

An Introduction to the Chemical Reaction Network Theory

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Abstract

Chemical reaction network theory is an area of applied mathematics that attempts to model the behavior of chemical and biochemical systems. In this paper we present the deficiency zero theorem and the global attractor conjecture for deterministic mass-action kinetics systems, the most widely used model in chemistry. The result reveal that a large class of systems with non-linear differential equations have very simple and stable dynamics.

Contents

1	Introduction	1
1.1	Motivation	1
1.2	Chemical Reaction Networks (CRN's)	1
1.3	Mass-Action Kinetics	2
1.4	Reaction Diagram	3
2	Deficiency Zero Theorem	5
2.1	Introduction to Deficiency Theory	5
2.2	The Deficiency Zero Theorem	7
2.2.1	Existence of a Positive Equilibrium	8
2.2.2	Uniqueness in Each Positive Stoichiometry Compatibility Class	9
2.2.3	Local Asymptotic Stability	10
3	Global Attractor Conjecture	12
3.1	Introduction to Toric Differential Inclusions	12
3.1.1	Definitions and Notation	12
3.1.2	Toric Differential Inclusions	13
3.2	Zero-separating Surfaces	14
3.3	Proof of the Global Attractor Conjecture	14
4	Conclusion	15
	References	16

1 Introduction

At the very beginning, we shall discuss some motivation for writing this paper. In particular, we shall briefly explain why chemists and mathematicians are interested in the Chemical Reaction Network theory. The rest of this introduction section provides some basic chemistry background, and establishes the abstract mathematical model for reaction network structure.

1.1 Motivation

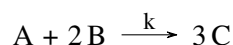
Informally speaking, a chemical reaction network is a collection of chemical reactions. One network, especially the biochemical network, often contains a large number of reactions with complex relationships. As a consequence, we know little about the parameters (e.g. rate constants) of those networks, and traditional ad hoc examinations are extremely difficult to control. To further study these systems, we want, as how Feinberg described it, a broad-based theory that doesn't require the study of parameters, a theory that can "provide qualitative information about large classes of networks all at once"[?].

This topic was first studied by Feinberg, Horn, and Jackson in the 1970s. The goal is to establish a reasonably general theory that can be easily used by engineers. Thus, one of the main focuses of the theory is about the existence and stability of equilibria, or steady states. Some big results are the deficiency theorems and the global attractor conjecture. The global attractor conjecture, which has just been proved several years ago, states that *all* solutions in the same compatibility class of a complex balanced mass-action network must converge to a unique equilibrium.¹ This has remarkable implications for the dynamics of large classes of polynomial and power-law dynamical systems. For example, if we have a nice system (so that we can apply the theorem), then within some groups of initial conditions, we know that the final state of the system would always be the same, and in particular no substance is absent.

The chemical reaction network theory is a promising area that has attracted a growing research community since its foundation in the 70s. Early studies mainly used techniques from linear algebra, dynamical systems, and graph theory. More recently, as motivated by problems in systems biology, other areas of mathematics like convex geometry and differential geometry have contributed to this subject. Herein we present a review of the chemical reaction network theory and highlight two results that we think are the most important: the deficiency zero theorem (Section 2) and the global attractor conjecture (Section 3).

1.2 Chemical Reaction Networks (CRN's)

We begin with a simple example of a chemical reaction:



This is often interpreted as "1 unit of A combines with 2 units of B to form 3 units of C ". We can write the reactants and products as column vectors:

$$y = \begin{bmatrix} 1 \\ 2 \\ 0 \end{bmatrix}, \quad y' = \begin{bmatrix} 0 \\ 0 \\ 3 \end{bmatrix},$$

where each entry of the vector is associated with the coefficient of one chemical substance in this system. Note that each reaction is now represented by $y \rightarrow y'$, and it changes the state of the system by $y' - y$.

¹We'll explain this more in Section 3.

Now we switch to general definitions.

Definition. A *chemical species* is a chemical substance that is involved in a reaction, either as a reactant or a product, or both.

If there are in total s species in some reactions and we label them by S_1, \dots, S_s , then we say

$$\mathcal{S} = \{S_1, \dots, S_s\}, \quad |\mathcal{S}| = s.$$

is the set of chemical species involved in this reaction network (a collection of those reactions).

Definition. A *complex* y_k is a non-negative vector that represents the number of units of each species consumed or created in the k -th reaction. The set of complexes is given by $\mathcal{C} = \{y_k\}$.

Often we denote the source vector by y_k and the product vector by y'_k , but both y_k and y'_k belong to \mathcal{C} . For instance, vectors y and y' defined in our simple example are both complexes. Each y_k is associated with a linear combination of the species, and the coefficient of S_i is given by y_{ki} . (e.g, if $y_k = [1, 2, 3]$, then the coefficient of S_2 is 2.) For simplicity, we say that the number of complexes is n , so $|\mathcal{C}| = n$.

Definition. A *reaction* R_k is given by $R_k = y_k \rightarrow y'_k$, where y_k and y'_k are complexes defined as above. The set of all reactions are given by (denote the size of the set by r):

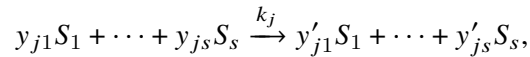
$$\mathcal{R} = \{y_k \rightarrow y'_k : y_k, y'_k \in \mathcal{C}\}, \quad |\mathcal{R}| = r.$$

Definition. The triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is then called a *chemical reaction network* (CRN).

1.3 Mass-Action Kinetics

We will introduce the mass-action kinetics in a deterministic setting.

In a deterministic setting, we describe the state of the system by the concentration of each species as a function of time. Let $c_k(t)$ denote the amount of species S_k per unit volume, which can be grouped together to form a concentration vector $c = (c_1, \dots, c_s)$. Mass-action kinetics assumes that every reactant reacts at a rate proportional to the product of the concentrations of all reactants (raised to the power of their stoichiometric coefficients), where the proportionality constant is the rate constant² k . That is, given a reaction $R_j = y_j \rightarrow y'_j$:



the rate of reaction is given by $K_j(c(t)) = k_j \prod_{i=1}^s c_i^{y_{ji}}(t)$.

Definition. Given the state has changed by $y'_j - y_j$, we say that the *rate of change of the concentration* $\frac{d}{dt}c$ is given by

$$\frac{d}{dt}c = (y'_j - y_j) \cdot k_j \prod_{i=1}^s c_i^{y_{ji}}(t).$$

For systems with multiple reactions, we have

$$\frac{d}{dt}c = \sum_{y_j \rightarrow y'_j \in \mathcal{R}} (y'_j - y_j) \cdot k_j \prod_{i=1}^s c_i^{y_{ji}}(t). \quad (1.1)$$

²A number associated with the reaction, which is often determined empirically.

1.4 Reaction Diagram

A different but equivalent way to represent chemical reaction network is to view it as a finite directed graph. This graph is sometimes called the *reaction diagram*.

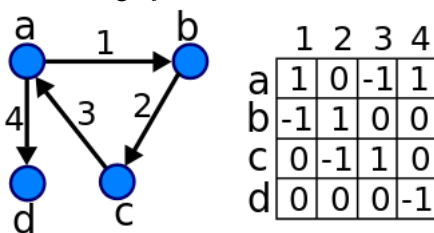
We think a chemical reaction network as a finite directed graph $G(V, E)$, where the vertices are complexes and the edges are labeled by rate constants. Let n denote the number of complexes ($|C| = n$), s denote the number of species ($|S| = s$), and r denote the number of reactions ($|\mathcal{R}| = r$). We have $V = \{1, 2, \dots, n\}$ and $E \subseteq \{(i, j) \in V \times V : i \neq j\}$. The vertex i represents the i -th complex, and it can be labeled by

$$c^{y_i} = c_1^{y_{i1}} c_2^{y_{i2}} \dots c_s^{y_{is}} = \prod_{j=1}^s c_j^{y_{ij}},$$

where c_j and y_{ij} represent the concentration and the coefficient of species S_j , respectively.

We can construct a matrix Y by letting y_i be its i -th column. Then Y is an $s \times n$ matrix whose i -th column contains the stoichiometric coefficients of the species in the i -th complex. Under the assumption of mass-action kinetics, Y has non-negative integer entries.

Another important matrix is the incidence matrix of G , denote it by B . In general, B is an $n \times r$ matrix, and $B_{ij} = -1$ if edge j leaves vertex i , 1 if edge j enters vertex i , and zero otherwise. Below is an example:



A notable feature of B is that for each column it has exactly one entry equals to 1 , one entry equals to -1 , and the other entries equal to 0 . This is a simple consequence of our definition of complexes. A chemical interpretation of the k -th column of B is the k -th reaction, and the i -th entry which is 1 is the product complex while the j -th entry which is -1 is the source complex. Essentially, the reaction takes one source complex and outputs a product complex.

Finally, define a $r \times 1$ column vector K that contains the rate of the reaction. Recall that the rate of the j -th reaction is given by $K_j(c(t)) = k_j \prod_{i=1}^s c_i^{y_{ji}}$. Then, the mass-action equations of this network is given by

$$\frac{d}{dt}c = Y \cdot B \cdot K(c(t)). \quad (1.2)$$

Sometimes, it's useful to combine Y and B . We define $S = Y \cdot B$, where S is often called the *stoichiometry matrix*. Then we obtain another way to write the differential equations:

$$\frac{d}{dt}c = S \cdot K(c(t)). \quad (1.3)$$

This is sometimes more useful than (1.2).

Now we introduce a few more terminologies associated with the graph. In a reaction diagram, each reaction from the i -th complex to the j -th complex is represented by a directed edge $(i, j) \in E$ and it is labeled with a rate constant k_{ij} .

Definition. A network is **reversible** if G is undirected, in which case each edge has two rate constants k_{ij} and k_{ji} .

But oftentimes we don't need such a strong assumption. The main type of networks we're interested in is the following:

Definition. A network is **weakly reversible** if each edge of G is contained in a cycle. That is, for each vertex i in G , there is a directed path with distinct intermediate vertices begins and ends at i .

We can partition the graph into (connected) components.

Definition. A **component** is a subgraph of an undirected graph (take the associated undirected graph if we are given a directed one) in which any two vertices are connected to each other by paths, and is connected to no additional vertices in the subgraph.

Definition. A graph is said to be **connected** if it has only one component.

Thus every component is connected by definition.

2 Deficiency Zero Theorem

The idea of deficiency was first introduced by Fritz Horn and Martin Feinberg as a way to characterize mass-action systems which permitted complex-balanced equilibria³. That is, if we wait enough time, our chemical network would contain every single species involved. Feinberg proved the oldest and most well-known Deficiency Zero Theorem in 1979. Since then, a series of generalizations have been made and the deficiency theory has expanded to systems with non-zero deficiency value.

The deficiency zero theorem is remarkable because it tells us some features of the equilibrium purely from the structure of network. The material in this section is based on the lecture notes written by de Leenheer [5]. For readers interested in Feinberg's original proofs, please see [6].

2.1 Introduction to Deficiency Theory

Here we present some definitions and handy lemmas.

Definition. A CRN is **complex-balanced** if there exists a positive vector d ($d_i > 0$ for all $i \in \{1, \dots, r\}$) such that

$$Bd = 0.$$

In particular, if we think d as a rate vector, then $\frac{d}{dt}c = Y \cdot B \cdot d = 0$. That is, there exists a positive equilibrium of the system. The following result is crucial.

Theorem 2.1. A CRN is complex-balanced if and only if it is weakly reversible.

Proof. Suppose the CRN is weakly reversible. We can partition the reaction diagram into l components, and since the CRN is weakly reversible, within each component there is a directed path from each vertex to each other vertex. That is, each component is strongly connected. We can relabel the vertices and edges so that the incidence matrix has the following structure:

$$B = \begin{pmatrix} B_1 & 0 & \dots & 0 \\ 0 & B_2 & \dots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & B_l \end{pmatrix},$$

where each B_j is the incidence matrix corresponding to each component G_j . A fact from graph theory states that a strongly connected directed graph has a directed cycle that contains all edges. Suppose there are k edges in G_j . We define the vector d_j such that for $i \in \{1, \dots, k\}$,

$$d_{j_i} = \text{number of times the } i\text{-th directed edge occurs in the directed cycle.}$$

Since each edge appears precisely once in the cycle, we know that $d_{j_i} > 0$ for all i . Let m be a vertex in G_j , it's clear that $(B_j d_j)_m$ is the difference between the number of incoming and outgoing edges of vertex m , which is zero because vertex m is contained in a cycle with no repetitive vertices. That is,

$$B_j d_j = 0.$$

Define the vector d by stacking the vectors d_1, \dots, d_l into a single column vector. Then we obtain the desired positive vector d such that

$$Bd = 0.$$

³Also known as *toric dynamical systems* in more recent works.

That is, a weakly reversible CRN is complex-balanced.

Conversely, suppose the CRN is not weakly reversible. Then the complex graph has a component that is not strongly connected. We focus on that component and partition the graph into two groups such that there are directed edges from the second group to the first, but not from the first into the second. Thus relabel the vertices we can obtain an incidence matrix such that

$$B' = \begin{pmatrix} B_1 & + \\ 0 & B_2 \end{pmatrix},$$

where $+$ is a nonzero block with non-negative entries only. Recall that each column of B' has exactly one 1 and one -1, so B_2 is a block matrix with only non-positive entries. Consider the vector v in the form of $[0, -1]$ such that

$$vB' = [0, -B_2].$$

Therefore, for any positive vector d , we have $vB'd > 0$, thus there is no d satisfies $B'd = 0$. Hence the CRN is not complex-balanced. \square

Remark. *Chemically, the term “complex-balance” means that the net flow into each complex of the CRN is zero. This is oftentimes hard to check. However, the weak reversibility of a CRN is quite straightforward (we can know it by simply looking at the structure). Thus, this theorem provides an easy way to check whether a system can be complex-balanced.*

Definition. *The linkage classes of a reaction network is the set $\{G_i\}$ where G_i 's are the components of the corresponding reaction diagram $G(V, E)$.*

Definition. *The deficiency of a CRN, denote by δ , is*

$$\delta = \dim(\text{Ker}(YB)) - \dim(\text{Ker}(B)).$$

Suppose $v \in \text{Ker}(B)$, then it's clear that $v \in \text{Ker}(YB)$ as $YB(v) = Y(Bv) = 0$. Hence, $\text{Ker}(B) \subseteq \text{Ker}(YB)$. It follows that $\dim(\text{Ker}(YB)) \geq \dim(\text{Ker}(B))$. More explicitly, the deficiency δ is always a non-negative integer. We choose the above definition of the deficiency because it illustrates this property clearly. In other literature, the following theorem is often taken as its definition. We'll show that they're indeed equivalent.

Theorem 2.2.

$$\delta = n - l - \text{rank}(S),$$

where n , l is the number of complexes and linkage classes of the network, respectively. S denotes the stoichiometry matrix.

Proof. Some algebraic property of the incidence matrix B (of the reaction diagram) is important:

$$\dim(\text{Im}(B)) = n - l, \quad \dim(\text{Ker}(B)) = r - (n - l). \quad (2.1)$$

(Note: $\text{Im}(B)$ is the image of B , while $\text{Ker}(B)$ denotes the kernel of B .)

Remark. *These properties comes from manipulating the reaction diagram, and we're not interested in the proof here.*

It follows that

$$\begin{aligned}
 \delta &= \dim(\text{Ker}(YB)) - \dim(\text{Ker}(B)) \\
 &= \dim(\text{Ker}(S)) - [r - (n - l)] \\
 &= [r - \text{rank}(S)] - r + n - l \\
 &= n - l - \text{rank}(S).
 \end{aligned}$$

The third step comes from the rank-nullity theorem. □

We conclude this section with another property of the deficiency that will be useful later.

Lemma 2.3.

$$\delta = \dim(\text{Ker}(Y) \cap \text{Im}(B)).$$

Proof. Note that $\text{Ker}(B) \subseteq \text{Ker}(YB)$, and for all $v \in \text{Ker}(YB)$,

$$YB(v) = Y(Bv) = 0 \Rightarrow B(v) \in \text{Ker}(Y) \cap \text{Im}(B).$$

Now define a new linear map T by inducing B to $\text{Ker}(YB)$. Then we have

$$\text{Ker}(T) = \text{Ker}(B), \quad \text{Im}(T) = \text{Ker}(Y) \cap \text{Im}(B).$$

By the rank-nullity theorem,

$$\dim(\text{Ker}(YB)) = \dim(\text{Ker}(B)) + \dim(\text{Ker}(Y) \cap \text{Im}(B)).$$

By definition, $\delta = \dim(\text{Ker}(YB)) - \dim(\text{Ker}(B))$; it follows that

$$\delta = \dim(\text{Ker}(Y) \cap \text{Im}(B)).$$

□

Once again, the definition and properties of the deficiency has nothing related to specific parameters of the network. It all comes from the structure.

2.2 The Deficiency Zero Theorem

Now we can finally state Feinberg's deficiency zero theorem.

Theorem 2.4 (Feinberg, 1979). *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network with deterministic mass-action kinetics. Suppose it's weakly reversible and has zero deficiency, then within each positive stoichiometric compatibility class⁴ there is precisely one equilibrium which is locally asymptotically stable.*

To prove this theorem, we need a new decomposition of the differential equations that displays linearity. First, recall that we have $K_j(c(t)) = k_j \prod_{i=1}^s c_i^{y_{ji}} c(t)$. If we embed those rate constants (k_j 's) in some complicated matrix, then we factor the rate vector $K(c(t))$ as

$$K(c(t)) = \Gamma \Psi(c(t)),$$

where Γ is a $r \times n$ matrix such that

$$\Gamma_{ij} = \begin{cases} k_{ij}, & \text{if complex } j \text{ is the reactant complex of the reaction } i; \\ 0, & \text{otherwise.} \end{cases}$$

⁴in short, it's a set $P = \{z : z = p + \text{Im}(S)\}$, where z, p are in the first orthant. It will be formally defined later.

The $\Psi(c(t))$ is an n vector whose components are vertices of the graph, that is

$$\Psi_i(c(t)) = \prod_{j=1}^s c_j^{Y_j^i}, \quad i = 1, \dots, n.$$

Thus we define

$$\frac{d}{dt}c = YA_k\Psi(c(t)), \quad \text{where } A_k = B\Gamma.$$

A_k is an $n \times n$ matrix whose off-diagonal entries are the k_{ij} and row sums are zero. A_k is indeed the negative Laplacian of the reaction diagram G .

We'll use this to prove Feinberg's deficiency zero theorem in the next three subsections.

2.2.1 Existence of a Positive Equilibrium

Theorem 2.5. *Suppose a CRN with mass-action kinetics is weakly reversible and has zero deficiency. Then it has a positive equilibrium c^* such that*

$$A_k\Psi(c^*) = 0.$$

Proof. Since the network has zero deficiency, by definition we have

$$\dim(\text{Ker}(YA_k)) = \dim(\text{Ker}(A_k)).$$

Combine it with the fact $\text{Ker}(A_k) \subseteq \text{Ker}(YA_k)$, we have $\text{Ker}(A_k) = \text{Ker}(YA_k)$. Thus we're trying to find a c such that $A_k\Psi(c) = 0$.

We can partition a weakly reversible graph into l strongly connected components, and we write A_k in block-diagonal form such that the diagonals are given by blocks $(A_k)_j$, $j \in \{1, \dots, l\}$. Then, we know that each $(A_k)_j$ is irreducible with non-negative off-diagonal entries. Thus⁵, there exist positive vectors d_j such that $(A_k)_j d_j = 0$ and those are the only eigenvectors having non-negative entries. Then solving $A_k\Psi(c) = 0$ for positive c is reduced to finding positive c such that

$$\Psi(c) = \sum_{i=1}^l \lambda_i d_i^e, \quad \lambda_i > 0,$$

where the d_i^e are n vectors with entries equal to d_i in the corresponding block, and zeros otherwise. Taking logarithms entry-wise, the equation becomes

$$Y^T \log(c) = \log \left(\sum_{i=1}^l \lambda_i d_i^e \right).$$

Letting $\lambda_i = e^{a_i}$ for real a_i and let s_i be a vector obtained by replacing positive entries of d_i^e by 1, and zeros by 0. Thus,

$$Y^T \log(c) = \sum_{i=1}^l a_i s_i + \log \left(\sum_{i=1}^l d_i^e \right). \quad (2.2)$$

The following linear algebra statement is useful here:

$$\dim(\text{Im}(Y^T) \oplus \text{span}\{s_i\}) = n - \delta. \quad (2.3)$$

⁵it's an application of Perron-Feobenius Theorem.

To see this, apply Theorem 2.3 and take the orthogonal component of both sides. Since our system has $\delta = 0$, we obtain $\text{Im}(Y^T) \oplus \text{span}\{s_i\} = \mathbb{R}^n$. Thus, any $w \in \mathbb{R}^n$ can be decomposed into

$$w = Y^T(v) - \sum_{i=1}^l b_i s_i, \quad b_i \in \mathbb{R}.$$

In particular, choose $w = \log(\sum_{i=1}^l d_i^e)$ and $c^* = e^v$, we obtain an equation in the form of (2.2), which concludes the proof. \square

Remark. *Again, the weak reversibility and zero deficiency of a CRN only relate to its structure and is easy to check. However, the existence of a positive equilibrium requires many experiments. It's almost impossible to conclude that such equilibrium does not exist, as one cannot go through all initial conditions.*

In particular, it can be used as a way of testing models of real-world systems. For example, suppose we model a system such that it is weakly reversible and has deficiency zero. However, our experimental results always have at least one species missing in the final state, regardless of the initial condition. Then, we know that there is a flaw in our model.

2.2.2 Uniqueness in Each Positive Stoichiometry Compatibility Class

For any vector $x, y \in \mathbb{R}^m$, we may abuse the notation and define the vector xy by taking the entry-wise products of the vectors x and y . The inner product is denoted by the usual way $\langle x, y \rangle$.

Let E_+ denote the set of positive equilibria of a CRN. By Theorem 2.5, we know that $E_+ \neq \emptyset$, and $c^* \in E_+$. We can then parametrize the set E_+ by the following:

$$\tilde{E} = \{c \mid c = c^* e^\mu, \mu \in [\text{Im}(S)]^\perp\}$$

We claim that $E_+ = \tilde{E}$. The proof is omitted here.

Definition. *A positive stoichiometry compatibility class P is given by*

$$P = \{z \in \mathbb{R}_+^s : z = p + \text{Im}(S)\}, \quad p \in \mathbb{R}_+^s,$$

where \mathbb{R}_+^s denotes the first (open) orthant⁶ of \mathbb{R}^s .

Theorem 2.6. *Suppose a CRN with mass-action kinetics is weakly reversible and has zero deficiency. Let P be an arbitrary positive stoichiometry compatibility class. Then $P \cap E_+$ is a singleton⁷.*

Proof. We first show that $P \cap E_+ \neq \emptyset$. Define a function $g : \mathbb{R}^s \rightarrow \mathbb{R}$ by

$$g(c) = \langle c^*, e^c \rangle - \langle c, p \rangle,$$

where c^* is a fixed positive equilibrium of the CRN. Taking the derivative, we have

$$\nabla g(c) = c^* e^c - p.$$

The Hessian is given by $H(c) = \text{diag}(c^* e^c)$. Since all its diagonal entries are positive, $H(c)$ is positive definite. Thus g is convex on \mathbb{R}^s . In addition, it's clear that g is radially unbounded:

$$\lim_{a \rightarrow \infty} g(ac) = \infty, \quad c \neq 0.$$

⁶the multi-dimension version of "first quadrant".

⁷A set with only one point.

Now restrict g to the set $[Im(S)]^\perp$, denote the induced function by g_0 . g_0 is continuous, convex, and radially unbounded. Define the set

$$F = \{c \in [Im(S)]^\perp : g_0(c) \leq g_0(0)\}.$$

F is closed by construction, and $0 \in F$. If $x, y \in F$, then for $t \in [0, 1]$,

$$g_0(tx + (1-t)y) \leq tg_0(x) + (1-t)g_0(y) \leq g_0(0)[t + 1 - t] = g_0(0).$$

Hence $tx + (1-t)y \in F$, i.e., F is convex. We claim that F is bounded. If it's not, then it would contain a half-ray through the origin, which implies that g_0 is unbounded on F , a contradiction (g_0 is bounded by $g_0(0)$). F is a closed and bounded subset of an Euclidean space, so F is compact.

Since F is compact and g_0 is continuous on F , there exists a point $\mu \in F$ such that $g_0(\mu) \leq g_0(c)$ for all $c \in F$. g_0 has a minimum at μ , so $\nabla g_0(\mu) = 0$. Then, for any $v \in [Im(S)]^\perp$, $\nabla g_0(\mu) \cdot v = 0$. That is, $\nabla g_0(\mu)$ is perpendicular to $[Im(S)]^\perp$, hence it belongs to $Im(S)$. More explicitly,

$$\nabla g(\mu) = c^* e^\mu - p \in Im(S).$$

That is, there exists $c \in \widetilde{E}$ such that $c \in P$. Since $E_+ = \widetilde{E}$, we know that $c \in E_+$ as well. Therefore, for any positive stoichiometry compatibility class P , there exists a $c \in E_+$ such that $c \in P \cap E_+ \neq \emptyset$.

Suppose that the intersection of E_+ with P is not unique. then there exist c_1, c_2 such that

$$c_1 = c^* e^{\mu_1}, \quad c_2 = c^* e^{\mu_2}, \quad \mu_1 \neq \mu_2, \mu_1, \mu_2 \in [Im(S)]^\perp.$$

Therefore, $c_1 - c_2 \in Im(S)$, $\mu_1 - \mu_2 \in [Im(S)]^\perp$. They're orthogonal, so we can take the inner product:

$$0 = \langle c_1 - c_2, \mu_1 - \mu_2 \rangle = \langle c^* (e^{\mu_1} - e^{\mu_2}), \mu_1 - \mu_2 \rangle.$$

However, the last expression is strictly positive because c^* is positive, and the exponential is a strictly increasing function (so $(\mu_{1_i} - \mu_{2_i})(e^{\mu_{1_i}} - e^{\mu_{2_i}}) > 0$). There is a contradiction, so our assumption is false. Hence, there exists precisely one point $c \in P \cap E_+$ for each positive stoichiometry compatibility class P . \square

Remark. *This shows that, if the initial condition only changes a little bit (within the same positive stoichiometry compatibility class), then the final state of the system would be the same. In particular, if the initial state of the system has all species involved in the network, so does the final state.*

2.2.3 Local Asymptotic Stability

Now we know those equilibria exists, but what else do we know? In this section, we show some characterizations of the unique equilibrium.

Theorem 2.7. *Suppose a CRN with mass-action kinetics is weakly reversible and has zero deficiency. Let $\{c^*\} = P \cap E_+$, so that c^* is the unique positive equilibrium in the positive stoichiometry compatibility class P , and c^* is locally asymptotically stable relative to P .*

Proof. The result comes from Lyapunov's stability theorem. We would not prove the stability theorem, but instead show how to apply this theorem to our problem. To see this, we define the following Lyapunov function in \mathbb{R}_+^s :

$$V(c) = \sum_{i=1}^s \int_{c_i^*}^{c_i} \log x_i - \log c_i^* dx_i,$$

where c^* is the given unique equilibrium in P . We have that $V(c)$ is of class C^1 and

$$\nabla V(c) = \log(c) - \log(c^*).$$

In addition, $V(c) \geq 0$ for all c and $V(c) = 0$ if and only if $c = c^*$.

We have that

$$\frac{d}{dt}V = \left\langle \frac{d}{dt}c, \log(c) - \log(c^*) \right\rangle = \sum_{l=1}^r \langle S_l K_l(c), \log(c) - \log(c^*) \rangle,$$

where S_l denotes the l -th column of the stoichiometry matrix S . Let α_l, β_l denote the (stoichiometry vector of) reaction and product complex of l -th reaction, respectively. Then,

$$\frac{d}{dt}V = \sum_{l=1}^r k_l c^{\alpha_l} \langle \beta_l - \alpha_l, \log(c) - \log(c^*) \rangle.$$

By simple algebraic rules, we can write c^{α_l} in terms of c^* :

$$c^{\alpha_l} = (c^*)^{\alpha_l} \cdot e^{\langle \alpha_l, \log(c/c^*) \rangle}.$$

Then,

$$\frac{d}{dt}V = \sum_{l=1}^r k_l (c^*)^{\alpha_l} e^{\langle \alpha_l, \log(c/c^*) \rangle} \cdot \langle \beta_l - \alpha_l, \log(c) - \log(c^*) \rangle. \quad (2.4)$$

(2.4) can be viewed as a tangent line of the exponential function. By strict convexity, we have

$$\frac{d}{dt}V \leq \sum_{l=1}^r k_l (c^*)^{\alpha_l} \cdot \left(e^{\langle \beta_l, \log(c/c^*) \rangle} - e^{\langle \alpha_l, \log(c/c^*) \rangle} \right).$$

Let e_i denote the standard basis of \mathbb{R}^n , we have

$$\frac{d}{dt}V \leq \sum_{l=1}^r k_l (c^*)^{\alpha_l} \cdot \langle B_l, \sum_{i=1}^n e^{\langle Y_i, \log(c/c^*) \rangle} e_i \rangle,$$

where B_l is the l -th column of the incidence matrix B and Y_i is the i -th column of the matrix Y . This can be written more elegantly as:

$$\frac{d}{dt}V \leq \left\langle BK(c^*), \sum_{i=1}^n e^{\langle Y_i, \log(c/c^*) \rangle} e_i \right\rangle. \quad (2.5)$$

However, since c^* is an equilibrium and the network has deficiency zero ($\text{Ker}(BK) = \text{Ker}(YBK)$), we have $BK(c^*) = 0$. Hence,

$$\frac{d}{dt}V \leq 0.$$

By definition, $dV/dt = 0$ when $c = c^*$ (as $\nabla V(c^*) = 0$). Therefore, for any positive initial condition, we have that $dV/dt < 0$ for all $c \in P \setminus \{c^*\}$, as c^* is the only equilibrium. By the Lyapunov's stability theorem, c^* is indeed locally asymptotically stable. \square

This completes the proof of deficiency zero theorem.

3 Global Attractor Conjecture

We have proved in Section 2 that zero-deficiency complex-balanced mass-action systems have a unique positive equilibrium within each positive stoichiometric compatibility class. In this section we will show that this equilibrium is in fact a global attractor, i.e., all solutions within the same compatibility class converge to it. This implies that a large class of polynomial and power-law dynamical systems on the first orthant have very simple and stable dynamics.

This is a big claim and it's not easy: it took more than four decades for mathematicians to prove this conjecture in full generality. In this section, however, we'll focus on the zero-deficiency CRN's. The proofs are accredited to Craciun [2]; in his paper he gives a complete proof of the global attractor conjecture (for all complex-balanced mass-action systems) by using toric differential inclusions.

3.1 Introduction to Toric Differential Inclusions

Recall that the dynamics of a CRN with mass-action kinetics can be represented as (1.1):

$$\frac{dc}{dt} = \sum_{y \rightarrow y' \in \mathcal{R}} k_{y \rightarrow y'} (y - y') c^y, \quad (3.1)$$

where c^y denotes the product $\prod_{i=1}^s c_i^{y_i}$. A slightly more complicated version is:

$$\frac{dc}{dt} = \sum_{y \rightarrow y' \in \mathcal{R}} k_{y \rightarrow y'}(t) (y - y') c^y. \quad (3.2)$$

That is, the rate constant in (3.1) is now a non-negative scalar function of t .

It turns out that, even though the systems we're interested in are given by (3.1), some properties of (3.2) are necessary. The main object used in this section is the systems of the form (3.2), such that the corresponding reaction diagram G is weakly reversible, and the function $k_{y \rightarrow y'}(t)$ is bounded away from zero and infinity. We call these systems *k-variable toric dynamical systems*.

In addition, we shall now call a "complex-balanced" system a *toric dynamical system*. This is just an alternate name introduced recently to emphasize the algebraic property of those systems. By Theorem 2.1, any toric dynamical system is weakly reversible.

We shall define a structure with rich geometric properties called *toric differential inclusions*. We begin with some definitions of geometric terms.

3.1.1 Definitions and Notation

Definition. A *cone* is a subset C of a vector space V such that for all $x \in C$, $\alpha \in \mathbb{R}$ and $\alpha > 0$, $\alpha x \in C$.

Definition. A *convex cone* is a cone C such that for any $x, y \in C$, and positive scalar α, β , $\alpha x + \beta y \in C$.

Definition. A *polar cone* of a cone $C \in \mathbb{R}^n$ is the cone

$$C^\circ = \{y \in \mathbb{R}^n : \langle x, y \rangle \leq 0, \forall x \in C\}.$$

Definition. A *dual cone* C^* of a cone $C \in \mathbb{R}^n$ is the negative of its polar cone: $C^* = -C^\circ$.

Definition. A *polyhedral cone* C in \mathbb{R}^n is given by a matrix A such that

$$C = \{x \in \mathbb{R}^n : Ax \geq 0\}.$$

Definition. A *face* τ of a polyhedral cone C is the set

$$\tau = \{x \in C : \langle x, u \rangle = 0\}, \quad \text{for some } u \in C^*.$$

Definition. A *polyhedral fan* in \mathbb{R}^n is a finite set \mathcal{F} of polyhedral cones such that:

1. any face of a cone in \mathcal{F} is also in \mathcal{F} ;
2. the intersection of two cones in \mathcal{F} is a face of both cones.

3.1.2 Toric Differential Inclusions

We first define the class of *polar differential inclusions* in the entire \mathbb{R}^n .

If a CRN is *reversible*, then we can group the reactions $y \rightarrow y'$ and $y' \rightarrow y$ such that

$$\frac{dc}{dt} = \sum_{y \rightleftharpoons y' \in \mathcal{R}} \left(k_{y \rightarrow y'}(t)c^y - k_{y' \rightarrow y}(t)c^{y'} \right) (y' - y). \quad (3.3)$$

Note that the solutions of (3.3) are also the solutions of the *differential inclusions* on \mathbb{R}_+^n ($0 < \epsilon < 1$):

$$\frac{dc}{dt} \in F(c), \quad \text{where } F(c) = \left\{ \sum_{y \rightleftharpoons y' \in \mathcal{R}} \left(k_{y \rightarrow y'}c^y - k_{y' \rightarrow y}c^{y'} \right) (y' - y) : \epsilon \leq k_{y \rightarrow y'}, k_{y' \rightarrow y} \leq \frac{1}{\epsilon} \right\}. \quad (3.4)$$

Now we can partition \mathbb{R}_+^n into three regions:

1. $\epsilon c^y \geq \frac{1}{\epsilon} c^{y'}$, thus $k_{y \rightarrow y'}(t)c^y - k_{y' \rightarrow y}(t)c^{y'} \geq 0$.
2. $\frac{1}{\epsilon} c^y \leq \epsilon c^{y'}$, thus $k_{y \rightarrow y'}(t)c^y - k_{y' \rightarrow y}(t)c^{y'} \leq 0$.
3. uncertainty region, where neither of the inequalities in 1 and 2 are satisfied.

In either case 1 or case 2, the state c of the system is always going *towards* the uncertainty region and the hypersurface $c^y = c^{y'}$. This can be seen more clearly by applying a logarithmic transformation $x = \log c$. Then the hypersurface $c^y = c^{y'}$ becomes a hyper-plane $(y' - y) \cdot x = 0$. Then the distance between any point x and the hyper-plane is given by

$$d_x = \frac{|(y' - y)x|}{\|y' - y\|}.$$

Recognize that for case 1 we have

$$\log(\epsilon c^y) \geq \log\left(\frac{1}{\epsilon} c^{y'}\right) \Rightarrow \log \epsilon + yx \geq y'x - \log \epsilon.$$

Since $0 < \epsilon < 1$, we have that $\log \epsilon < 0$. Thus,

$$x \geq \frac{2|\log \epsilon|}{|y - y'|}.$$

The same inequality applies for case 2. Therefore, the uncertainty region is now the set of x such that

$$d_x = \frac{|(y' - y)x|}{\|y' - y\|} < \frac{2|\log \epsilon|}{\|y' - y\|} = \delta.$$

In addition, observe that the direction of changing is given by the vector $y' - y$, which is the normal vector of the hyper-plane.

In conclusion, if the CRN consists of single reversible reactions $y \rightleftharpoons y'$, then the dynamics of the system at c is the following: c moves along a line with direction $y' - y$; and we're able to specify the direction by mapping c to $x = \log c$ and checking the distance between x and $(y' - y) \cdot x = 0$. If we can specify the direction, then it's always *towards* the hyper-plane and orthogonal to it.

For CRN's with *several* reversible reactions, we simply treat each reaction separately.

Thus, a reversible k -variable toric dynamical system can be embedded into hyperplane-generated toric differential inclusions defined as following:

Let \mathcal{H} be a finite set of hyperplanes in \mathbb{R}^n and let $\delta > 0$ be some constant. For each $c \in \mathbb{R}_+^n$ we define $F_{\mathcal{H},\delta}(\log c)$ to be the convex cone generated by vectors orthogonal to the hyperplanes of \mathcal{H} , in the direction that towards each hyperplane if the distance between x and the hyperplane is larger than or equal to δ . If the distance is smaller than δ , we shall took the opposite direction.

That is, solutions of any reversible k -variable toric dynamical systems are also solutions of the toric differential inclusions given by

$$\frac{dc}{dt} \in F_{\mathcal{H},\delta}(\log c), \quad (3.5)$$

where $F_{\mathcal{H},\delta}(\log c)$ is the convex cone generated by the union of polar cones C° for all $C \in \mathcal{F}(\mathcal{H})$ ⁸ such that $d(\log c, C) < \delta$.

Theorem 3.1. *Any k -variable toric dynamical system (which implies it's weakly reversible) can be embedded into a (hyper-plane generated) toric differential inclusion.*

Remark. *The general idea of the proof is to partition the graph of the toric dynamical system (i.e. the reaction diagram of CRN) into several single oriented cycles. The details are omitted here and can be found in [2] Section 3.*

3.2 Zero-separating Surfaces

A *zero separating surface* is a hypersurface Z such that $\mathbb{R}_+^n \setminus Z = Z^0 \cup Z^1$, where Z^0, Z^1 are open connected sets such that $Z^0 \subset N_0$ where N_0 is a small neighborhood of the origin, and $0 \notin \overline{Z^1}$.

Theorem 3.2. *For any hyper-plane generated toric differential inclusions \mathcal{T} on \mathbb{R}_+^n and a small enough neighborhood of the origin N_0 , there exists a zero-separating surface $Z_{\mathcal{T},N_0}$. The resulting sets $Z_{\mathcal{T},N_0}^0$ and $Z_{\mathcal{T},N_0}^1$ are open and connected, and $Z_{\mathcal{T},N_0}^1$ is an invariant region of \mathcal{T} .*

Remark. *This implies that any solution of \mathcal{T} with initial conditions $c_0 \in \mathbb{R}_+^n$ is contained in the invariant region $Z_{\mathcal{T}}^1$ as described above. In particular, the solution cannot be the origin.*

For our purposes, we only need the fact that those zero-separating surfaces *do* exist. The details of constructing are not included, as they do not play a big role in the proof of the conjecture. See [2] for details.

3.3 Proof of the Global Attractor Conjecture

We'll only focus on the zero deficiency weakly reversible networks. Again, the more general conclusion that involves all complex-balanced mass-action systems can be found in [2].

⁸the polyhedral fan determined by the set of hyperplanes \mathcal{H}

Theorem 3.3 (The Global Attractor Conjecture (deficiency zero version)). *Complex-balanced mass-action systems with zero deficiency have a globally attracting point within each positive stoichiometric compatibility class.*

Proof. Consider a zero-deficiency complex-balanced mass-action CRN. Let $T_n \in \mathbb{R}_+^n$ denote the toric dynamical system given by the CRN, i.e., a dynamical system of the form (3.1). By the deficiency zero theorem, T_n has a unique positive equilibrium within each positive stoichiometry compatibility class and the equilibrium is *locally asymptotically stable*. We'll show that this point is in fact *globally asymptotically stable*.

Recall that in the proof of Theorem 2.7, there exists a Lyapunov function $V(c)$ within any positive stoichiometry compatibility class. In addition, $V(c) > 0$ for all $c \neq c^*$. That is, there exists some $\epsilon_0 > 0$ such that

$$\{x \in \mathbb{R}_+^n : d(x, 0) < \epsilon_0\} = \emptyset.$$

Lemma. *The trajectory $T(c_0)$ of the concentration with initial condition c_0 is bounded by some $1/\epsilon_0$. See [4] for the proof. That is, we can find an invariant region \mathcal{R}_n^0 for T_n such that*

$$\mathcal{R}_n^0 = \{x \in \mathbb{R}_+^n : \epsilon_0 \leq d(x, 0) \leq \frac{1}{\epsilon_0}\}.$$

In particular, fix some $0 < \epsilon < 1$, the set of hypercubes $H_\epsilon = \{a^n\}$, $a \in [\epsilon, \frac{1}{\epsilon}]$ is contained inside of \mathcal{R}_n^0 .

Then, we proceed as [4] to build an invariant region $\mathcal{R}_n^1 \subset \mathcal{R}_n^0$ that also contains H_ϵ and does not have any points at distance less than $\epsilon_1 > 0$ from the *coordinate axes* of \mathbb{R}_+^n . This is possible because T_n restricted to \mathcal{R}_n^0 can be treated as $(n - 1)$ -dimensional k -variable toric dynamical system in the neighborhood of each coordinate axes. We proceed inductively to build an invariant region \mathcal{R}_n^k that contains H_ϵ that does not have any points at distance less than $\epsilon_k > 0$ of the coordinate k -spaces of \mathbb{R}_+^n .

Repeat for $n - 1$ times and we obtain an invariant region \mathcal{R}_n^{n-1} . It contains H_ϵ and no points at distance less than $\epsilon_{n-1} > 0$ from the *boundary* of \mathbb{R}_+^n .

Therefore, for each initial condition $c_0 \in \mathbb{R}_+^n$, we construct the invariant region \mathcal{R}_n^{n-1} above. It has the property $c_0 \in \mathcal{R}_n^{n-1}$. Then with the power of LaSalle's invariance principle, the equilibrium is indeed *globally asymptotically stable*. \square

4 Conclusion

In this paper we presented the deficiency zero theorem and the global attractor conjecture, two results which are of central importance in the Chemical Reaction Network Theory. The theory is aimed for practical use at birth, and it now plays a big role in the field of systems biology [3].

There are still open questions remaining. The current studies are mainly focused on the deterministic mass-action kinetics systems. Those are classical systems studied in chemistry, but certainly not the *only* systems. What about the stochastic models and systems with other kinetics? Some partial results are obtained, but more are waiting for exploration.

References

- [1] D. F. Anderson. *The Deficiency Zero Theorem, Global Stability, and Stationary Distributions*.
<https://www.math.wisc.edu/~anderson/RecentTalks/2008/MBI2008.pdf>
- [2] G. Craciun. *Toric Differential Inclusions and a Proof of the Global Attractor Conjecture*. 2016, arXiv.
- [3] G. Craciun, A. Dickenstein, A. Shiu, B. Sturmfels. *Toric Dynamical Systems*. *J. Symb. Comp.* 44:11, 1551-1565, 2009.
- [4] G. Craciun, F. Nazarov, C. Pantea. *Persistence and permanence of mass-action and power-law dynamical systems*. *SIAM J. Appl. Math.* 73:1, 305-329, 2013.
- [5] P. de Leenheer. *The Zero Deficiency Theorem*
<http://sites.science.oregonstate.edu/~deleenhp/teaching/fall09/MAP6487/notes-zero-def.pdf>
- [6] M. A. Feinberg. *Lectures on Chemical Reaction Networks*. University of Rochester, 1979.