \] From Lemma 3.3 we know that there exists \( r_0 > 0 \), such that for all \( z \in P_m, |z| > r_0 \), we have \( (G(z), z) < 0 \). Let \( t_0 = \max(0, \max_{z \in P_m, |z| \leq r_0} |(G(z), z)|). \]
Since \((G(z), z)\) is continuous for \(z \in B_{P_m}(r_0) = \{z \in P_m : |z| \leq r_0\}\), we have \(0 < t_0 < +\infty\).

From Lemma 3.3 we obtain easily

**Lemma 3.7.** If the CRN has only one linkage class, then for any subspace \(H\) of \(P_m\), we have that

\[
(3.10) \quad G(H) \cap H^\perp \neq \emptyset
\]

**Proof.** Since \(R^m = H \oplus H^\perp\), we can define the projection operator \(\Pi_H : R^m \to H\) as

\[
(3.11) \quad \Pi_H(z) = z_1
\]

where \(z = z_1 + z_2, z_1 \in H, z_2 \in H^\perp\).

Then \(G(H) \cap H^\perp \neq \emptyset\) if and only if \(0 \in \Pi_H(G(H))\). From (3.3) we know that for \(r\) sufficiently large,

\[
(\Pi_H \circ G(z), z) = (G(z), z) \leq -c(|z|)e^{|z|} < 0
\]

for \(z \in S_H(r) = \{z \in H : |z| = r\}\).

By Brouwer’s Fixed Point Theorem, there exists \(z_0 \in B_H(r) = \{z \in H : |z| < r\}\) such that \(\Pi_H \circ G(z_0) = 0\). Thus we have

\[
0 \in \Pi_H(G(H))
\]

which means \(G(H) \cap H^\perp \neq \emptyset\).

**4. The case of \(l\) linkage classes.** In this section we will discuss the case of \(l\) linkage classes. Without loss of generality we assume the relation matrix \(R\) has block form (22), and each \(R_i\) is a \(m_i \times m_i\) matrix for \(i = 1, 2, \ldots, l\).

The content of this section is divided into two parts: the first part is about the estimate of \((G(z), z)\). Similar to the case of one linkage class, there exists an \(l\)-dimensional degenerate subspace \(D_l\) for \(G\), i.e., \((G(z), z) = 0\) restricted to \(D_l\). We will give an estimate of \((G(z), z)\) restricted to the orthogonal subspace \(P_{m,l}\) of \(D_l\) (Lemma 4.3), and correspondingly show that \(G(H) \cap H^\perp \neq \emptyset\) when \(H \subset P_{m,l}\) (Lemma 4.4).

**Definition 4.1.** Let \(P_{m,l} = \{z \in R^m : \sum_{i=1}^{m_1} z_i = 0, \sum_{i=m_1+1}^{m_1+m_2} z_i = 0, \ldots, \sum_{i=m-m_1+1}^{m} z_i = 0\}\).

Since \(P_{m,l} \subset P_m, |z|\) is still a norm for \(z \in P_{m,l}\).

For \(z = (z^{(1)}, z^{(2)}, \ldots, z^{(l)}) \in P_{m,l}\) where

\[
z^{(1)} = (z_1, z_2, \ldots, z_{m_1}), z^{(2)} = (z_{m_1+1}, z_{m_1+2}, \ldots, z_{m_1+m_2}), \ldots, z^{(l)} = (z_{m-m_1+1}, z_{m-m_1+2}, \ldots, z_m),
\]

we define \(\Pi_i : P_{m,l} \to P_m, \) as

\[
\Pi_i(z) = z^{(i)}, \quad i = 1, 2, \ldots, l.
\]

**Remark 4.2.** By Lemma 3.3, there exists \(0 < R_0 < +\infty\) such that
for all $z^{(i)} \in P_{m,i}$,

$|z^{(i)}| > R_0$, $i = 1, 2, \ldots, l$.

We have the following

**Lemma 4.3.** If the CRN has exactly $l$ linkage classes, then there exists a function $c^*(r)$ on $R^1$ with $c^*(r) \to +\infty$ as $r \to +\infty$ such that

$$\tag{4.2} (G(z), z) \leq -c^*(|z|)|z|$$

for all $z \in P_{m,l}$.

**Proof.** Using the estimate in Lemma 3.3 for one linkage class we have

$$\begin{cases}
(G(z), z) = (e^{z(1)} - e^{z(2)} \ldots e^{z(l)})R_1(z^{(1)}) + e^{z(2)} R_2(z^{(2)}) + \ldots \ \\
+ e^{z(l)} R_l(z^{(l)}) \leq -\min \{c_1(|z|), c_2(|z|), \ldots, c_l(|z|)\} e^{|z|} + \sum_{i=1}^l \leq -c^*(|z|)|z| \tag{4.3}
\end{cases}$$

where $c^*(r) = \min \{c_1(r), c_2(r), \ldots, c_l(r)\} - \sum_{i=1}^l t_i$, with $c_i(r), t_i$ corresponding to the relation matrix $R_i, i = 1, 2, \ldots, l$, respectively. 

From Lemma 4.3 we obtain easily

**Lemma 4.4.** If the CRN has exactly $l$ linkage classes, then for any subspace $H$ of $P_{m,l}$, we have that

$$\tag{4.4} G(H) \cap H^\perp \neq \emptyset$$

**Proof.** Since $R^m = H \oplus H^\perp$, we can define the projection operator $\Pi_H : R^m \to H$ as

$$\tag{4.5} \Pi_H(z) = z_1$$

where $z = z_1 + z_2$, $z_1 \in H, z_2 \in H^\perp$.

It follows that $G(H) \cap H^\perp \neq \emptyset$ iff $0 \in \Pi_H(G(H))$. From (4.2) we know that for $r$ sufficiently large,

$$\Pi_H \circ G(z), z) = (G(z), z) \leq -c^*(|z|)|z| < 0$$

for $z \in S_H(r) = \{z \in H : |z| = r\}$.

By the Brouwer Fixed Point Theorem, there exists $z_0 \in B_H(r) = \{z \in H : |z| < r\}$ such that $\Pi_H \circ G(z_0) = 0$. Thus we have

$$0 \in \Pi_H(G(H))$$

which means $G(H) \cap H^\perp \neq \emptyset$. \qed
Now we turn to the second part of this section. We want to discuss an arbitrary subspace $K$ of $R^m$ and show that (2.3) is true. The natural idea is to transfer the intersection problem for $K$ to that for $P_{m,l}$. Therefore the possible configuration of $K$ in $R^m = D_l \oplus P_{m,l}$ is first discussed, then via Lemma 4.5 the intersection problem (2.3) is transformed to (4.6), which is an intersection problem with respect to $P_{m,l}$. This is achieved at the expense of adding an arbitrary linear map $F$ from some subspace of $P_{m,l}$ to $D_l$, which leads to the change of relation function $G$ to that of $G^*$.

But the essence of this section is actually Lemma 4.5, so a few words about the idea of proof are helpful. The idea is to construct a domain $\Omega_H(r) \subset H$ which resembles the ball $B_H(r)$ with a slight modification. We want to choose $\Omega_H(r)$ so that it is compact and convex and thus homeomorphic to the ball. Moreover, we want to show that on the boundary of $\Omega_H(r)$ we have

$$(\Pi_H \circ G^*(z), \hat{n}(z)) = (G^*(z), \hat{n}(z)) < 0$$

where $z \in \partial \Omega_H(r)$, $\hat{n}(z)$ means the outward normal of $\partial \Omega_H(r)$ at $z$.

Then the Brouwer Fixed Point Theorem can be applied to obtain Lemma 4.5.

**Lemma 4.5.** For any subspace $H \subset P_{m,l}$, and for any linear map $F : H \rightarrow D_1$, we have

(4.6) \[ G \circ (I + F)(H) \cap H^\perp \neq \emptyset \]

or, equivalently, there exists $x \in H$, such that $G(x + F(x)) \in H^\perp$.

**Proof.** For the sake of simplicity, we give the proof for $l = 2$. The proof for $l \geq 3$ case is similar.

When $l = 2$, we define

(4.7) \[ H_1 = H \cap \Pi_{1}^{-1}(0), \quad H_2 = H \cap \Pi_{2}^{-1}(0), \quad H_3 = H \cap (H_1 + H_2)^\perp \]

where $\Pi_i : P_{m,l} \rightarrow P_{m,i}, i = 1, 2$ is as given in Definition 4.1. Then $H = H_1 \oplus H_2 \oplus H_3$ and $H_i \perp H_j$ for $i \neq j \in \{1, 2, 3\}$.

Thus given $z \in H$, we have

(4.8) \[ z = z_1 + z_2 + z_3 = (0, x_1) + (x_2, 0) + (y_1, y_2) \]

where $z_1 = (0, x_1) \in H_1$, $z_2 = (x_2, 0) \in H_2$, $z_3 = (y_1, y_2) \in H_3$. Then there exists $C_1 > C_2 > 0$ such that

$C_2 \|y_2\|_2 \leq \|y_1\|_2 \leq C_1 \|y_2\|_2$

for all $z_3 = (y_1, y_2) \in H_3$, since by construction $\Pi_i$ restricted to $H_3$ are isomorphisms for $i = 1, 2$.

Now define $\Omega_H(r) = \left\{ z \in H : \|z\|_2 \leq r, \|z_1\|_2 \leq r - \frac{C^{(2)}_2}{r}, \|z_2\|_2 \leq r - \frac{C^{(2)}_2}{r}, \|z_3\|_2 \leq r - \frac{C^{(2)}_2}{r} \right\}$, where $C^{(2)}_2 = 3 \max \left\{ 1, R_0^2 \cdot \frac{1+C_1^2}{C_2^2}, R_0^2 \cdot (1 + C_1^2) \right\}$ is a constant.
First, we have the following

**Claim 4.6.** If \( r > C^{(2)} \), then we have that \( \Omega_H(r) \) is homeomorphic to \( \tilde{B}_H(1) = \{ z \in H : |z|^2 \leq 1 \} \); thus \( \partial \Omega_H(r) \) is homeomorphic to \( S_H(1) = \partial B_H(1) = \{ z \in H : |z| = 1 \} \).

Proof of Claim 4.6: \( \Omega_H(r) \) is homeomorphic to \( \tilde{B}_H(1) \) due to the fact that for \( r > C^{(2)} \), \( \Omega_H(r) \subset H \) is a compact and convex set, with nonempty interior, thus is homeomorphic to \( \tilde{B}_H(1) \). The second claim follows from the fact that the restriction of a homeomorphism is also a homeomorphism. Q.E.D.

**Notation 4.** We define the structure function \( G^* : H \to P_{m,l} \) as

\[
(4.9) \\
G^*(x) = G(x + F(x)).
\]

For the linear map \( F : H \to D_1 \), we will also write \( F \) as

\[
F(z) = \left( F_1(z)\underline{l}_{m_1}, \ldots, F_l(z)\underline{l}_{m_l} \right),
\]

where \( F_i(z) : H \to R \) is a linear function for \( i = 1, 2, \ldots, l \).

Next we show that

**Claim 4.7.** For \( r > 0 \) sufficiently large, we have \( (\Pi_H \circ G^*(z), \hat{n}(z)) < 0 \), for all \( z \in \partial \Omega_H(r) \), where \( \hat{n}(z) \) means the outer normal of \( \Omega_H(r) \) at \( z \in \partial \Omega_H(r) \).

Proof of Claim 4.7: When \( r > 0 \) is sufficiently large, we have \( \partial \Omega_H(r) = S_1 \cup S_2 \cup S_3 \cup S_4 \),

\[
S_1 = \left\{ z \in H : |z|^2 = r, |z_1|^2 \leq r - \frac{C^{(2)}_1}{r}, |z_2|^2 \leq r - \frac{C^{(2)}_2}{r}, |z_3|^2 \leq r - \frac{C^{(2)}_3}{r} \right\},
\]

\[
S_2 = \left\{ z \in H : |z|^2 = r - \frac{C^{(2)}_1}{r}, |z_1|^2 \leq r, |z_2|^2 \leq r - \frac{C^{(2)}_2}{r}, |z_3|^2 \leq r - \frac{C^{(2)}_3}{r} \right\},
\]

\[
S_3 = \left\{ z \in H : |z|^2 = r - \frac{C^{(2)}_1}{r}, |z_1|^2 \leq r - \frac{C^{(2)}_2}{r}, |z_2|^2 \leq r, |z_3|^2 \leq r - \frac{C^{(2)}_3}{r} \right\},
\]

\[
S_4 = \left\{ z \in H : |z|^2 = r - \frac{C^{(2)}_1}{r}, |z_1|^2 \leq r - \frac{C^{(2)}_2}{r}, |z_2|^2 \leq r - \frac{C^{(2)}_3}{r}, |z_3|^2 \leq r \right\}
\]

with outer normal \( \hat{n}(z) = \frac{T_{\hat{z}}}{|T_{\hat{z}}|} \), respectively.

Thus for \( z \in S_1 \), we have

\[
(4.10) \\
(\Pi_H \circ G^*(z), \hat{n}(z)) = (\Pi_H \circ G^*(z), \frac{T_{\hat{z}}}{|T_{\hat{z}}|}) = (G^*(z), \frac{T_{\hat{z}}}{|T_{\hat{z}}|}) = \frac{s + \epsilon + \eta \epsilon \eta}{|\hat{z}|^2} = \frac{s + \epsilon + \eta \epsilon \eta}{|\hat{z}|^2} = \frac{s + \epsilon + \eta \epsilon \eta}{|\hat{z}|^2} = \frac{s + \epsilon + \eta \epsilon \eta}{|\hat{z}|^2}.
\]

Now from \( z \in S_1 \) we have \( |z|^2 \geq r, |z_1|^2 \leq r - \frac{C^{(2)}_1}{r}, |z_2|^2 \leq r - \frac{C^{(2)}_2}{r}, |z_3|^2 \leq r - \frac{C^{(2)}_3}{r}, \) thus

\[
(4.11) \\
|z_2|^2 + |z_3|^2 = |z_1|^2 - |z_1|^2 \geq r^2 - (r - \frac{C^{(2)}_1}{r})^2 = 2C^{(2)}_1 - \frac{C^{(2)}_1}{r^2} > C^{(2)}_1,
\]

\[
|z_1|^2 + |z_2|^2 = |z_1|^2 - |z_2|^2 \geq r^2 - (r - \frac{C^{(2)}_2}{r})^2 = 2C^{(2)}_2 - \frac{C^{(2)}_2}{r^2} > C^{(2)}_2,
\]

for \( r > C^{(2)}_1 \).

- If \( |z_3|^2 \leq \frac{C^{(2)}_3}{r^2} \), then from (4.11) we have

\[
(4.12) \\
|z_1|^2 + |z_2|^2 \geq |z_1|^2 + |z_2|^2 > C^{(2)}_1 > R_0^2,
\]

since \( H_1 \perp H_3, H_2 \perp H_3 \). Thus by Remark 4.2 and (4.10) we have
for all \( r > r \)
such that when
\[
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\]
which means

\[
(4.17)
\]

Thus, similarly, we also have that (4.13) holds.
Summarizing the estimate above, we have shown that if \( r > C^{(2)} \), then

\[
(4.15)
\]

for all \( z \in S_1 \).
For \( z \in S_2 \), we have

\[
(4.16)
\]

Now, from \( z \in S_2 \) we have \( |z_2|_2 = r - \frac{C^{(2)}}{r}, |z_2| \leq r \), thus we have

\[
(4.17)
\]

which means \( |y_2|_2 < \sqrt{2C^{(2)}} \).

With Corollary 3.5 of Section 3 in mind, we choose \( r_1 > 0 \) satisfying \( r_1 - \frac{C^{(2)}}{r_1} > r(\sqrt{2C^{(2)}},R_2) \), such that when \( r > r_1 \), we have \( |x_1|_2 = |z_1|_2 = r - \frac{C^{(2)}}{r} > r_1 - \frac{C^{(2)}}{r_1} \), thus combining the two inequalities above we have

\[
(4.18)
\]

Thus we have shown that if \( r > r_1 \), then

\[
(4.19)
\]

for all \( z \in S_2 \).
Similarly for \( z \in S_3 \), we can choose \( r_2 > 0 \) satisfying \( r_2 - \frac{C^{(2)}}{r_2} > r(\sqrt{2C^{(2)}},R_1) \), such that when \( r > r_2 \), we have
(4.20) \( \Pi_H \circ G^*(z), \hat{n}(z) = \frac{e^{x_2 + y_1 + F_1(z)} \mathbf{R}_1(x_2)^t}{|z_2|^t} = \frac{e^{F_1(z)} \cdot e^{x_2 + y_1} \mathbf{R}_1(x_2)^t}{|z_2|^t} < 0 \)

for all \( z \in S_3 \).

Now for \( z \in S_4 \), we have

(4.21) \( (\Pi_H \circ G^*(z), \hat{n}(z)) = (\Pi_H \circ G^*(z), \frac{z_3}{|z_3|}) = (G^*(z), \frac{z_3}{|z_3|}) = \frac{e^{x_2 + y_1 + F_1(z)} \mathbf{R}_1(x_2)^t}{|z_3|^t} \)

\( z \in S_4 \) implies \( |z_3|^2 = r - \frac{C_3}{r^2} \), \( |z_2|^2 \leq r \), thus

(4.22) \[
\begin{aligned}
|z_1|^2 &= |z_2|^2 - |z_3|^2 \leq r^2 - \left(r - \frac{C_3}{r^2}\right)^2 = 2C_3 - \frac{C_3^2}{r^2} < 2C_3,
|z_2|^2 &= |z_2|^2 - |z_3|^2 \leq r^2 - \left(r - \frac{C_3}{r^2}\right)^2 = 2C_3 - \frac{C_3^2}{r^2} < 2C_3
\end{aligned}
\]

which means that \( |z_1|^2 < \sqrt{2C_3}, |z_2|^2 < \sqrt{2C_3} \).

By Corollary 3.5 of Section 3, we can choose \( r_3 > 0 \) satisfying \( r_3 - \frac{C_3}{r_3^2} > \max(\frac{1 + C_2}{C_2^2}, \frac{1}{\sqrt{1 + C_2}}) \cdot \max(r(\sqrt{2C_3}, \mathbf{R}_1), r(\sqrt{2C_3}, \mathbf{R}_2)) \), such that when \( r > r_3 \), we have \( |z_3|^2 = r - \frac{C_3}{r^2} > r_3 - \frac{C_3}{r_3^2} \), which leads to

(4.23) \[
\begin{aligned}
|y_1|^2 &\geq \sqrt{\frac{C_2}{r + C_2}} |z_3|^2 > r(\sqrt{2C_3}, \mathbf{R}_1), \\
|y_2|^2 &\geq \sqrt{\frac{C_2}{r + C_2}} |z_3|^2 > r(\sqrt{2C_3}, \mathbf{R}_2)
\end{aligned}
\]

Thus, we have that when \( r > r_3 \),

(4.24) \[
(\Pi_H \circ G^*(z), \hat{n}(z)) = \frac{e^{x_2 + y_1 + F_1(z)} \mathbf{R}_1(x_2)^t + e^{x_1 + y_2 + F_2(z)} \mathbf{R}_2(y_2)^t}{|z_3|^t} \]

\( \frac{e^{F_1(z)} \cdot e^{x_2 + y_1} \mathbf{R}_1(x_2)^t + e^{F_2(z)} \cdot e^{x_1 + y_2} \mathbf{R}_2(y_2)^t}{|z_3|^t} < 0 \)

for all \( z \in S_4 \).

So combining (4.15), (4.19), (4.20) and (4.24) we have finished the proof of Claim 4.7. Q.E.D.

Combining Claim 4.6 and Claim 4.7, also noticing the discussion before Lemma 4.5, we finish the proof of Lemma 4.5.

\[ \square \]

Remark 4.8. It is easy to see that \( \Pi_H \circ G^* \) is an analytic function defined on \( H \), so there can only be finitely many \( z \in \Omega_H(r) \subset H \) such that \( \Pi_H \circ G^*(z) = 0 \). Also from the proof of Lemma 4.5 we can see that outside \( \Omega_H(r) \) there is no \( z \in H \) belonging to \( G^*(H) \cap H^\perp \).

Remark 4.9. It is an interesting observation that in the proof of Lemma 4.5, we never use the fact that \( F : H \to D_1 \) is linear. In fact, the reader may readily check
that if we change the word “linear” to “nonlinear” in Lemma 4.5, the proof of Lemma 4.5 still goes through. This observation will play a fundamental role in the proof of Theorem 1.1. We write it as the following

**Corollary 4.10.** For all $H \subset P_{m,l}$ and for all continuous map $F : H \to D_l$, we have

\[
G^*(H) \cap H^\perp = G \circ (I + F)(H) \cap H^\perp \neq \emptyset
\]

or, equivalently, $G(x + F(x)) \in H^\perp$ for some $x \in H$.

**Lemma 4.11.** For all $H' \subset \mathbb{R}^n$ such that $H' \cap D_l = \{\theta\}$, we have

\[
G(H') \cap H'^\perp \neq \emptyset.
\]

**Proof.** Let $H = \Pi_{P_{m,l}}(H')$. From the assumption $H' \cap D_l = H' \cap P_{m,l}^\perp = \{\theta\}$ we know that $\Pi_{P_{m,l}} : H' \to H$ is one-to-one and onto, thus is an isomorphism. It then follows that there exists a linear map $F : H \to D_l$ such that for all $z \in H'$, there exists unique $x \in H$ such that

\[
z = x + F(x)
\]

**Claim 4.12.** $G(H') \cap H'^\perp = G(H') \cap H^\perp$

**Proof of Claim 4.12:** For all $y \in G(H') \cap H'^\perp$, $z \in H'$, we have $y \in G(H') \subset P_{m,l}$, thus

\[
(y, z) = (y, x + F(x)) = (y, x) = 0,
\]

which shows that $y \in H^\perp$, so we obtain

\[
G(H') \cap H'^\perp \subset G(H') \cap H^\perp
\]

Now, for all $y' \in G(H') \cap H^\perp$, $x \in H$, we have

\[
(y', x) = (y', x + F(x)) = (y', z) = 0
\]

Thus

\[
G(H') \cap H^\perp \subset G(H') \cap H'^\perp
\]

Combining (4.28) and (4.30), we obtain

\[
G(H') \cap H'^\perp = G(H') \cap H^\perp.
\]

Q.E.D.
Now utilizing Claim 4.12 we obtain

\[ G(H') \cap H'^\perp = G(H') \cap H^\perp = G \circ (I + F)(H) \cap H^\perp \neq \emptyset \]

where the last statement follows from Lemma 4.5.

**Lemma 4.13.** If the CR has exactly \( l \) linkage classes, then for any subspace \( H \) of \( R^m \), we have that

\[ G(H) \cap H^\perp \neq \emptyset \]

Proof. If the CR has \( l \) linkage classes, by relabeling \( Y_1, Y_2, \ldots, Y_m \) we may assume that \( R \) has the same diagonal block form as that of (2.2).

Now let \( H \subset R^n \) be fixed. By linear algebra, we know that \( H = H(1) \oplus H(2) \), where \( H(1) = H \cap D_l \subset D_l, H(2) \cap D_l = \{ \theta \} \). Thus we have

\[
\begin{cases}
G(H) \cap H^\perp = G(H(1) \oplus H(2)) \cap (H(1) \oplus H(2))^\perp = G(H(1) \oplus H(2)) \cap H(1)^\perp \cap H(2)^\perp \\
= G(H(1) \oplus H(2)) \cap H(2)^\perp
\end{cases}
\]

(4.34)

since combining \( H(1) \subset D_l = P_{m,l}^\perp \) and \( G(R^m) \subset P_{m,l} \) we have \( G(H(1) \oplus H(2)) \subset P_{m,l} \subset H(1)^\perp \). Finally noting that

\[ G(H(2)) \cap H(2)^\perp \neq \emptyset \]

due to Lemma 4.9, we have

\[ G(H(1) \oplus H(2)) \cap H(2)^\perp \supset G(H(2)) \cap H(2)^\perp \neq \emptyset. \]

**5. Proof of Main Result and the index formula.** Now we only need to observe that the existence problem for each compatibility class can be reduced to one of intersection problem type as in the previous section.

Proof of **Theorem 1.1:** First a few words about the notation and definitions.

Let \( C, R, K, N \) be defined as in Section 2. Suppose that the CR has \( l \) linkage classes, by relabeling \( Y_1, Y_2, \ldots, Y_m \) we may assume that the relation matrix \( R \) has the same diagonal block form as that of (2.2). Let \( S \) be the stoichiometric subspace in \( R^n \), and define \( W(x_0) = \ln((x_0 + S) \cap R^m_n) \cdot C \subset K \), where \( x_0 \in R^m_n \).

As in the proof of Lemma 4.13, we have the decomposition of \( K \) as \( K = K_1 \oplus K_2', \) where \( K_1 = K \cap D_l \subset D_l, K_2' \cap D_l = \{ \theta \} \). Now let \( K_2 = \Pi_{P_{m,l}}(K_2') \). Then similar to the proof of Lemma 4.11 we have

\[ G(W(x_0)) \cap K^\perp = G(W(x_0)) \cap K_2'^\perp = G(W(x_0)) \cap K_2^\perp \]

(5.1)
Next we will need the following lemma, for the proof, the reader is referred to Proposition B.1 in [4].

**Lemma 5.1.** Given $x_0 \in R^+_n$, we have $\Psi : (x_0 + S) \cap R^+_n \rightarrow K_2$ given by $\Psi(x) = \Pi_{K_2}(\ln x \cdot C^t)$ is one-to-one and onto, actually, a diffeomorphism.

Due to Lemma 5.1 and the fact that $W(x_0) \subset K$, $\Pi_{P_m,l}K = K_2$, there exists a continuous (probably nonlinear) map $F : K_2 \rightarrow D_l$ such that for all $x \in W(x_0)$, there exists unique $z \in K_2$ such that $x = z + F(z)$. Defining a function $G : K_2 \rightarrow P_{m,l}$ as

\[
G(z) = G(z + F(z))
\]

for all $z \in K_2$. Note that $\hat{G}(K_2) = G(W(x_0))$.

Due to Remark 4.9 (or Corollary 4.10) of Section 4 we know that

\[
\hat{G}(K_2) \cap K_2^\perp = G \circ (I + F)(K_2) \cap K_2^\perp \neq \emptyset,
\]

i.e., we have $G(W(x_0)) \cap K_2^\perp \neq \emptyset$.

Combining (5.1) with (5.2) we have that $G(W(x_0)) \cap K_2^\perp \neq \emptyset$. Now we only need to observe that the map $F$ we defined above is an analytic function, thus by Remark 4.8 of Section 4, we must have $\text{car}(G(W(x_0)) \cap K_2^\perp)$ is finite, where $\text{car}(Q)$ means the cardinality of the set $Q$. The proof of Theorem 1.1 is complete.

**Corollary 5.2.** Let $s$ be the dimension of the stiochiometric subspace. If we restrict the vector field $f$ in (4.1) to some fixed positive stiochiometric compatibility class, denote the steady states in the stiochiometric compatibility class as $x_1, x_2, \ldots, x_t$ (the number $t$ of steady states depends on the stiochiometric compatibility class we choose), then we have

\[
\sum_{i=1}^{t} \text{ind}(x_i) = (-1)^s
\]

where $\text{ind}(x_i)$ is the index of vector field $f$ at steady state $x_i, i = 1, 2, \ldots, t$.

**Proof.** Let $C, R, K, K_2, S$ be defined as above.

First, we give the following

**Definition 5.3.** For the configuration matrix $C = \begin{pmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_m \end{pmatrix} \in R^{m \times n}$, we define the reduced configuration matrix $\tilde{C}$ as

\[
\tilde{C} = C - \begin{pmatrix} D_1 \\ D_2 \\ \vdots \\ D_l \end{pmatrix} \cdot C
\]
where \( D_i = \frac{1}{m_i} \begin{pmatrix} 1 & 1 & \ldots & 1 \\ 1 & 1 & \ldots & 1 \\ \vdots & \vdots & \ddots & \vdots \\ 1 & 1 & \ldots & 1 \end{pmatrix} \), with \( m_i \) given at the beginning of section 4 for \( i = 1, 2, \ldots, l \).

It is easy to check that \( \tilde{C} \) has the following property

\[
(5.4) \quad \begin{cases} 
R : C = R : \tilde{C} \\
\Pi_{K_2}(x \cdot C^t) = \Pi_{K_2}(x \cdot \tilde{C}^t)
\end{cases}
\]

Now fix \( x_0 \in R^d_+ \), from the proof of Theorem 1.1 above we know the vector field \( f \) on \( x_0 + S \) can be written as

\[
(5.5) \quad \frac{dx}{dt} = f(x) = e^{\ln x \cdot C^t} \cdot R \cdot C = e^{z + F(z)} \cdot R \cdot \tilde{C}
\]

where \( z = \Psi(x) = \Pi_{K_2}(\ln x \cdot C^t) \in K_2 \). By Lemma 5.1 we know that \( \Psi : x_0 + S \to K_2 \) is a diffeomorphism. Thus considering the induced vector field \( \Psi_* \circ f \) on \( K_2 \) we have

\[
(5.6) \quad \begin{cases} 
\frac{dz}{dt} = \Psi_* \circ f \circ \Psi^{-1}(z) = \Pi_{K_2}(\frac{dx}{dt} \cdot Diag(\frac{1}{x}) \cdot C^t) \\
= \Pi_{K_2}(e^{z + F(z)} \cdot R \cdot \tilde{C} \cdot Diag(\frac{1}{x}) \cdot \tilde{C}^t) \\
= \Pi_{K_2}(e^{z + F(z)} \cdot R) \cdot \tilde{C} \cdot Diag(\frac{1}{x}) \cdot \tilde{C}^t
\end{cases}
\]

where \( Diag(\frac{1}{x}) = \begin{pmatrix} \frac{1}{x_1} & & \\ & \frac{1}{x_2} & \\ & & \ddots \\ & & & \frac{1}{x_n} \end{pmatrix} \) and we have used property (5.4) of the reduced configuration matrix \( \tilde{C} \).

Now notice that the matrix \( \tilde{C} \cdot \begin{pmatrix} \frac{1}{x_1} & & \\ & \frac{1}{x_2} & \\ & & \ddots \\ & & & \frac{1}{x_n} \end{pmatrix} \cdot \tilde{C}^t \) is positive definite when the action is restricted to \( K_2 \), thus by a simple homotopy between \( \tilde{C} \cdot \begin{pmatrix} \frac{1}{x_1} & & \\ & \frac{1}{x_2} & \\ & & \ddots \\ & & & \frac{1}{x_n} \end{pmatrix} \).

\( \tilde{C}^t \) and the identity matrix we see that the vector field \( \Psi_* \circ f \circ \Psi^{-1} \) is homotopic to \( \Pi_{K_2}(e^{z + F(z)} \cdot R) \), while the critical points and corresponding indices remain invariant under this homotopy.

We observe that in the proof of Lemma 4.5 we construct a bounded, convex domain \( \Omega \) so that the vector field \( \Pi_{K_2}(e^{z + F(z)} \cdot R) \) is pointing inwards at each point of \( \partial \Omega \), thus by a standard result of degree theory we have that

\[
(5.7) \quad \sum_{i=1}^{s} ind_f(x_i) = \sum_{i=1}^{s} ind_{\Psi_* \circ f \circ \Psi^{-1}}(x_i(z)) = \sum_{i=1}^{s} ind_{\Pi_{K_2}(e^{z + F(z)} \cdot R)}(\tilde{x}_i(z)) = (-1)^s
\]
where $s$ is the dimension of $K_2$, which by Lemma 5.1 is equal to the dimension of $S$, the stoichiometric subspace.

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