Toric Dynamical Systems

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Abstract

Toric dynamical systems are known as complex balancing mass action systems in the mathematical chemistry literature, where many of their remarkable properties have been established. They include as special cases all deficiency zero systems and all detailed balancing systems. One feature is that the steady state locus of a toric dynamical system is a toric variety, which has a unique point within each invariant polyhedron. We develop the basic theory of toric dynamical systems in the context of computational algebraic geometry and show that the associated moduli space is also a toric variety. It is conjectured that the complex balancing state is a global attractor. We prove this for detailed balancing systems whose invariant polyhedron is two-dimensional and bounded.

This paper is dedicated to the memory of Karin Gatermann (1961–2005).

Key words: chemical reaction network, toric ideal, complex balancing, detailed balancing, deficiency zero, trajectory, Birch's Theorem, Matrix-Tree Theorem, moduli space, polyhedron

1. Introduction

Toric dynamical systems describe mass-action kinetics with complex balancing states. These systems have been studied extensively in mathematical chemistry, starting with the work of Horn and Jackson (1972), Feinberg (1972) and Horn (1972, 1973), and continuing with the deficiency theory in (Feinberg, 1979, 1987, 1989, 1995). Mass-action kinetics has a wide range of applications in the physical sciences, and now it is beginning to play a role in systems biology (Craciun, Tang and Feinberg, 2006; Gnacadja *et al.*, 2007; Gunawardena, 2003; Sontag, 2001). Important special cases of these dynamical systems include recombination equations in population genetics (Akin, 1979) and quadratic dynamical systems in computer science (Rabinovich, Sinclair and Wigderson, 1992).

Karin Gatermann introduced the connection between mass-action kinetics and computational algebra. Our work drew inspiration both from her publications (Gatermann, 2001; Gatermann and Huber, 2002; Gatermann and Wolfrum, 2005) and from her unpublished research notes on toric dynamical systems. We wholeheartedly agree with her view that *"the advantages of toric varieties are well-known"* (Gatermann, 2001, page 5).

We now review the basic set-up. A *chemical reaction network* is a finite directed graph whose vertices are labeled by monomials and whose edges are labeled by parameters. The digraph is denoted $G = (V, E)$, with vertex set $V = \{1, 2, \ldots, n\}$ and edge set $E \subseteq \{(i, j) \in V \times V : i \neq j\}$. The node i of G represents the ith chemical complex and is labeled with the monomial

$$c^{y_i} \quad = \quad c_1^{y_{i1}} c_2^{y_{i2}} \cdots c_s^{y_{is}}.$$

Here $Y = (y_{ij})$ is an $n \times s$-matrix of non-negative integers. The unknowns $c_1, c_2, \ldots, c_s$ represent the concentrations of the s species in the network, and we regard them as functions $c_i(t)$ of time t. The monomial labels are the entries in the row vector

$$\Psi(c) \quad = \quad \bigl(c^{y_1}, c^{y_2}, \ldots, c^{y_n}\bigr).$$

Each directed edge $(i, j) \in E$ is labeled by a positive parameter κ_{ij} which represents the rate constant in the reaction from the i-th chemical complex to the j-th chemical complex. Note that if there is an edge from i to j and an edge from j to i then we have two unknowns κ_{ij} and κ_{ji}. Let A_κ denote the negative of the *Laplacian* of the digraph G. Hence A_κ is the $n \times n$-matrix whose off-diagonal entries are the κ_{ij} and whose row sums are zero. Mass-action kinetics specified by the digraph G is the dynamical system

$$\frac{dc}{dt} \quad = \quad \Psi(c) \cdot A_\kappa \cdot Y. \tag{1}$$

A *toric dynamical system* is a dynamical system (1) for which the algebraic equations $\Psi(c) \cdot A_\kappa = 0$ admit a strictly positive solution $c^* \in \mathbb{R}^s_{>0}$. Such a solution c^* is a *steady state* of the system, i.e., the s coordinates of $\Psi(c^*) \cdot A_\kappa \cdot Y$ vanish. The requirement that all n coordinates of $\Psi(c^*) \cdot A_\kappa$ be zero is stronger. The first to study toric dynamical

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systems, Horn and Jackson (1972), called these systems *complex balancing mass action systems* and called c^* a *complex balancing steady state*. A system (1) being complex balancing (i.e., toric) depends on both the digraph G and the rate constants κ_{ij}.

Example 1. Let $s = 2$, $n = 3$ and let G be the complete bidirected graph on three nodes labeled by c_1^2, c_1c_2 and c_2^2. Here the mass-action kinetics system (1) equals

$$\frac{d}{dt}(c_1, c_2) \;=\; \begin{pmatrix} c_1^2 & c_1c_2 & c_2^2 \end{pmatrix} \cdot \begin{pmatrix} -\kappa_{12}-\kappa_{13} & \kappa_{12} & \kappa_{13} \\ \kappa_{21} & -\kappa_{21}-\kappa_{23} & \kappa_{23} \\ \kappa_{31} & \kappa_{32} & -\kappa_{31}-\kappa_{32} \end{pmatrix} \cdot \begin{pmatrix} 2 & 0 \\ 1 & 1 \\ 0 & 2 \end{pmatrix} \quad (2)$$

This is a toric dynamical system if and only if the following algebraic identity holds:

$$(\kappa_{21}\kappa_{31}+\kappa_{32}\kappa_{21}+\kappa_{23}\kappa_{31})(\kappa_{13}\kappa_{23}+\kappa_{21}\kappa_{13}+\kappa_{12}\kappa_{23}) \;=\; (\kappa_{12}\kappa_{32}+\kappa_{13}\kappa_{32}+\kappa_{31}\kappa_{12})^2. \quad (3)$$

The equation (3) appears in (Horn, 1973, Equation (3.12)) where it is derived from the necessary and sufficient conditions for complex balancing in mass-action kinetics given by Horn (1972). Our results in Section 2 provide a refinement of these conditions.

Let us now replace G by the digraph with four edges $(1,3), (2,1), (2,3), (3,1)$. This corresponds to setting $\kappa_{12} = \kappa_{32} = 0$ in (3). We can check that, for this new G, the system (1) is not toric for any positive rate constants. Note that G is not strongly connected. □

Among all chemical reaction networks, toric dynamical systems have very remarkable properties. Some of these properties are explained in (Feinberg, 1979), starting with Proposition 5.3; see also (Gunawardena, 2003, Theorem 6.4). We shall review them in detail in Sections 2 and 3. From our point of view, the foremost among these remarkable properties is that the set Z of all steady states is a toric variety (Gatermann, 2001, §3). Each trajectory of (1) is confined to a certain *invariant polyhedron*, known to chemists as the *stoichiometric compatibility class*, which intersects the toric variety Z in precisely one point c^*. In order to highlight the parallels between toric dynamical systems and *toric models* in algebraic statistics (Pachter and Sturmfels, 2005, §1.2), we shall refer to the steady state c^* as the *Birch point*; see (Sturmfels, 1996, Theorem 8.20). In Example 1, the steady state variety Z is a line through the origin, and the Birch point equals

$$c^* \;=\; \text{const} \cdot \bigl(\kappa_{12}\kappa_{32} + \kappa_{13}\kappa_{32} + \kappa_{31}\kappa_{12},\, \kappa_{13}\kappa_{23} + \kappa_{21}\kappa_{13} + \kappa_{12}\kappa_{23}\bigr).$$

Here the constant is determined because $c_1 + c_2$ is conserved along trajectories of (2).

This article is organized as follows. In Section 2 we develop the basic theory of toric dynamical systems within the context of computational algebraic geometry. For each directed graph G we introduce the moduli space of toric dynamical systems on G. This space parametrizes all rate constants κ for which (1) is toric. In Example 1 this space is the hypersurface (3). Theorem 9 states that this moduli space is itself a toric variety in a suitable system of coordinates. These coordinates are the maximal non-zero minors of the Laplacian of G, and their explicit form as positive polynomials in the κ_{ij} is given by the *Matrix-Tree Theorem* (Stanley, 1999, §5.6). Our results in Section 2 furnish a two-fold justification for attaching the adjective "toric" to chemical reaction networks with complex balancing, namely, both the steady state variety and the moduli space are toric. In addition, the subvariety of reaction networks with detailed balancing is toric.

In Section 3 we introduce the *Global Attractor Conjecture* which states that the Birch point is a global attractor for any toric dynamical system. More precisely, we conjecture that all trajectories beginning at strictly positive vectors c^0 will converge to the Birch point c^* in the invariant polyhedron of c^0. The conjecture is currently open, even for *deficiency zero systems* (cf. Theorem 9). De Leenheer, Angeli and Sontag (2007) found a proof for a class of "monotone" deficiency zero networks where the monomials c^{y_i} involve distinct unknowns. We prove the conjecture in Section 5 for toric dynamical systems with detailed balancing that evolve in a bounded polygon in s-dimensional space. The algebraic theory of detailed balancing systems is developed in Section 4.

2. Ideals, Varieties and Chemistry

This section concerns the connection between chemical reaction network theory and toric geometry. We use the language of ideals and varieties as in (Cox, Little and O'Shea, 2007). Our reference on toric geometry and its relations with computational algebra is (Sturmfels, 1996). With regard to the dynamical system (1), we use the notation from (Feinberg, 1979, §5) and (Gunawardena, 2003, §3) which has the virtue of separating the roles played by the concentrations c_i, the monomials c^{y_i}, and the rate constants κ_{ij}.

To study the dynamical system (1) algebraically, we work in the polynomial ring

$$\mathbb{Q}[c,\kappa] \;=\; \mathbb{Q}\big[\{c_1,c_2,\ldots,c_s\} \cup \{\kappa_{ij} : (i,j) \in E\}\big],$$

and we introduce various ideals in this polynomial ring. First, there is the *steady state ideal* $\langle \Psi(c) \cdot A_\kappa \cdot Y \rangle$ which is generated by the s entries of the row vector on the right hand side of (1). Second, we consider the ideal $\langle \Psi(c) \cdot A_\kappa \rangle$ which is generated by the n entries of the row vector $\Psi(c) \cdot A_\kappa$. The generators of both ideals are linear in the κ_{ij} but they are usually non-linear in the c_i. Next, we define the *complex balancing ideal* of G to be the following ideal quotient whose generators are usually non-linear in the κ_{ij}:

$$C_G \quad := \quad \big(\langle \Psi(c) \cdot A_\kappa \rangle \,:\, (c_1 c_2 \cdots c_s)^\infty \big).$$

We have thus introduced three ideals in $\mathbb{Q}[c,\kappa]$. They are related by the inclusions

$$\langle \Psi(c) \cdot A_\kappa \cdot Y \rangle \;\subseteq\; \langle \Psi(c) \cdot A_\kappa \rangle \;\subseteq\; C_G.$$

If I is any polynomial ideal then we write $V(I)$ for its complex variety. Likewise, we define the positive variety $V_{>0}(I)$ and the non-negative variety $V_{\geq 0}(I)$. They consist of all points in $V(I)$ whose coordinates are real and positive or, respectively, non-negative. Our algebraic approach to chemical reaction network theory focuses on the study of these varieties. The inclusions of ideals above imply the following inclusions of varieties:

$$V(C_G) \;\subseteq\; V\big(\langle \Psi(c) \cdot A_\kappa \rangle\big) \;\subseteq\; V\big(\langle \Psi(c) \cdot A_\kappa \cdot Y \rangle\big). \tag{4}$$

The definition of C_G by means of saturation implies that the left hand inclusion becomes equality when we restrict to the points with all coordinates non-zero. In particular,

$$V_{>0}(C_G) \;=\; V_{>0}\big(\langle \Psi(c) \cdot A_\kappa \rangle\big). \tag{5}$$

Recall from (Sturmfels, 1996) that a *toric ideal* is a prime ideal which is generated by binomials. We soon will replace C_G by a subideal T_G which is toric. This is possible by Proposition 5.3 (ii,iv) in (Feinberg, 1979) or Theorem 6.4 (3) in (Gunawardena, 2003), which essentially state that $V_{>0}(C_G)$ is a positive toric variety. But let us first examine the case when C_G is a toric ideal already.

Example 2. Suppose that each chemical complex appears in only one reaction, and each reaction is bi-directional. Hence $n = 2m$ is even and, after relabeling, we have $E = \{(1,2),(2,1),(3,4),(4,3),\ldots,(n-1,n),(n,n-1)\}$. We start with the binomial ideal

$$\langle \Psi(c) \cdot A_\kappa \rangle \;=\; \bigl\langle \kappa_{12} c^{y_1} - \kappa_{21} c^{y_2},\, \kappa_{34} c^{y_3} - \kappa_{43} c^{y_4},\, \ldots\,,\, \kappa_{n-1,n} c^{y_{n-1}} - \kappa_{n,n-1} c^{y_n} \bigr\rangle.$$

The complex balancing ideal C_G is a saturation of $\langle \Psi(c) \cdot A_\kappa \rangle$, and it coincides with the toric ideal of the extended Cayley matrix in the proof of Theorem 7. There are many programs for computing toric ideals. For instance, the methods in (Sturmfels, 1996, §12.A) are available in `maple` under the command `ToricIdealBasis`. Explicitly, the complex balancing ideal C_G is generated by all binomials $\kappa^{u+} c^{v+} - \kappa^{u-} c^{v-}$ where

$$\sum_{i=1}^{m} u_{2i-1,2i}(y_{2i-1} - y_{2i}) \;=\; v \quad \text{and} \quad u_{2i-1,2i} + u_{2i,2i-1} = 0 \text{ for } i = 1,2,\ldots,m. \qquad (6)$$

Eliminating $c_1,\ldots,c_s$ from C_G, we obtain the ideal of all binomials $\kappa^{u+} - \kappa^{u-}$ where $u \in \mathbb{N}^E$ satisfies (6) with $v = 0$. This is the moduli ideal M_G to be featured in Theorems 7 and 9 below. It is a prime binomial ideal of Lawrence type (Sturmfels, 1996, §7). $\square$

Let us next assume that $G = (V,E)$ is an arbitrary digraph with n nodes which is *strongly connected*. This means that, for any two nodes i and j, there exists a directed path from i to j. In this case the matrix A_κ has rank $n-1$, and all its minors of size $(n-1)\times(n-1)$ are non-zero. The next result gives a formula for these comaximal minors.

Consider any directed subgraph T of G whose underlying graph is a spanning tree. This means that T has $n-1$ edges and contains no cycle. We write κ^T for the product of all edge labels of the edges in T. This is a squarefree monomial in $\mathbb{Q}[\kappa]$. Let i be one of the nodes of G. The directed tree T is called an *i-tree* if the node i is its unique sink, i.e., all edges are directed towards node i. We introduce the following polynomial of degree $n-1$:

$$K_i \;=\; \sum_{T \text{ an } i\text{-tree}} \kappa^T. \qquad (7)$$

The following result is a restatement of the *Matrix-Tree Theorem* (Stanley, 1999, §5.6).

Proposition 3. *Consider a submatrix of A_κ obtained by deleting the i^{th} row and any one of the columns. The signed determinant of this $(n-1)\times(n-1)$-matrix equals $(-1)^{n-1} K_i$.*

This minor is independent of the choice of columns because the row sums of A_κ are zero. Combining Proposition 3 with a little linear algebra leads to the following corollary:

Corollary 4. *The complex balancing ideal C_G contains the polynomials $K_i c^{y_j} - K_j c^{y_i}$.*

We now form the ideal generated by these $\binom{n}{2}$ polynomials and we again saturate with respect to $c_1 c_2 \cdots c_s$. The resulting ideal T_G will be called the *toric balancing ideal*:

$$T_G \quad := \quad \bigl(\langle K_i c^{y_j} - K_j c^{y_i} \,:\, 1 \leq i < j \leq n \rangle \,:\, (c_1 c_2 \cdots c_s)^\infty \bigr).$$

It is thus natural to consider T_G as an ideal in the polynomial subring

$$\mathbb{Q}[c,K] \;=\; \mathbb{Q}[c_1,\ldots,c_s,K_1,\ldots,K_n] \quad \subset \quad \mathbb{Q}[c,\kappa].$$

The following lemma states that this subring is a polynomial ring.

Lemma 5. *The polynomials $K_1, \ldots, K_n \in \mathbb{Q}[\kappa]$ are algebraically independent over $\mathbb{Q}$.*

Proof. Let $K_i' \in \mathbb{Q}[\kappa_1, \kappa_2, \ldots, \kappa_n]$ denote the polynomial obtained from K_i by substituting the new unknown κ_i for all κ_{ij}. We need only verify that the K_i' are algebraically independent, because an algebraic relation among the K_i would be satisfied by the K_i' as well. Our polynomials are

$$K_i' \quad = \quad (\text{number of } i\text{-trees in } G) \cdot \prod_{t \neq i} \kappa_t .$$

The n squarefree monomials $\prod_{t \neq i} \kappa_t$ (for $i = 1 \ldots n$) are algebraically independent because an algebraic dependence among these monomials would specify a dependence among $1/\kappa_1, 1/\kappa_2, \ldots, 1/\kappa_n$. Hence, $K_1', K_2', \ldots, K_n'$ are algebraically independent. $\square$

We now discuss the toric balancing ideal T_G.

Proposition 6. *The toric balancing ideal T_G is a toric ideal in $\mathbb{Q}[c, K]$. Moreover, the ideal T_G is generated by the binomials $K^{u_+} \cdot c^{(uY)_-} - K^{u_-} \cdot c^{(uY)_+}$ where u is any row vector in $\mathbb{Z}^n$ whose coordinate sum $u_1 + u_2 + \cdots + u_n$ is equal to zero.*

Proof. Let Δ denote the edge-node incidence matrix of the complete directed graph on n nodes. Thus Δ is the $\binom{n}{2} \times n$-matrix whose rows are $e_i - e_j$ for $1 \leq i < j \leq n$. We also consider the $n \times (n+s)$-matrix $\begin{pmatrix} -Y & \mathbf{I}_n \end{pmatrix}$. The binomials $K_i c^{y_j} - K_j c^{y_i}$ which define the ideal T_G correspond to the rows of the $\binom{n}{2} \times (n+s)$-matrix $\Delta \cdot \begin{pmatrix} -Y & \mathbf{I}_n \end{pmatrix}$, and the binomial $K^{u_+} \cdot c^{(uY)_-} - K^{u_-} \cdot c^{(uY)_+}$ corresponds to the row vector $U \cdot \Delta \cdot \begin{pmatrix} -Y & \mathbf{I}_n \end{pmatrix}$, where U is any row vector of length $\binom{n}{2}$ such that $u = U \cdot \Delta$. The binomial $K^{u_+} \cdot c^{(uY)_-} - K^{u_-} \cdot c^{(uY)_+}$ is a $\mathbb{Q}[c_1^{\pm 1}, \ldots, c_s^{\pm 1}, K_1, \ldots, K_n]$-linear combination of the binomials $K_i c^{y_j} - K_j c^{y_i}$. This shows that T_G is the *lattice ideal* in $\mathbb{Q}[c, K]$ associated with the lattice spanned by the rows of $\Delta \cdot \begin{pmatrix} -Y & \mathbf{I}_n \end{pmatrix}$, i.e., there are no monomial zero-divisors modulo T_G. To see that T_G is actually a toric ideal, i.e., T_G is prime, it suffices to note that $\mathbb{Z}^{n+s}$ modulo the lattice spanned by the rows of $\Delta \cdot \begin{pmatrix} -Y & \mathbf{I}_n \end{pmatrix}$ is free abelian of rank $s+1$. Indeed, the latter matrix has rank $n-1$, and its $(n-1) \times (n-1)$-minors span the unit ideal in the ring of integers $\mathbb{Z}$, because each $(n-1) \times (n-1)$-minor of Δ is either $+1$ or -1. $\square$

The variety of T_G is a toric variety in $\operatorname{Spec} \mathbb{Q}[c, K]$, but we continue to regard it as a subvariety of $\mathbb{C}^s \times \mathbb{C}^E$ (or of $\operatorname{Spec} \mathbb{Q}[c, \kappa]$). In this interpretation we have

$$V_{>0}(T_G) \quad = \quad V_{>0}(C_G) \quad = \quad V_{>0}\big(\langle \Psi(c) \cdot A_\kappa \rangle\big). \tag{8}$$

Thus T_G still correctly describes the steady state locus of the toric dynamical system. The equation (8) holds because the matrix A_κ has rank $n-1$ over the rational function field $\mathbb{Q}(\kappa)$, and the vector $(K_1, K_2, \ldots, K_n)$ spans its kernel under left multiplication.

Finally, the following elimination ideal is called the *moduli ideal* of the digraph G:

$$M_G \quad = \quad T_G \,\cap\, \mathbb{Q}[\kappa]. \tag{9}$$

Here $\mathbb{Q}[\kappa]$ is the polynomial ring in only the edge unknowns κ_{ij}. The generators of M_G are obtained from the generators of C_G by eliminating the unknown concentrations c_i. For instance, if G is the complete bidirected graph on c_1^2, $c_1 c_2$ and c_2^2 as in Example 1

then the moduli ideal M_G is the principal ideal generated by $K_1K_3 - K_2^2$. This coincides with condition (3) because $K_1 = \kappa_{21}\kappa_{31} + \kappa_{32}\kappa_{21} + \kappa_{23}\kappa_{31}$, and similarly for K_2, K_3.

Suppose now that G is an arbitrary directed graph, and let l be the number of connected components of G. If one of the components G_i fails to be strongly connected, then $V_{>0}(C_{G_i})$ is empty and hence $V_{>0}(C_G)$ is empty, by (Feinberg, 1979, Remark 5.2). In that case we define T_G and M_G to be the ideal generated by 1. If each connected component G_i of G is strongly connected then we define the toric steady state ideal as

$$T_G \quad := \quad \big((\, T_{G_1} + T_{G_2} + \cdots + T_{G_l}) : (c_1 c_2 \cdots c_s)^\infty \big).$$

The moduli ideal M_G is defined as before in (9). The equality in (8) still holds and this positive variety is in fact non-empty. Here is the first main result of this section:

Theorem 7. *The equations (1) specify a toric dynamical system if and only if the positive vector of rate constants κ_{ij} lies in the toric variety $V(M_G)$. In this case, the set of steady states of (1) with all $c_i > 0$ equals the set of positive points on the toric variety $V(T_G)$.*

Proof. The positive variety $V_{>0}(T_G)$ consists of all pairs (c, κ) where κ is a strictly positive vector of rate constants and c is a strictly positive solution of the complex balancing equations $\Psi(c) \cdot A_\kappa = 0$. The elimination in (9) corresponds to the map of toric varieties $V(T_G) \to V(M_G)$ given by $(c, \kappa) \mapsto \kappa$. This map is a dominant morphism (by definition of M_G), so its image is Zariski dense in $V(M_G)$. The restriction to real positive points, $V_{>0}(T_G) \to V_{>0}(M_G)$, is a homomorphism of abelian groups $(\mathbb{R}_{>0})^*$ whose image is dense, so it is the monomial map specified by a matrix with maximal row rank. It follows that this restriction is surjective, and this proves our first assertion. The second assertion follows from (Feinberg, 1979, Proposition 5.3). $\square$

We now justify calling $V(M_G)$ a toric variety by writing M_G explicitly as a toric ideal in $\mathbb{Q}[K]$. As before, G is a directed graph with n nodes labeled by monomials $c^{y_1}, \ldots, c^{y_n}$. We assume that each connected component $G_1, G_2, \ldots, G_l$ of G is strongly connected, for otherwise $M_G = \langle 1 \rangle$. Let Y_i denote the matrix with s rows whose columns are the vectors y_j where j runs over the nodes of the component G_i. We define the *Cayley matrix*

$$\mathrm{Cay}_G(Y) \quad = \quad \begin{pmatrix} Y_1 & Y_2 & \cdots & Y_l \\ \mathbf{1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{1} & \cdots & \mathbf{0} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & \mathbf{1} \end{pmatrix}.$$

This is an $(s+l) \times n$-matrix. Here $\mathbf{1}$ and $\mathbf{0}$ are appropriate row vectors with all entries 1 and 0 respectively. The term "Cayley matrix" comes from geometric combinatorics, and it refers to the Cayley trick in elimination theory (Huber, Rambau and Santos, 2000).

Let S denote the linear subspace of $\mathbb{R}^s$ which is spanned by the *reaction vectors* $y_j - y_i$ where $(i, j) \in E$. This space is known in chemistry as the *stoichiometric subspace*. We write $\sigma = \dim(S)$ for its dimension. The quantity $\delta := n - \sigma - l$ is known as the *deficiency* of the chemical reaction network G. For instance, $\delta = 3 - 1 - 1 = 1$ in Example 1.

Remark 8. The rank of the Cayley matrix $\mathrm{Cay}_G(Y)$ equals $\sigma+l$. Hence the deficiency δ of the reaction network coincides with the dimension of the kernel of the Cayley matrix.

The following theorem is the second main result in this section.

Theorem 9. *The moduli ideal M_G equals the toric ideal of the Cayley matrix $\mathrm{Cay}_G(Y)$, i.e., M_G is the ideal in $\mathbb{Q}[K]$ generated by all binomials $K^u - K^v$ where $u, v \in \mathbb{N}^n$ satisfy $\mathrm{Cay}_G(Y) \cdot (u-v) = 0$. The codimension of this toric ideal equals the deficiency δ.*

Proof. Let $\mathbf{Id}_s$ denote the $s \times s$ identity matrix and consider the extended Cayley matrix

$$\begin{pmatrix} -\mathbf{Id}_s & Y_1 & Y_2 & \cdots & Y_l \\ \mathbf{0} & \mathbf{1} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{1} & \cdots & \mathbf{0} \\ \mathbf{0} & \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{1} \end{pmatrix}.$$

The toric ideal of this matrix is precisely the toric balancing ideal T_G, where the unknowns $c_1, c_2, \ldots, c_s$ correspond to the first s columns. Deleting these s columns corresponds to forming the elimination ideal M_G as in (9). This shows that M_G is the toric ideal of the matrix $\mathrm{Cay}_G(Y)$. The dimension of the affine toric variety $V(M_G)$ in $\mathbb{C}^n$ is equal to $\sigma+l = \mathrm{rank}(\mathrm{Cay}_G(Y))$, and hence its codimension equals the deficiency $\delta = n-\sigma-l$. $\square$

We conclude that $V_{>0}(M_G)$ is a positive toric variety of codimension δ in $\mathbb{R}^n_{>0}$. The moment map of toric geometry establishes a natural bijection between $V_{>0}(M_G)$ and the interior of the *Cayley polytope*, which is the convex hull of the columns of $\mathrm{Cay}_G(Y)$.

In summary, given any chemical reaction network whose components are strongly connected, we have shown that the positive toric variety of the Cayley polytope equals the moduli space $V_{>0}(M_G)$ of toric dynamical systems on G. The deficiency δ is precisely the codimension of this moduli space. In particular, if the deficiency is zero then the Cayley polytope is a simplex and (1) is toric for all rate constants κ_{ij}. Moreover, the positive steady states of a toric dynamical system form a positive toric variety $V_{>0}(T_G)$.

3. The Global Attractor Conjecture and Some Biological Applications

We now consider a fixed toric dynamical system or, equivalently, a chemical reaction network (1) which admits a complex balancing state. The underlying directed graph $G = (V, E)$ has n nodes labeled by monomials c^{y_1}, c^{y_2}, ..., c^{y_n}, and we specify positive rate constants by fixing a point κ^0 in the moduli space $V_{>0}(M_G)$. We also fix a strictly positive vector $c^0 \in \mathbb{R}^s_{>0}$ which represents the initial concentrations of the s species. The equations (1) describe the evolution of these concentrations over time. We seek to understand the long-term behavior of the trajectory which starts at c^0, that is, $c(0) = c^0$.

Let $T_G(\kappa^0)$ denote the toric ideal in $\mathbb{R}[c]$ obtained from T_G by substituting the specific rate constants $\kappa^0_{ij} \in \mathbb{R}_{>0}$ for the unknowns κ_{ij}. Then $V_{>0}(T_G(\kappa^0))$ coincides with the set of all steady states of the toric dynamical system (1). The following result is well-known:

Proposition 10. [Existence and Uniqueness of the Birch Point] *The affine subspace $c^0 + S$ of $\mathbb{R}^s$ intersects the positive toric variety $V_{>0}(T_G(\kappa^0))$ in precisely one point c^*.*

For a proof and references in the chemistry literature see Horn and Jackson (1972); a different proof can be found in Feinberg (1979, Proposition 5.3) or Gunawardena (2003, Proposition 6.4). We remark that variants of Proposition 10 are ubiquitous across the mathematical sciences, and the result has been rediscovered many times. In statistics, this result is known as Birch's Theorem; see (Pachter and Sturmfels, 2005, Theorem 1.10). To stress the link with toric models in algebraic statistics we call c^* the *Birch point* of the toric dynamical system (1) with starting point c^0.

The right hand side of (1) is always a vector in the stoichiometric subspace $S = \mathbb{R}\{y_j - y_i : (i,j) \in E\}$. Hence the trajectory starting at c^0 stays in the affine subspace $c^0 + S$. In fact, concentrations remain non-negative, so the trajectory stays in $P := (c^0 + S) \cap \mathbb{R}^s_{\geq 0}$. We call P the *invariant polyhedron*. Chemists use the term *stoichiometric compatibility class* for P. The relative interior of P in $c^0 + S$ is denoted by $P^o := (c^0 + S) \cap \mathbb{R}^s_{>0}$.

Proposition 11. *The Birch point c^* is the unique point in the invariant polyhedron P for which the* transformed entropy function

$$E(c) \;=\; \sum_{i=1}^{s} \big(c_i \cdot \log(c_i) \;-\; c_i \cdot \log(c_i^*) \;-\; c_i \;+ c_i^* \big) \tag{10}$$

is a strict Lyapunov function *of the toric dynamical system (1). This means the following:*
(a) For all $c \in P$ we have $E(c) \geq 0$ and equality holds if and only if $c = c^*$,
(b) we have $dE(c)/dt \leq 0$ along any trajectory $c(t)$ in P, and
(c) equality in (b) holds at a point t^* of any trajectory $c(t)$ in P° if and only if $c(t^*) = c^*$.

This proposition was proved by Horn and Jackson (1972). A different proof can be found in (Feinberg, 1979); see especially Proposition 5.3 and its corollaries; see also (Gunawardena, 2003, Theorem 6.4) and the paragraph before it. We suggest comparing this with the proof of (Pachter and Sturmfels, 2005, Theorem 1.10).

Any trajectory of the toric dynamical system (1) which starts in the relatively open polyhedron $P^o = (c^0 + S) \cap \mathbb{R}^s_{>0}$ will stay in the closed polyhedron $P = (c^0 + S) \cap \mathbb{R}^s_{\geq 0}$; actually, it is not hard to show that P^o is an invariant set. The main conjecture below states that any such trajectory converges to the Birch point. This conjecture was first formulated by Horn (1974). A steady state x in P^o is called a *global attractor* if any trajectory that begins in P^o converges to x.

Global Attractor Conjecture. *For any toric dynamical system (1) and any starting point c^0, the Birch point c^* is a global attractor of the invariant set $P^o = (c^0 + S) \cap \mathbb{R}^s_{>0}$.*

An important subclass of toric dynamical systems consists of the chemical reaction networks of deficiency zero. If the deficiency $\delta = n - \sigma - l$ is zero then the moduli ideal M_G is the zero ideal, by Theorem 9, and (1) is toric for all choices of rate constants. As remarked in the Introduction, the Global Attractor Conjecture is open even for deficiency zero systems. Our last section is devoted to partial results on the conjecture. First, however, we discuss biological examples which illustrate the concepts developed so far.

Example 12. [Networks with trivial moduli] We expect that our toric approach will be useful for parametric analyses of chemical reaction networks in *systems biology*. Analyses of this kind include (Kuepfer, Sauer and Parrilo, 2007), (Gnacadja *et al.*, 2007) and (Sontag, 2001). Many of the explicit examples we found in the literature have trivial toric moduli in the sense that either M_G is the unit ideal or M_G is the zero ideal.

If $M_G = \langle 1 \rangle$ then (1) is **never** a toric dynamical system regardless of what values the κ_{ij} take. This happens when at least one component of G is not strongly connected. Examples include *Michaelis-Menten kinetics* and the *covalent modification cycle* in (Gunawardena, 2003, §5). If $M_G = \{0\}$ then the network has deficiency zero and (1) is **always** a toric dynamical system, regardless of what the κ_{ij} are. Examples include the cycle in (Kuepfer, Sauer and Parrilo, 2007, Equation (9)), the monotone networks in (De Leenheer, Angeli and Sontag, 2007), and the following network which is taken from (Gnacadja *et al.*, 2007).

The *ligand-receptor-antagonist-trap network* has $s = 8$ species and $n = 8$ complexes. This network G has four reversible reactions which we write in binomial notation:

$$\kappa_{15} \cdot c_5 c_6 \,-\, \kappa_{51} \cdot c_1,\ \kappa_{26} \cdot c_6 c_7 \,-\, \kappa_{62} \cdot c_2,\ \kappa_{37} \cdot c_7 c_8 \,-\, \kappa_{73} \cdot c_3,\ \kappa_{48} \cdot c_8 c_5 \,-\, \kappa_{84} \cdot c_4. \quad (11)$$

Here $l = 4$ and $\sigma = 4$, so $\delta = 0$. In the algebraic notation of Section 2, the toric ideal T_G equals the complex balancing ideal $\langle \Psi(c) \cdot A_\kappa \rangle$ and is generated by the four binomials in (11). Eliminating $c_1, c_2, \ldots, c_8$ as prescribed by (9) yields the zero ideal $M_G = \{0\}$. $\square$

Example 13. [DHFR catalysis] Here are some examples from systems biology which show a more complicated dynamical behavior. We consider the reaction network in (Craciun, Tang and Feinberg, 2006, Figure 5); this reaction network has several positive equilibria for certain values of the reaction rate parameters (see Craciun, Tang and Feinberg, 2006, Figure 7). This reaction network allows for inflow and outflow of some chemical species; in the language of deficiency theory, we say that one of the complexes of this reaction network is the zero complex (see Feinberg (1979)), i.e., one of the vectors y_i is zero. Note that the group A of reactions in this network has almost the same structure as mechanism 6 in (Craciun, Tang and Feinberg, 2006, Table 1), shown below:

$$\begin{aligned} &E + S1 \rightleftharpoons ES1,\ E + S2 \rightleftharpoons ES2,\ ES1 + S2 \rightleftharpoons ES1S2 \rightleftharpoons ES2 + S1, \\ &ES1S2 \rightarrow E + P,\ S1 \rightleftharpoons 0,\ S2 \rightleftharpoons 0,\ P \rightarrow 0. \end{aligned} \quad (12)$$

Like the more complicated DHFR catalysis network, the network (12) also has several positive equilibria for some values of the reaction rate parameters. It is easy to compute the deficiency of this simpler mechanism: the number of complexes is $n = 12$ (including the zero complex), the number of linkage classes is $l = 4$ (including the linkage class that contains the inflow and outflow reactions for the substrates $S1$, $S2$ and the product P), and the dimension of its stoichiometric subspace is $\sigma = 6$. Therefore the deficiency of the network (12) is $\delta = 12 - 4 - 6 = 2$. This network cannot be toric for any choice of the constant rates because it is not weakly reversible. If we make all reactions reversible in (12), then the complexes, the linkage classes, and the stoichiometric subspace do not change, so the deficiency of the reversible version of (12) is also 2.

Example 14. [Recombination on the 3-cube] In *population genetics* (Akin, 1979, 1982), the evolution of a population is modeled by a dynamical system whose right hand side is the sum of three terms, corresponding to *mutation*, *selection* and *recombination*. The contribution made by recombination alone is a quadratic dynamical system (Rabinovich, Sinclair and Wigderson, 1992) which can be written in the form (1). In our view, toric dynamical systems are particularly well-suited to model recombination. Here we consider a population of three-locus diploids, so the underlying *genotope* of the haploid gametes is the standard three-dimensional cube (Beerenwinkel, Pachter and Sturmfels, 2007, Example 3.9). The eight vertices of the cube are the genotypes. They now play the role of the species in chemistry:

$$s = 8 \qquad \begin{matrix} \text{genotypes} & [000] & [001] & [010] & [011] & [100] & [101] & [110] & [111] \\ \text{frequencies} & c_1 & c_2 & c_3 & c_4 & c_5 & c_6 & c_7 & c_8. \end{matrix}$$

The *recombination network* G has $n = 16$ nodes which correspond to the pairs of genotypes which are not adjacent on the cube. There are twelve bidirectional edges, representing interactions, and we label them using the notation of (Beerenwinkel, Pachter and Sturmfels, 2007, Example 3.9). Six of the interactions correspond to *conditional epistasis*:

$$\begin{matrix}
[000]+[110] \leftrightarrow [010]+[100] & \kappa_{1,2}\cdot c_1c_7 - \kappa_{2,1}\cdot c_3c_5 & K_1 = \kappa_{2,1} \text{ and } K_2 = \kappa_{1,2} \\
[001]+[111] \leftrightarrow [011]+[101] & \kappa_{3,4}\cdot c_2c_8 - \kappa_{4,3}\cdot c_4c_6 & K_3 = \kappa_{4,3} \text{ and } K_4 = \kappa_{3,4} \\
[000]+[101] \leftrightarrow [001]+[100] & \kappa_{5,6}\cdot c_1c_6 - \kappa_{6,5}\cdot c_2c_5 & K_5 = \kappa_{6,5} \text{ and } K_6 = \kappa_{5,6} \\
[010]+[111] \leftrightarrow [011]+[110] & \kappa_{7,8}\cdot c_3c_8 - \kappa_{8,7}\cdot c_4c_7 & K_7 = \kappa_{8,7} \text{ and } K_8 = \kappa_{7,8} \\
[000]+[011] \leftrightarrow [001]+[010] & \kappa_{9,10}\cdot c_1c_4 - \kappa_{10,9}\cdot c_2c_3 & K_9 = \kappa_{10,9} \text{ and } K_{10} = \kappa_{9,10} \\
[100]+[111] \leftrightarrow [101]+[110] & \kappa_{11,12}\cdot c_5c_8 - \kappa_{12,11}\cdot c_6c_7 & K_{11} = \kappa_{12,11} \text{ and } K_{12} = \kappa_{11,12}.
\end{matrix}$$

Secondly, we have *marginal epistasis*, giving rise to the six pairwise interactions among

$$\begin{matrix} \text{four complexes} & [000]+[111] & [001]+[110] & [010]+[101] & [100]+[011] \\ \text{four monomials} & K_{13}\cdot c_1c_8 & K_{14}\cdot c_2c_7 & K_{15}\cdot c_3c_6 & K_{16}\cdot c_4c_5. \end{matrix}$$

Here $K_{13}, K_{14}, K_{15}, K_{16}$ are cubic polynomials with 16 terms indexed by trees as in (7). By Proposition 3, they are the 3×3 minors of the Laplacian of the complete graph $\mathbf{K}_4$:

$$\begin{pmatrix}
\kappa_{13,14}+\kappa_{13,15}+\kappa_{13,16} & -\kappa_{13,14} & -\kappa_{13,15} & -\kappa_{13,16} \\
-\kappa_{14,13} & \kappa_{14,13}+\kappa_{14,15}+\kappa_{14,16} & -\kappa_{14,15} & -\kappa_{14,16} \\
-\kappa_{15,13} & -\kappa_{15,14} & \kappa_{15,13}+\kappa_{15,14}+\kappa_{15,16} & -\kappa_{15,16} \\
-\kappa_{16,13} & -\kappa_{16,14} & -\kappa_{16,15} & \kappa_{16,13}+\kappa_{16,14}+\kappa_{16,15}
\end{pmatrix}.$$

The recombination network G has $l = 7$ connected components and its deficiency is $\delta = 5$, as there $n = 16$ complexes, and the stoichiometric subspace S has dimension $\sigma = 4$. The

moduli ideal M_G is minimally generated by 18 binomials. Twelve of them are cubics:

$$\begin{matrix}
K_8K_{11}K_{15} - K_7K_{12}K_{16} & K_6K_9K_{15} - K_5K_{10}K_{16} & K_4K_{11}K_{14} - K_3K_{12}K_{16} \\
K_2K_9K_{14} - K_1K_{10}K_{16} & K_4K_7K_{14} - K_3K_8K_{15} & K_2K_5K_{14} - K_1K_6K_{15} \\
K_6K_{12}K_{13} - K_5K_{11}K_{14} & K_2K_{12}K_{13} - K_1K_{11}K_{15} & K_8K_{10}K_{13} - K_7K_9K_{14} \\
K_4K_{10}K_{13} - K_3K_9K_{15} & K_2K_8K_{13} - K_1K_7K_{16} & K_4K_6K_{13} - K_3K_5K_{16}.
\end{matrix}$$

The remaining six generators of M_G are quartics:

$$\begin{matrix}
K_9K_{11}K_{14}K_{15} - K_{10}K_{12}K_{13}K_{16} & K_6K_8K_{13}K_{15} - K_5K_7K_{14}K_{16} \\
K_2K_4K_{13}K_{14} - K_1K_3K_{15}K_{16} & K_5K_8K_{10}K_{11} - K_6K_7K_9K_{12} \\
K_1K_4K_{10}K_{11} - K_2K_3K_9K_{12} & K_1K_4K_6K_7 - K_2K_3K_5K_8.
\end{matrix}$$

The moduli space (of toric dynamical systems on G) is the toric variety $V(M_G)$ defined by these 18 binomials. It has codimension 5 and degree 56. For any recombination rates $\kappa^0 \in V_{>0}(M_G)$ and any starting point c^0 in the *population simplex* Δ_7, the trajectory of the toric dynamical system (1) stays in the 4-dimensional polytope $(c^0 + S) \cap \Delta_7$ and is conjectured to converge to the Birch point c^*. Akin (1979) calls c^* the *Wright point*. It generalizes the classical *Hardy-Weinberg equilibrium* in the 2-locus system. $\square$

4. Detailed Balancing Systems

In this section we discuss an important subclass of toric dynamical systems called detailed balancing systems. Here, every edge of the digraph G exists in both directions. We can thus identify $G = (V, E)$ with the underlying undirected graph $\tilde{G} = (V, \tilde{E})$, where $\tilde{E} = \big\{\{i,j\} : (i,j) \in E\big\}$. For each undirected edge $\{i,j\} \in \tilde{E}$ of the graph $\tilde{G}$ we define an $n \times n$-matrix $A_\kappa^{\{i,j\}}$ as follows. In rows i,j and columns i,j the matrix $A_\kappa^{\{i,j\}}$ equals

$$\begin{pmatrix} -\kappa_{ij} & \kappa_{ij} \\ \kappa_{ji} & -\kappa_{ji} \end{pmatrix},$$

and all other entries of the matrix $A_\kappa^{\{i,j\}}$ are 0. The Laplacian of G decomposes as

$$A_\kappa \;=\; \sum_{\{i,j\} \in \tilde{E}} A_\kappa^{\{i,j\}}. \tag{13}$$

A *detailed balancing system* is a dynamical system (1) for which the algebraic equations $\Psi(c) \cdot A_\kappa^{\{i,j\}} = 0$ for $\{i,j\} \in \tilde{E}$ admit a strictly positive solution $c^* \in \mathbb{R}^s_{>0}$. In light of (13), every detailed balancing system is a toric dynamical system, so the positive solution c^* is unique and coincides with the Birch point. As it is for toric dynamical systems, the condition of being detailed balancing depends on the graph $\tilde{G}$ and the constants κ_{ij}.

We rewrite this condition in terms of binomials in $\mathbb{Q}[c, \kappa]$. The two non-zero entries of the row vector $\Psi(c) \cdot A_\kappa^{\{i,j\}}$ are $\kappa_{ij}c^{y_i} - \kappa_{ji}c^{y_j}$ and its negative. Moreover, we find

$$\Psi(c) \cdot A_\kappa^{\{i,j\}} \cdot Y \quad = \quad (\kappa_{ij}c^{y_i} - \kappa_{ji}c^{y_j}) \cdot (y_j - y_i),$$

and hence the right hand side of the dynamical system (1) can be rewritten as follows:

$$\Psi(c) \cdot A_\kappa \cdot Y \;=\; \sum_{\{i,j\}\in\tilde{E}} \Psi(c) \cdot A_\kappa^{\{i,j\}} \cdot Y \;=\; \sum_{\{i,j\}\in\tilde{E}} (\kappa_{ij} c^{y_i} - \kappa_{ji} c^{y_j}) \cdot (y_j - y_i). \qquad (14)$$

For a detailed balancing system, each summand in (14) vanishes at the Birch point c^*.

Example 15. We revisit Example 1. Let $s = 2, n = 3$ and $\tilde{G}$ the complete graph on three nodes labeled by c_1^2, c_1c_2 and c_2^2. The dynamical system (2) is now written as

$$\frac{d}{dt}(c_1, c_2) \;=\; (\kappa_{12}c_1^2 - \kappa_{21}c_1c_2)\cdot(-1,1) + (\kappa_{13}c_1^2 - \kappa_{31}c_2^2)\cdot(-2,2) + (\kappa_{23}c_1c_2 - \kappa_{32}c_2^2)\cdot(-1,1).$$

This is a detailed balancing system if and only if the following algebraic identities hold:

$$\kappa_{12}^2\kappa_{31} - \kappa_{21}^2\kappa_{13} \;=\; \kappa_{23}^2\kappa_{31} - \kappa_{32}^2\kappa_{13} \;=\; \kappa_{12}\kappa_{32} - \kappa_{21}\kappa_{23} \;=\; 0. \qquad (15)$$

This defines a toric variety of codimension two which lies in the hypersurface (3). □

To fit our discussion into the algebraic framework of Section 2, we now propose the following definitions. The *detailed balancing ideal* is the following toric ideal in $\mathbb{Q}[\kappa, c]$:

$$\widetilde{T}_G \;:=\; \big(\langle\, \kappa_{ij}c^{y_i} - \kappa_{ji}c^{y_j} \mid \{i,j\} \in \tilde{E}\,\rangle \;:\; (c_1c_2\cdots c_s)^\infty\big). \qquad (16)$$

The corresponding elimination ideal in $\mathbb{Q}[\kappa]$ will be called the *detailed moduli ideal*:

$$\widetilde{M}_G \quad := \quad \widetilde{T}_G \cap \mathbb{Q}[\kappa].$$

The ideal $\widetilde{T}_G$ is toric, by the same reasoning as in Proposition 6. The detailed moduli ideal $\widetilde{M}_G$ is a toric ideal of Lawrence type, as was the ideal in Example 2. Note, however, that the ideals $\widetilde{T}_G$ and $\widetilde{M}_G$ are toric in the original coordinates κ_{ij}. Here, we did not need the transformation to the new coordinates $K_1, \ldots, K_n$ in (7).

Using the ring inclusion $\mathbb{Q}[K, c] \subset \mathbb{Q}[\kappa, c]$, we have the following inclusions of ideals:

$$T_G \subseteq \widetilde{T}_G \quad \text{and} \quad M_G \subseteq \widetilde{M}_G.$$

Here the equality holds precisely in the situation of Example 2, namely, when each chemical complex appears in only one reaction and each reaction is reversible. In general, as seen in Example 15, the corresponding inclusion of moduli spaces will be strict:

$$V_{>0}(\widetilde{M}_G) \;\subset\; V_{>0}(M_G).$$

In words: every detailed balancing system is a toric dynamical system but not vice versa.

The following characterization of detailed balancing systems will be used in the next section. If L is any vector in $\mathbb{R}^s$ and c the unknown concentration vector then we write

$$L * c \;:=\; (L_1c_1, L_2c_2, \ldots, L_sc_s).$$

Lemma 16. *A toric dynamical system is detailed balancing if and only if all the binomials $\kappa_{ij}c^{y_i} - \kappa_{ji}c^{y_j}$ in (16) have the form $(L*c)^{y_i} - (L*c)^{y_j}$, for some positive vector $L \in \mathbb{R}^s_{>0}$. Thus, a detailed balancing system is a toric dynamical system of the special form*

$$\frac{dc}{dt} \quad = \quad \sum_{\{i,j\}\in\tilde{E}} \big((L*c)^{y_i} - (L*c)^{y_j}\big) \cdot (y_j - y_i). \qquad (17)$$

Proof. The if-direction is easy: if our binomials have the special form $(L*c)^{y_i} - (L*c)^{y_j}$ then $c^* = (1/L_1, 1/L_2, \ldots, 1/L_s)$ is a positive solution to the equations $\Psi(c) \cdot A_\kappa^{\{i,j\}} = 0$. Conversely, for the only-if direction, we define L as the reciprocal of the Birch point $L = (1/c_1^*, 1/c_2^*, \ldots, 1/c_n^*)$, and the result follows the fact that $c^{y_i - y_j} = (c^*)^{y_i - y_j}$ remains valid for all stationary points c of the system (1) as the starting point $c(0)$ varies. □

We now fix a detailed balancing system (17) with a particular starting point $c(0)$. Then the trajectory $c(t)$ evolves inside the invariant polyhedron $P = (c(0) + S) \cap \mathbb{R}^s_{\geq 0}$. Consider any *acyclic orientation* $E' \subset \tilde{E}$ of the graph $\tilde{G}$. This means that E' contains one from each pair of directed edges (i,j) and (j,i) in E, in such a way that the resulting directed subgraph of G has no directed cycles. The acyclic orientation E' specifies a *stratum* $\mathcal{S}$ inside the relatively open polyhedron $P^o = (c(0) + S) \cap \mathbb{R}^s_{>0}$ as follows:

$$\mathcal{S} \;:=\; \big\{\, c \in P^o \mid (L*c)^{y_i} > (L*c)^{y_j} \text{ for all } (i,j) \text{ in } E' \,\big\}.$$

The invariant polyhedron P is partitioned into such strata and their boundaries. We are interested in how the strata meet the boundary of P. Each face of P has the form $F_I := \{c \in P \,|\, c_i = 0 \text{ for } i \in I\}$ where I is subset of $\{1, 2, \ldots, s\}$. This includes $F_\emptyset = P$.

Lemma 17. *Consider a detailed balancing system (17) and fix an acyclic orientation E' of the graph $\tilde{G}$. If the closure of the stratum $\mathcal{S}$ corresponding to E' intersects the relative interior of a face F_I of the invariant polyhedron P, then there exists a strictly positive vector $\alpha \in \mathbb{R}^I_{>0}$ such that $\sum_{k \in I}(y_{jk} - y_{ik}) \cdot \alpha_k \geq 0$ for all directed edges (i,j) in E'.*

Proof. We proceed by contradiction: assume that the inequalities $\sum_{k \in I}(y_{jk} - y_{ik})\alpha_k \geq 0$ have no strictly positive solution $\alpha \in \mathbb{R}^I_{>0}$. By Linear Programming Duality (Farkas' Lemma), there is a non-negative linear combination $v = \sum_{(i,j) \in E'} \lambda_{ij}(y_j - y_i)$ such that the following two conditions on v hold: (a) $\mathrm{supp}(v^+) \cap I = \emptyset$, and (b) $\mathrm{supp}(v^-)$ contains some $j_0 \in I$. We shall prove the following two claims, which give the desired contradiction:

Claim One: *If c is a point in the relative interior of F_I, then $(L*c)^{v_+} > (L*c)^{v_-}$.*

Since $(L*c)_i = 0$ if and only if $i \in I$, and $(L*c)_j > 0$ for all $j \notin I$, (a) implies that $(L*c)^{v+}$ is strictly positive, while (b) implies that $(L*c)^{v-} = 0$, and we are done.

Claim Two: *If c is a point in the closure of the stratum $\mathcal{S}$, then $(L*c)^{v_+} \leq (L*c)^{v_-}$.*

Consider any point $s \in \mathcal{S}$. By the construction of v, the following equation holds:

$$(L*s)^v \;=\; (L*s)^{\sum_{(i,j) \in E'} \lambda_{ij}(y_j - y_i)} \;=\; \prod_{(i,j) \in E'} \big((L*s)^{y_j - y_i}\big)^{\lambda_{ij}}. \tag{18}$$

Recall that $(L*s)^{y_j - y_i} \leq 1$ for each oriented edge $(i,j) \in E'$. Also, each λ_{ij} is non-negative, so $((L*s)^{y_j - y_i})^{\lambda_{ij}} \leq 1$. Using (18), this implies that $(L*s)^v \leq 1$, and therefore $(L*s)^{v_+} \leq (L*s)^{v_-}$. By continuity we can replace s by c in this last inequality. □

The vector $\alpha \in \mathbb{R}^I_{>0}$ in Lemma 17 will play a special role in the next section. In Corollary 18 below we regard α as a vector in $\mathbb{R}^s_{\geq 0}$ by setting $\alpha_j = 0$ for all $j \in \{1, \ldots, s\} \backslash I$.

Corollary 18. *Let $c(t)$ be a trajectory of a detailed balancing system (17) on the invariant polyhedron P, and suppose that a point $c(t_0)$ on this trajectory lies both in the closure of a stratum $\mathcal{S}$ and in the relative interior of a face F_I of P. Let $\alpha \in \mathbb{R}^s_{\geq 0}$ be the vector obtained as in Lemma 17. Then, the inner product $\langle\, \alpha, \frac{dc}{dt}(t_0) \,\rangle$ is non-negative.*

Proof. Let E' denote the orientation which specifies $\mathcal{S}$. The velocity vector $\frac{dc}{dt}(t_0)$ equals

$$\sum_{(i,j)\in E'} \bigl((L*c(t_0))^{y_i} - (L*c(t_0))^{y_j}\bigr)\cdot(y_j - y_i).$$

Since $c(t_0)$ is in the closure of the stratum $\mathcal{S}$, we have $(L*c(t_0))^{y_i} - (L*c(t_0))^{y_j} \geq 0$. We also have $\langle \alpha, y_j - y_i\rangle \geq 0$ because α comes from Lemma 17. This implies

$$\langle\, \alpha\,,\ \frac{dc}{dt}(t_0)\,\rangle \ = \sum_{(i,j)\in E'} \bigl((L*c(t_0))^{y_i} - (L*c(t_0))^{y_j}\bigr)\cdot\langle\, \alpha\,,\ y_j - y_i\,\rangle \ \geq\ 0.$$

This is the claimed inequality. It will be used in the proof of Theorem 23. □

5. Partial Results on the Global Attractor Conjecture

This section contains what we presently know about the Global Attractor Conjecture which was stated in Section 3. This conjecture is proved for detailed balancing systems whose invariant polyhedron is bounded and of dimension two. We begin with some general facts on trajectories of toric dynamical systems, which are interesting in their own right.

Consider a fixed toric dynamical system (1) with strictly positive starting point $c(0) = c^0 \in \mathbb{R}^s_{>0}$. The trajectory $c(t)$ remains in the invariant polyhedron $P = (c^0 + S) \cap \mathbb{R}^s_{\geq 0}$. Recall that any face of P has the form $F_I := \{c \in P \,|\, c_i = 0 \text{ if } i \in I\}$, where $I \subseteq \{1,\ldots s\}$. The boundary ∂P of P is the union of all faces F_I where I is a proper subset of $\{1,\ldots,s\}$. For positive ε, the ε-neighborhood in P of the boundary of P will be denoted by $V_\varepsilon(\partial P)$.

We note that the transformed entropy function (10) can be extended continuously to the boundary of P, because $c_i \log c_i \to 0$ as $c_i \to 0^+$. Equivalent formulations of the following result are well known. For instance, see Siegel and Chen (1994); Sontag (2001).

Proposition 19. *Suppose that the invariant polyhedron P is bounded and the distance between the boundary of P and the set $\{c(t) \in P \mid t > 0\}$ is strictly positive. Then the trajectory $c(t)$ converges to the Birch point c^* of P.*

Proof. We assume that $c(t)$ does not converge to c^*. Let $\varepsilon > 0$ be such that $c(t) \notin V_\varepsilon(\partial P)$ for all $t > t_0$. The strict Lyapunov function (10) ensures that there exists a neighborhood $V_{\varepsilon'}(c^*)$ of the Birch point c^* such that all trajectories that visit $V_{\varepsilon'}(c^*)$ converge to c^*. Then $c(t) \notin V_{\varepsilon'}(c^*)$ for all $t > t_0$. Denote the complement of the two open neighborhoods by $P_0 := P \setminus (V_\varepsilon(\partial P) \cup V_{\varepsilon'}(c^*))$. Then the non-positive and continuous function $c \mapsto (\nabla E \cdot \frac{dc}{dt})(c)$ does not vanish on P_0 by Proposition 11, so it is bounded above by some $-\delta < 0$ on P_0. Therefore, the value of $E(c(t))$ decreases at a rate of at least δ for all $t > t_0$, which implies that E is unbounded on P_0. This is a contradiction. □

Given a trajectory $c(t)$ of (1), a point $\bar{c} \in P$ is called an *ω-limit point* if there exists a sequence $t_n \to \infty$ with $\lim_{n\to\infty} c(t_n) = \bar{c}$. Proposition 19 says that if the trajectory $c(t)$ does not have any ω-limit points on the boundary of P, then it must converge to the Birch point c^*. Thus, in order to prove the Global Attractor Conjecture, it would suffice to show that no boundary point of P is an ω-limit point. We first rule out the vertices.

Proposition 20. *Let r be a vertex of P and consider any $\varepsilon > 0$. Then, there exists a neighborhood W of r such that any trajectory $c(t)$ with starting point $c(0) = c^0$ satisfying $dist(c^0, r) > \varepsilon$, does not visit W for any $t > 0$.*

Proof. The following set is the intersection of a closed cone with a sphere of radius one:

$$\mathcal{V} \;:=\; \left\{ \frac{v}{\|v\|} \mid v \in S\backslash\{0\} \text{ and } r + v \text{ lies in } P \right\}.$$

Hence $\mathcal{V}$ is compact. We set $I = \big\{ j \in \{1, \ldots, s\} \,:\, r_j = 0 \big\}$. For each $v \in \mathcal{V}$, the ray $\gamma_v(t) := r + tv$ extends from the vertex $\gamma_v(0) = r$ into the polyhedron P for small $t > 0$. We consider how the transformed entropy function changes along such a ray:

$$\begin{aligned} \frac{d}{dt} E(\gamma_v(t)) \;&=\; \sum_{j \in I} v_j (\log(0 + tv_j)) \;+\; \sum_{j \notin I} v_j \log(r_j + tv_j) \;-\; \sum_{i=1}^{s} \log(c_j^* v_j) \\ &=\; (\Sigma_{j \in I} v_j) \cdot \log(t) \;+\; w(t), \end{aligned}$$

where the function $w(t)$ admits a universal upper bound for t close to 0 and $v \in \mathcal{V}$. For each $j \in I$ we have $v_j \geq 0$ because $r_j = 0$ and $r + tv \in P$ for small $t > 0$. Also, since v points into P, there exist $j \in I$ with $v_j > 0$. Thus, the function $\Sigma_{j \in I} v_j$ has a positive minimum over $\mathcal{V}$. It follows that $\frac{d}{dt} E(\gamma_v(t))$ tends to $-\infty$ for $t \to 0$. There exists $t_0 < \varepsilon$ such that for all $v \in \mathcal{V}$ the function $t \mapsto E(r + tv)$ decreases for $0 < t \leq t_0$. So, $E(r) > \mu := \max_{v \in \mathcal{V}} E(r + t_0 v)$. On the other hand, E is continuous, so there is a neighborhood W of the vertex r (contained in $\{r + tv \mid t < t_0, v \in \mathcal{V}\}$) such that $E(c) > (E(r) + \mu)/2$ for all $c \in W$. Since E decreases along trajectories, we conclude that no trajectory $c(t)$ that starts at distance $\geq \varepsilon$ from the vertex r can enter W. $\square$

We note that this proposition provides an alternate proof of the main result in Anderson (2008). Namely, Theorem 3.3 of that paper says that for a complex balancing chemical reaction network, if the only possible boundary steady states are vertices of P, then the Birch point is a global attractor. Our proposition above proves that vertices are never ω-limit points, so the theorem of Anderson (2008) follows.

Remark 21. Chemical reaction networks for which P is bounded are called *conservative*. For conservative networks, there exists a positive mass assignment for each species that is conserved by all reactions (Feinberg, 1979). On the other hand, if $0 \in P$, then the reaction network is not conservative. Thus Proposition 20 ensures that, for a toric dynamical system, complete depletion of all the concentrations $c_1, c_2, ..., c_s$ is impossible.

Lemma 22. *Suppose that P is bounded and that the trajectory $c(t)$ has an ω-limit point on the boundary of P. Then for any $\varepsilon > 0$ there exists a positive number $t_\varepsilon > 0$ such that $c(t)$ belongs to $V_\varepsilon(\partial P)$ for all $t > t_\varepsilon$. In other words, the trajectory approaches the boundary.*

Proof. Suppose that for some $\varepsilon > 0$ there exists a sequence $t_n \to \infty$ such that $c(t_n) \notin V_\varepsilon(\partial P)$ for all n. As P is bounded, the trajectory $c(t)$ has an ω-limit point $p \in P\backslash V_\varepsilon(\partial P)$. On the other hand, $c(t)$ also has an ω-limit point on the boundary of P. Consider a ball $B_{2\delta}(p)$ of radius 2δ around p, whose closure lies fully in the relative interior of P. The

trajectory $c(t)$ enters and exits the neighborhood $B_\delta(p)$ of p infinitely many times, and also enters and exits the neighborhood $P\backslash B_{2\delta}(p)$ of the boundary infinitely many times. The trajectory $c(t)$ travels repeatedly between these two sets which are at distance δ from each other. Note that $|dc/dt|$ is bounded above, and $\nabla E \cdot dc/dt$ is bounded away from zero on the annulus $B_{2\delta}(p)\backslash B_\delta(p)$. Then, as in the proof of Proposition 19, each traversal between the neighborhoods decreases the value of $E(c(t))$ by a positive amount that is bounded away from zero. This contradicts the fact that E is bounded on P. $\square$

We shall now prove the main result of this section. Admittedly, Theorem 23 has three rather restrictive hypotheses, namely, "dimension two," "bounded polyhedron," and "detailed balancing." At present we do not know how to remove any of these hypotheses.

Theorem 23. *Consider a detailed balancing system (17) whose stoichiometric subspace* $S = \mathbb{R}\{y_j - y_i \,|\, (i,j) \in \tilde{E}\}$ *is two-dimensional and assume that the invariant polygon* $P = (c^0 + S) \cap \mathbb{R}^s_{\geq 0}$ *is bounded. Then the Birch point* c^* *is a global attractor for* P.

Proof. By Proposition 19, we need only rule out the possibility that the trajectory $c(t)$ has an ω-limit point on the boundary of P. Proposition 20 gives the existence of open neighborhoods of the vertices such that no trajectory $c(t)$ that starts outside them can visit them. Let V denote the union of these neighborhoods. Suppose now that $c(t)$ has an ω-limit point on ∂P. That limit point lies in the relative interior of some edge F of P. Let F_ε denote the set of points in P which have distance at most ε from the edge F.

We claim that there exists $\varepsilon > 0$ and $t_\varepsilon > 0$, such that the trajectory $c(t)$ remains in the subset $F_\varepsilon\backslash V$ for all $t > t_\varepsilon$. This is true because $c(t)$ belongs to the neighborhood $V_\varepsilon(\partial P)$ of the boundary for $t \gg 0$, by Lemma 22, and hence $c(t)$ belongs to $V_\varepsilon(\partial P)\backslash V$ for $t \gg 0$. But this implies that $c(t)$ belongs to $F_\varepsilon\backslash V$ for $t \gg 0$ because $F_\varepsilon\backslash V$ is a connected component of $V_\varepsilon(\partial P)\backslash V$ for ε sufficiently small. This uses the dimension two assumption.

Consider the closures of all strata $\mathcal{S}$ that intersect the relative interior of F. After decreasing ε if necessary, we may assume that the union of these closures contains the set $F_\varepsilon\backslash V$, which contains the trajectory $c(t)$ for $t > t_\varepsilon$. To complete the proof, we will show that the distance from $c(t)$ to the edge F never decreases after $c(t)$ enters $F_\varepsilon\backslash V$.

Any stratum $\mathcal{S}$ whose closure intersects the relative interior of F contributes a vector $\alpha = \alpha(\mathcal{S})$ which satisfies the statement of Lemma 17 for $F = F_I$. The orthogonal projection of $\alpha(\mathcal{S})$ into the two-dimensional stoichiometric subspace is a positive multiple of the unit inner normal $\alpha_0 \in S$ to F in P. By Corollary 18 we have $\langle \alpha(S), \frac{dc}{dt}(t) \rangle \geq 0$ and hence $\langle \alpha_0, \frac{dc}{dt}(t) \rangle \geq 0$ for $t > t_\varepsilon$. Therefore the distance from $c(t)$ to F cannot decrease. This is a contradiction to the assumption that F contains an ω-limit point. $\square$

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