

# Notes on Chemical Reaction Networks

JWR

May 19, 2009, last update: Nov 27, 2009

These notes are shamelessly cribbed from the extremely helpful online notes [2]. Even some of the notation is the same. I wrote them because, like Goethe's Frenchman, I wanted to translate them into my own language. I also benefitted from conversations with Moe Hirsch and Gheorghe Craciun and from lectures by Gheorghe Craciun and David Anderson.

**1. Notation.** The positive real numbers, nonnegative real numbers, and non-negative integers are denoted respectively by

$$\mathbb{P} := \{x \in \mathbb{R} : x > 0\}, \quad \bar{\mathbb{P}} := \{x \in \mathbb{R} : x \geq 0\}, \quad \mathbb{N} := \{n \in \mathbb{Z} : n \geq 0\}.$$

For a finite set  $\mathcal{X}$  we view a real valued function  $x \in \mathbb{R}^{\mathcal{X}}$  on  $\mathcal{X}$  as a vector and write  $x_i$  for the value of  $x$  on  $i \in \mathcal{X}$ . The vector space  $\mathbb{R}^{\mathcal{X}}$  has a **standard basis**  $\{\omega_i : i \in \mathcal{X}\}$  defined by  $\omega_i(j) = 1$  if  $j = i$  and 0 otherwise. For any subset  $\mathcal{L} \subseteq \mathcal{X}$  define

$$\omega_{\mathcal{L}} := \sum_{i \in \mathcal{L}} \omega_i$$

so  $\omega_{\mathcal{L}}$  is the indicator function of  $\mathcal{L}$  and  $\omega_i = \omega_{\{i\}}$ . We always equip the vector space  $\mathbb{R}^{\mathcal{X}}$  with its **standard inner product**

$$\langle x, y \rangle := \sum_{i \in \mathcal{S}} x_i y_i$$

so the standard basis is an orthonormal basis in the standard inner product. An integer vector  $\alpha \in \mathbb{N}^{\mathcal{X}}$  is interpreted both as a vector in  $\mathbb{R}^{\mathcal{X}}$  and as a multiindex. Thus for  $x \in \mathbb{R}^{\mathcal{X}}$  we denote the monomial with exponents  $\alpha$  by

$$x^{\alpha} := \prod_{i \in \mathcal{S}} x_i^{\alpha_i}.$$

**Definition 2.** A **mass action kinetics** dynamical system is a system of polynomial differential equations on  $\mathbb{R}^{\mathcal{S}}$  of form

$$\dot{x} = \sum_{(\alpha, \beta) \in \mathcal{R}} \kappa_{\alpha\beta} x^{\alpha} (x^{\beta} - x^{\alpha}) \quad (1)$$

where  $\mathcal{S}$  is a finite set, the sum is over a finite set  $\mathcal{R} \subseteq \mathbb{N}^{\mathcal{S}} \times \mathbb{N}^{\mathcal{S}}$  of pairs of multiindices, and the coefficients  $\kappa_{\alpha\beta}$  are positive. The finite set  $\mathcal{S}$  is called the

set of **species**, the finite set  $\mathcal{C}$  of all multiindices  $\alpha$  such that either  $\kappa_{\alpha\beta} > 0$  or  $\kappa_{\beta\alpha} > 0$  for some  $\beta$  is called the set of **complexes**, the set  $\mathcal{R}$  is called the set of **reactions**, and the constants  $\kappa_{\alpha\beta}$  are called the **rate constants** of the system. It is convenient to define  $\kappa_{\alpha\beta} = 0$  if  $\alpha, \beta \in \mathcal{C}$  but  $(\alpha, \beta) \notin \mathcal{R}$ ; this allows us to write the sum in (1) as a sum over all pairs  $(\alpha, \beta) \in \mathcal{C} \times \mathcal{C}$ . We view the relation  $\mathcal{R}$  as the edges of a directed graph whose vertices are the elements of  $\mathcal{S}$ . We often write  $\alpha \rightarrow \beta$  instead of  $(\alpha, \beta) \in \mathcal{R}$ , i.e.

$$\alpha \rightarrow \beta \iff (\alpha, \beta) \in \mathcal{R} \iff \kappa_{\alpha\beta} > 0.$$

The quadruple  $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$  is called the **chemical reaction network** of the system. The idea behind equation (1) is that whenever a chemical reaction  $\alpha \rightarrow \beta$  occurs,  $\beta_i$  molecules of species  $i$  are created,  $\alpha_i$  molecules of species  $i$  are destroyed, and the reaction occurs at a rate proportional to  $x^\alpha$  where  $x_i$  is the amount of species  $i$  present.

**Proposition 3.** *The most general system of polynomial differential equations on  $\mathbb{R}^S$  has the form*

$$\dot{x}_i = p_i(x), \quad p_i(x) = \sum_{\alpha} p_{i,\alpha} x^\alpha, \quad (2)$$

for  $i \in \mathcal{S}$  where the sums are finite. The equation (2) may be written in the form (1) if and only if the system (2) has the form

$$p_i(x) = b_i(x) + x_i a_i(x) \quad (3)$$

where the polynomial  $b_i(x)$  is independent of  $x_i$  and has only positive coefficients.

*Proof.* Equating the right hand sides of (2) and (1) gives

$$p_{i,\alpha} = \sum_{\beta} \kappa_{\alpha\beta} (\beta_i - \alpha_i).$$

We collect in  $b_i(x)$  all the terms where  $\alpha_i = 0$ . These terms have form  $\kappa_{\alpha\beta} x^\alpha \beta_i$  as required. The remaining terms contain a positive power of  $x_i$ . For the converse it is enough (since the space of all right hand sides of (1) form a cone) to consider systems of form  $\dot{x} = \pm x^\alpha \omega_i$ . The system  $\dot{x} = x^\alpha \omega_i$  can be written as  $\dot{x} = x^\alpha (\beta - \alpha)$  where  $\beta_j = \alpha_j$  for  $j \neq i$  and  $\beta_i = \alpha_i + 1$ . If  $\alpha_i > 0$ , the system  $\dot{x} = -x^\alpha \omega_i$  can be written as  $\dot{x} = x^\alpha (\beta - \alpha)$  where  $\beta_j = \alpha_j$  for  $j \neq i$  and  $\beta_i = \alpha_i - 1$ .  $\square$

**Remark 4.** A system has the form (3) if and only if it has the form

$$p_i(x) = \tilde{b}_i(x) - x_i \tilde{a}_i(x) \quad (4)$$

where all the coefficients in both  $\tilde{b}_i$  and  $\tilde{a}_i$  are positive: reverse the signs of all the terms in  $a_i$  and move the terms with positive coefficients to  $b_i$ .

**Corollary 5.** *If the system (2) is a mass action kinetics dynamical system, then both the closed cone  $\bar{\mathbb{P}}^{\mathcal{S}}$  and the open cone  $\mathbb{P}^{\mathcal{S}}$  are forward invariant.*

*Proof.* For each  $i \in \mathcal{S}$  we have  $p_i(x) \geq 0$  on the boundary facet  $x_i = 0$  of  $\bar{\mathbb{P}}^{\mathcal{S}}$  by (3). Thus the set  $\bar{\mathbb{P}}^{\mathcal{S}}$  is forward invariant for the modified system  $\dot{x}_i = p_i(x) + \varepsilon$  where  $\varepsilon > 0$ : the right hand side points into the interior  $\mathbb{P}^{\mathcal{S}}$  so that integral curves in  $\bar{\mathbb{P}}^{\mathcal{S}}$  starting in the coordinate hyperplane  $x_i = 0$  immediately moves into the open half space  $x_i > 0$ . Letting  $\varepsilon \rightarrow 0$  we conclude (by the continuity of the solution of the differential equation with respect to  $\varepsilon$ ) that a solution to (2) starting in the (intersection of the closed cone  $\bar{\mathbb{P}}^{\mathcal{S}}$  with the) coordinate hyperplane  $x_i = 0$  remains in the closed cone.

To show that the open cone  $\mathbb{P}^{\mathcal{S}}$  is forward invariant, assume the contrary. Then there is an integral curve  $u : I \rightarrow \mathbb{R}^{\mathcal{S}}$  solving (1), defined on an open interval  $I$  in about 0 in  $\mathbb{R}$  which begins in the open cone and leaves it at some positive time. Let  $\bar{t} \in I$  be the first time when the integral curve is not in  $\mathbb{P}^{\mathcal{S}}$  so that  $u(t) \in \bar{\mathbb{P}}^{\mathcal{S}}$  (i.e.  $u_j(t) > 0$  for all  $j \in \mathcal{S}$ ) and all  $0 \leq t < \bar{t}$  and  $u(\bar{t}) \notin \mathbb{P}^{\mathcal{S}}$ . Define

$$\mathcal{J} := \{i \in \mathcal{S} : u_i(\bar{t}) = 0\}, \quad \mathbf{X} := \bigcap_{i \in \mathcal{J}} \{x \in \mathbb{R}^{\mathcal{S}} : x_i = 0\},$$

so  $u(\bar{t}) \in \mathbf{X} \subset \bar{\mathbb{P}}^{\mathcal{S}} \setminus \mathbb{P}^{\mathcal{S}}$  but  $u(t) \in \mathbb{P}^{\mathcal{S}}$  for  $0 \leq t < \bar{t}$ . Since the closed cone  $\bar{\mathbb{P}}^{\mathcal{S}}$  is forward invariant, we have that  $u_i(t) \geq 0$  for  $t \geq 0$ ,  $i \in \mathcal{J}$ . Now

$$\dot{u}_i(t) = p_i(u(t)) = b_i(u(t)) + u_i(t)a_i(u(t))$$

as in (2) and (3). Since for  $i \in \mathcal{J}$  the function  $u_i(t)$  has a minimum at  $t = \bar{t}$  it follows that  $\dot{u}_i(\bar{t}) = 0$ . As  $u_i(\bar{t}) = 0$  as well, we must have  $p_i(u(\bar{t})) = 0$  for  $i \in \mathcal{J}$  and hence  $b_i(u(\bar{t})) = 0$ . But since no monomial which appears in  $b_i(x)$  has a negative coefficient, it follows that for  $i \in \mathcal{J}$  each monomial which appears in  $b_i(x)$  contains some  $x_j$  with  $j \in \mathcal{J}$  as a factor. Hence  $b_i(x)$ , and so also  $p_i(x) = b_i(x) + x_i a_i(x)$ , vanishes for  $i \in \mathcal{J}$  and  $x \in \mathbf{X}$ . This says that the subspace  $\mathbf{X}$  is a invariant under the dynamical system (1) contradicting the fact that  $u(0) \notin \mathbf{X}$  and  $u(\bar{t}) \in \mathbf{X}$ .  $\square$

**6.** The mass action kinetics dynamical system (1) can be written as

$$\dot{x} = YA\Psi(x) \tag{5}$$

where  $Y : \mathbb{R}^{\mathcal{C}} \rightarrow \mathbb{R}^{\mathcal{S}}$  is the linear map defined by

$$Y\omega_\alpha := \alpha,$$

$A : \mathbb{R}^{\mathcal{C}} \rightarrow \mathbb{R}^{\mathcal{C}}$  is the linear map defined by

$$A\omega_\alpha := \sum_{\beta} \kappa_{\alpha\beta}(\omega_\beta - \omega_\alpha)$$

and  $\Psi : \mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}^{\mathcal{C}}$  is the nonlinear map defined by

$$\Psi(x) := \sum_{\alpha} x^\alpha \omega_\alpha.$$

It is convenient to write

$$A = K - D$$

where the linear maps  $K, D : \mathbb{R}^{\mathcal{C}} \rightarrow \mathbb{R}^{\mathcal{C}}$  are defined by

$$K\omega_\alpha := \sum_{\beta} \kappa_{\alpha\beta} \omega_\beta, \quad D\omega_\alpha := \left( \sum_{\beta} \kappa_{\alpha\beta} \right) \omega_\alpha.$$

**Definition 7.** A point  $c \in \mathbb{P}^{\mathcal{S}}$  where

$$YA\Psi(c) = 0$$

is called an **equilibrium** of the mass action kinetics dynamical system (1) and (5). The equilibrium is called **balanced** if it satisfies the stronger condition

$$A\Psi(c) = 0.$$

Since

$$A\Psi(c) = A \sum_{\alpha} c^\alpha \omega_\alpha = \sum_{\alpha} c^\alpha A\omega_\alpha = \sum_{\alpha, \beta} c^\alpha \kappa_{\alpha\beta} (\omega_\beta - \omega_\alpha)$$

the point  $c$  is a balanced equilibrium iff

$$\sum_{\alpha} c^\alpha \kappa_{\alpha\gamma} = c^\gamma \sum_{\beta} \kappa_{\gamma\beta} \tag{6}$$

for each  $\gamma \in \mathcal{C}$ . This says that in the state  $c$ , the rate at which a complex  $\gamma$  is destroyed equals the rate at which it is produced.

**Conjecture 8** (Global Attractor Conjecture). *If a mass action kinetics dynamical system has a balanced equilibrium, then any trajectory with positive initial condition converges to a balanced equilibrium. (In particular every equilibrium is balanced.)*

**9.** It is handy to introduce matrix notation at this point. An enumeration

$$\mathcal{C} = \{\alpha_1, \alpha_2, \dots, \alpha_n\}$$

of  $\mathcal{C}$  (without repetitions) determines a one-one correspondence between the standard basis vectors  $\omega_\alpha$  of  $\mathbb{R}^{\mathcal{C}}$  and the standard basis vectors of  $\mathbb{R}^n$  and hence a matrix representation (which we denote by the same letter) for each of the linear maps  $A, K, D : \mathbb{R}^{\mathcal{C}} \rightarrow \mathbb{R}^{\mathcal{C}}$ . The  $(\alpha, \beta)$  entry of  $K$  is  $\kappa_{\alpha\beta}$  and the matrix  $D$  is diagonal. Recall that a square matrix  $P$  with nonnegative entries is called **irreducible** iff for each pair  $(\alpha, \beta)$  of indices, some positive power of  $P$  has a positive  $(\alpha, \beta)$  entry. The following lemma holds for any square matrix  $K$  with nonnegative entries.

**Lemma 10.** *There is an enumeration of  $\mathcal{C}$  such that the matrix  $K$  has block triangular form*

$$K = \begin{pmatrix} K_{11} & K_{12} & \cdots & K_{1k} \\ 0 & K_{22} & \cdots & K_{2k} \\ & & \ddots & \\ 0 & 0 & \cdots & K_{kk} \end{pmatrix}$$

where each diagonal block  $K_{aa}$  is either irreducible or a  $1 \times 1$  zero matrix.

*Proof.* Let  $\Rightarrow$  be the reflexive transitive closure of the edge relation  $\mathcal{R}$  of the directed graph  $(\mathcal{C}, \mathcal{R})$ , i.e.  $\alpha \Rightarrow \beta$  iff there exist  $\gamma_0, \dots, \gamma_m \in \mathcal{C}$  such that  $\gamma_0 = \alpha$ ,  $\gamma_m = \beta$  and  $\gamma_{i-1} \rightarrow \gamma_i$  for  $i = 1, \dots, m$ . Equivalently  $\alpha \Rightarrow \beta$  iff either  $\alpha = \beta$  or the  $(\alpha, \beta)$  entry in  $K^m$  is nonzero for some  $m > 0$ . We say that  $\alpha$  and  $\beta$  are **linked** iff both  $\alpha \Rightarrow \beta$  and  $\beta \Rightarrow \alpha$ . The equivalence classes of this equivalence relation are called the **linkage classes**.

Let  $\mathcal{C}_1, \mathcal{C}_2, \dots, \mathcal{C}_k$  be the linkage classes so that

$$\mathcal{C} = \mathcal{C}_1 \cup \mathcal{C}_2 \cup \cdots \cup \mathcal{C}_k$$

and the terms in the union are pairwise disjoint. The relation  $\Rightarrow$  induces a partial order, also denoted by  $\Rightarrow$ , on the set of linkage classes, i.e.  $\mathcal{C}_a \Rightarrow \mathcal{C}_b$  iff  $\alpha \Rightarrow \beta$  for some (and hence all)  $\alpha \in \mathcal{C}_a$  and  $\beta \in \mathcal{C}_b$ . A partial order can always be refined to a linear order so we may choose the enumeration so that  $\mathcal{C}_a \Rightarrow \mathcal{C}_b$  implies  $a \leq b$ . Now refine this enumeration to a enumeration (again without repetitions) of  $\mathcal{C}$ . It follows that the elements of each linkage class  $\mathcal{C}_a$  are adjacent in this enumeration. Let  $K_{ab}$  be the submatrix with entries indexed by  $\mathcal{C}_a \times \mathcal{C}_b$ . If  $\alpha \in \mathcal{C}_a$ ,  $\beta \in \mathcal{C}_b$ , and  $b < a$ , then  $\kappa_{\alpha\beta} = 0$  since otherwise  $\mathcal{C}_a \Rightarrow \mathcal{C}_b$  (which implies  $a \leq b$ ). Hence  $K_{ab} = 0$  for  $b < a$  so the matrix has the displayed block triangular structure.

Choose a linkage class  $\mathcal{C}_a$ . Then  $\alpha \Rightarrow \beta$  for all pairs  $(\alpha, \beta) \in \mathcal{C}_a \times \mathcal{C}_a$ . If  $\alpha \neq \beta$ , then, as noted above, there must be a positive power of  $K_{aa}$  having positive  $(\alpha, \beta)$  entry. If  $\mathcal{C}_a$  has two or more elements and  $\alpha \in \mathcal{C}_a$  then there is a  $\beta \in \mathcal{C}_a$  distinct from  $\alpha$ , so  $\alpha \Rightarrow \beta$  and  $\beta \Rightarrow \alpha$  and hence some positive power of  $K_{aa}$  has a positive  $(\alpha, \beta)$  entry and some other positive power has a positive  $(\beta, \alpha)$  entry. The product of these two powers has a positive  $(\alpha, \alpha)$  entry. This shows that  $K_{aa}$  is irreducible. If  $\mathcal{C}_a$  is a singleton and  $K_{aa}$  is not zero, then trivially  $K_{aa}$  is  $1 \times 1$  and irreducible.  $\square$

**Definition 11.** Continue the notation and terminology of Lemma 10 and its proof. The network is said to be **strongly reversible** iff  $\beta \rightarrow \alpha$  whenever  $\alpha \rightarrow \beta$ . The network is said to be **weakly reversible** iff it satisfies any (and hence all) of the following conditions:

- (i)  $\beta \Rightarrow \alpha$  whenever  $\alpha \Rightarrow \beta$ .
- (ii) The matrix  $K$  is block diagonal, i.e  $K_{ab} = 0$  for  $a \neq b$ .
- (iii) Every linkage class is a connected component of the (underlying undirected graph of the directed) graph  $(\mathcal{C}, \mathcal{R})$ .

**Proposition 12.** *If the system has a balanced equilibrium, then the linear map  $D$  is invertible and the system is weakly reversible.*

*Proof.* If  $D_{\gamma\gamma} = \sum_{\beta} \kappa_{\gamma\beta} = 0$  for some  $\gamma \in \mathcal{C}$ , then, as  $\kappa_{\gamma\beta} \geq 0$ , we have  $\kappa_{\gamma\beta} = 0$  for all  $\beta$ . Then (6) implies that  $\sum_{\alpha} c^{\alpha} \kappa_{\alpha\gamma} = 0$ , so  $\kappa_{\alpha\gamma} = 0$  for all  $\alpha$  (as  $c^{\alpha} > 0$ ). But this contradicts  $\gamma \in \mathcal{C}$  as  $\mathcal{C}$  is the set of  $\gamma \in \mathbb{N}^S$  such that either  $\gamma \rightarrow \beta$  for some  $\beta$  or  $\alpha \rightarrow \gamma$  for some  $\alpha$ .

Assume that the system is not weakly reversible. Then some off diagonal block  $K_{ab}$  with  $a < b$  is nonzero. Take for  $a$  the least index for which this is true. Then  $K_{aa}$  is the only nonzero block in its column, so for  $\gamma \in \mathcal{C}_a$  equation (6) takes the form

$$\sum_{\alpha \in \mathcal{C}_a} c^{\alpha} \kappa_{\alpha\gamma} = c^{\gamma} \sum_{\beta \in \mathcal{C}} \kappa_{\gamma\beta},$$

i.e. the sum on the left in (6) is restricted to  $\mathcal{C}_a$ . Now sum over  $\gamma \in \mathcal{C}_a$  to get

$$\sum_{\gamma \in \mathcal{C}_a} \sum_{\alpha \in \mathcal{C}_a} c^{\alpha} \kappa_{\alpha\gamma} = \sum_{\gamma \in \mathcal{C}_a} \sum_{\beta \in \mathcal{C}} c^{\gamma} \kappa_{\gamma\beta}.$$

But this is a contradiction since every term on the left also appears on the right and some positive term on the right (namely  $c^{\gamma} \kappa_{\gamma\beta}$  where  $\kappa_{\gamma\beta}$  is a nonzero entry in  $K_{ab}$ ) does not appear on the left.  $\square$

### 13. The subspaces

$$\mathbf{S} := \text{span} \{ \beta - \alpha : \kappa_{\alpha\beta} > 0 \} \subseteq \mathbb{R}^S, \quad \mathbf{F} := \text{span} \{ \omega_{\beta} - \omega_{\alpha} : \kappa_{\alpha\beta} > 0 \} \subseteq \mathbb{R}^C$$

are called respectively the **stoichiometric subspace** and the **formal stoichiometric subspace**. (The stoichiometric subspace  $\mathbf{S}$  is the image of the formal stoichiometric subspace  $\mathbf{F}$  under the linear map  $Y : \mathbb{R}^C \rightarrow \mathbb{R}^S$  defined above.) The intersection of a translate of  $\mathbf{S}$  with the positive cone  $\mathbb{P}^S$  is called (if it is nonempty) a **positive stoichiometric compatibility class**.

**14.** A vector  $\xi \in \mathbb{R}^C$  is orthogonal to the generator  $\omega_{\beta} - \omega_{\alpha}$  of  $\mathbf{F}$  if and only if  $\xi_{\beta} = \xi_{\alpha}$ . Thus  $\mathbf{F}^{\perp}$  is the set of all  $\xi \in \mathbb{R}^C$  such that  $\xi_{\beta} = \xi_{\alpha}$  whenever  $\kappa_{\alpha\beta} > 0$ . A vector  $u \in \mathbb{R}^S$  lies the orthogonal complement  $\mathbf{S}^{\perp}$  to the stoichiometric subspace  $\mathbf{S}$  if and only if  $\langle \alpha - \beta, u \rangle = 0$  whenever  $\kappa_{\alpha\beta} > 0$ .

**Proposition 15.** *The image  $A(\mathbb{R}^C)$  of  $A$  is a subspace of the formal stoichiometric subspace  $\mathbf{F}$ . If the system is weakly reversible, both spaces have codimension  $k$  (the number of linkage classes) so they are equal.*

*Proof.* The first statement is immediate. To prove the second, assume weak reversibility. The vectors  $\omega_{\mathcal{L}} := \sum_{\alpha \in \mathcal{L}} \omega_{\alpha}$  as  $\mathcal{L}$  ranges over the connected components of the graph  $(\mathcal{C}, \mathcal{R})$  form an orthogonal basis for the orthogonal complement  $\mathbf{F}^{\perp}$  to the formal stoichiometric subspace  $\mathbf{F} \subseteq \mathbb{R}^C$ . By the part (iii) of definition 11 the number of such connected components is  $k$ , the number of linkage classes. This shows that the codimension of  $\mathbf{F}$ , i.e. the dimension of  $\mathbf{F}^{\perp}$ , is  $k$ .

The codimension of the image  $A(\mathbb{R}^C)$  of  $A$  is the same as the dimension of the kernel of  $A$  so it suffices to a basis  $\zeta_1, \zeta_2, \dots, \zeta_k$  for the kernel. The number  $k$  of linkage classes is also the number of diagonal blocks in the block decomposition of  $K$  in Lemma 10. Let  $D_a$  denote the submatrix of the diagonal matrix  $D$  with entries indexed by  $\mathcal{C}_a \times \mathcal{C}_a$ . Then the matrix  $K_{aa}D_a^{-1}$  is irreducible. By Perron Frobenius it has a positive eigenvector unique up to a scalar multiple. Extend it to an element of  $\mathbb{R}^C$  by setting the components indexed by the complement to  $\mathcal{C}_a$  to zero. Denote the product of this vector with  $D$  by  $\zeta_a$ . Then  $A\zeta_a = K\zeta_a - D\zeta_a = 0$  and the vectors  $\zeta_n$  form a basis for the kernel of  $A$ .  $\square$

**Proposition 16.** *Each positive stoichiometric compatibility class is forward invariant.*

*Proof.* The translates of  $\mathbf{S}$  are invariant under the dynamical system (1) as the vector field (1) takes values in  $\mathbf{S}$ . The result follows from Corollary 5.  $\square$

**17.** Choose  $c \in \mathbb{P}^S$  and define a diffeomorphism  $\Phi : \mathbb{R}^S \rightarrow \mathbb{P}^S$  via the formula

$$\Phi(u)_i := c_i e^{u_i}, \quad i \in \mathcal{S}. \quad (7)$$

We denote the set of balanced equilibria by

$$Z := \{x \in \mathbb{R}^S : A\Psi(x) = 0\}.$$

**Theorem 18.** *Assume that the set  $Z$  of balanced equilibria is nonempty and that the point  $c$  in which appears in equation (7) lies in  $Z$ . Then the diffeomorphism  $\Phi$  maps  $\mathbf{S}^\perp$  onto  $Z$  and the set  $Z$  of balanced equilibria intersects each positive stoichiometric compatibility class in a single point.*

*Proof. Step 1.* We prove  $\Phi(\mathbf{S}^\perp) \subseteq Z$ . Suppose that  $x = \Phi(u)$ . Then  $x^\alpha = c^\alpha e^{\langle \alpha, u \rangle}$ . If  $u \in \mathbf{S}^\perp$  then  $\langle \alpha - \gamma, u \rangle = 0$  whenever  $\kappa_{\alpha\gamma} > 0$  so  $x^\alpha \kappa_{\alpha\gamma} = c^\alpha e^{\langle \gamma, u \rangle} \kappa_{\alpha\gamma}$ . Hence by (6)

$$\sum_\alpha x^\alpha \kappa_{\alpha\gamma} = e^{\langle \gamma, u \rangle} \sum_\alpha c^\alpha \kappa_{\alpha\gamma} = e^{\langle \gamma, u \rangle} c^\gamma \sum_\beta \kappa_{\gamma\beta} = x^\gamma \sum_\beta \kappa_{\gamma\beta}$$

which confirms that  $x$  also satisfies (6).

**Step 2.** We prove that  $Z \subseteq \Phi(\mathbf{S}^\perp)$ . Choose  $x = \Phi(u) \in Z$ . Equation (6) says that both the row vector with components  $c^\alpha$  and also the row vector with components  $x^\alpha$  are fixed points of the map  $\xi \mapsto \xi KD^{-1}$ . The matrix  $KD^{-1}$  has the same block structure as the matrix  $K$ ; only the entries have been rescaled. Hence restricting  $\alpha$  to  $\mathcal{C}_a$  we see that both  $(c^\alpha)_{\alpha \in \mathcal{C}_a}$  and  $(x^\alpha)_{\alpha \in \mathcal{C}_a}$  are eigen row vectors of the same irreducible block in  $KD^{-1}$ . By Perron-Frobenius these two vectors must be positive multiples of one another, i.e. there exists  $\mu_a > 0$  such that  $x^\alpha = \mu_a c^\alpha$  for  $\alpha \in \mathcal{C}_a$ . As  $x = \Phi(u)$  this says  $c^\alpha e^{\langle \alpha, u \rangle} = \mu_a c^\alpha$  and hence  $e^{\langle \alpha, u \rangle} = \mu_a$  for  $\alpha \in \mathcal{C}_a$ . Hence  $e^{\langle \alpha - \beta, u \rangle} = 1$  for  $\alpha, \beta \in \mathcal{C}_a$  and so  $\langle \alpha - \beta, u \rangle = 0$  whenever  $\alpha \rightarrow \beta$ , i.e.  $u \in \mathbf{S}^\perp$ .

**Step 3.** We prove that  $Z$  intersects each positive stoichiometric compatibility class in at most one point. Suppose that  $x, y \in Z$  lie in the same positive stoichiometric compatibility class. Since they lie in stoichiometric class we have  $x - y \in \mathbf{S}$ . Since they lie in  $Z$  we have  $x = \Phi(u)$  and  $y = \Phi(v)$  where  $u, v \in \mathbf{S}^\perp$ . Hence  $\langle x - y, u - v \rangle = 0$ . But

$$\langle x - y, u - v \rangle = \sum_{i \in \mathcal{S}} c_i (e^{u_i} - e^{v_i})(u_i - v_i)$$

and each term in the sum is nonnegative as  $(e^{u_i} - e^{v_i})$  and  $u_i - v_i$  have the same sign. As  $c_i > 0$  the sum vanishes only if  $u = v$ .

**Step 4.** We prove that  $Z$  intersects each positive stoichiometric compatibility class in at least one point. Choose a positive stoichiometric compatibility class  $(b + \mathbf{S}) \cap \mathbb{P}^{\mathcal{S}}$ ,  $b \in \mathbb{P}^{\mathcal{S}}$ . Consider the function  $\phi : \mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}$  defined by

$$\phi(u) := \sum_{i \in \mathcal{S}} c_i e^{u_i} - b_i u_i.$$

The gradient of  $\phi$  is  $\Phi(u) - b$ . It is enough to show that the restriction of  $\phi$  to  $\mathbf{S}^\perp$  has a critical point  $u \in \mathbf{S}^\perp$  for then its gradient is orthogonal to  $\mathbf{S}^\perp$ , i.e.  $\Phi(u) - b \in (\mathbf{S}^\perp)^\perp = \mathbf{S}$  and so  $\Phi(u) \in b + \mathbf{S}$ . The function  $\phi$  is strictly convex, i.e. its Hessian is positive definite. This is because the matrix of second partials is diagonal with positive entries on the diagonal. Hence also the restriction of  $\phi$  to  $\mathbf{S}^\perp$  is strictly convex. Furthermore  $\phi(u)$  tends to infinity along every ray  $u = w + sv$ ,  $s \geq 0$ ,  $v \neq 0$ . To see this evaluate  $\phi$  on the ray to get

$$\phi(w + sv) = \sum_{i \in \mathcal{S}} a_i e^{sv_i} - sb_i v_i - b_i w_i$$

where  $a_i := c_i e^{w_i} > 0$ . Either some  $v_i > 0$  or all  $v_i \leq 0$ . In the former case  $\phi(w + sv) \rightarrow \infty$  as  $s \rightarrow \infty$ . In the latter case the exponentials are bounded and  $-sb_i v_i \geq 0$  with strict inequality for some  $i$  (as  $v \neq 0$ ) so again  $\phi(w + sv) \rightarrow \infty$  as  $s \rightarrow \infty$ . Now on the boundary of a sufficiently large ball  $\phi$  takes values strictly greater than its value at the center of that ball. Therefore  $\phi$  must have an interior minimum which is the desired critical point. (Since  $\phi$  has a positive definite Hessian, Morse theory tells us that it has only one critical point; this provides an alternate proof of Step 3.)  $\square$

**Theorem 19.** *If the system (1) has a balanced equilibrium  $c$ , then the function  $V : \mathbb{P}^{\mathcal{S}} \rightarrow \mathbb{R}$  defined by*

$$V(x) := \sum_{i \in \mathcal{S}} x_i (\ln x_i - \ln c_i - 1)$$

*is a strict Lyapunov function. In fact,  $V$  is strictly decreasing along any integral curve which is not a balanced equilibrium and hence every equilibrium is balanced.*

*Proof.* We use the diffeomorphism  $\Phi$  to rewrite (1) as a differential equation on  $\mathbb{R}^S$ . By (7) we have  $\dot{x}_i = c_i e^{u_i} \dot{u}_i$  and  $x^\alpha = c^\alpha e^{\langle \alpha, u \rangle}$  so (1) becomes  $\dot{u} = f(u)$  where

$$f_i(u) := \sum_{\alpha, \beta} \frac{\kappa_{\alpha\beta} c^\alpha}{c_i} e^{\langle \alpha, u \rangle - u_i} (\beta_i - \alpha_i).$$

The formula for the function  $W := V \circ \Phi$  is

$$W(u) = \sum_{i \in S} c_i e^{u_i} (u_i - 1)$$

so

$$dW = \sum_{i \in S} c_i e^{u_i} u_i du_i$$

and hence

$$dW(u)f(u) = \sum_{\alpha, \beta} \kappa_{\alpha\beta} c^\alpha e^{\langle \alpha, u \rangle} \langle \beta - \alpha, u \rangle.$$

Now for any two real numbers  $a$  and  $b$  we have that

$$e^a(b-a) \leq e^b - e^a$$

with equality if and only if  $a = b$ . Taking  $a = \langle \alpha, u \rangle$  and  $b = \langle \beta, u \rangle$  gives

$$dW(u)f(u) \leq \sum_{\alpha, \beta} \kappa_{\alpha\beta} c^\alpha \left( e^{\langle \alpha, u \rangle} - e^{\langle \beta, u \rangle} \right)$$

with equality if and only if  $\langle \alpha, u \rangle = \langle \beta, u \rangle$  for all  $\alpha, \beta$  such that  $\kappa_{\alpha\beta} > 0$ , i.e. if and only if  $u \in \mathbf{S}^\perp$ , i.e. if and only if  $x = \Phi(u)$  is a balanced equilibrium. Let  $\Omega = \sum_{\alpha} e^{\langle \alpha, u \rangle} \omega_\alpha \in \mathbb{R}^C$ . Then  $e^{\langle \alpha, u \rangle} = \langle \omega_\alpha, \Omega \rangle$  so the last inequality can be written

$$dW(u)f(u) \leq \left\langle \sum_{\alpha, \beta} \kappa_{\alpha\beta} c^\alpha (\omega_\alpha - \omega_\beta), \Omega \right\rangle = \langle A\Psi(c), \Omega \rangle = 0$$

as  $c$  is a balanced equilibrium.  $\square$

**Remark 20.** The function  $W$  has form  $W(x) = \sum_i W_i(x_i)$  where each  $W_i$  maps  $\mathbb{R}$  onto  $\mathbb{R}$ . Such a function can never be proper if the sum contains more than one term. We can take  $x_{n,1} = n$ , choose  $x_{n,2}$  to solve  $W_1(x_{n,1}) + W_2(x_{n,2}) = 0$ , and  $x_{n,i} = 0$  for  $i > 2$ . Then the sequence  $W(x_n)$  converges (it is constant) but the sequence  $x_n$  contains no convergent subsequence. Because  $W$  is not proper, Theorem 19 does not prove that every integral curve converges to an equilibrium.

**Definition 21.** The **deficiency** of the mass action kinetics dynamical system (5) is the dimension of the intersection  $\ker(Y) \cap A(\mathbb{R}^C)$  of the kernel of  $Y : \mathbb{R}^C \rightarrow \mathbb{R}^S$  with the image of the map  $A : \mathbb{R}^C \rightarrow \mathbb{R}^C$ . The point of this definition is the following

**Proposition 22.** *If the deficiency is zero, then every equilibrium is balanced.*

*Proof.* If  $YA\Psi(c) = 0$  then  $A\Psi(c) \in \ker(Y) \cap A(\mathbb{R}^C)$ .  $\square$

**Theorem 23.** *If the deficiency is zero and the network is weakly reversible, then there is a balanced equilibrium.*

*Proof.* Define diffeomorphisms  $\Lambda : \mathbb{P}^C \rightarrow \mathbb{R}^C$  and  $\lambda : \mathbb{P}^S \rightarrow \mathbb{R}^S$  by

$$\lambda(\xi)_\alpha = \ln(\xi_\alpha), \quad \lambda(x)_i = \ln(x_i)$$

for  $\alpha \in \mathcal{C}$  and  $i \in \mathcal{S}$ . (Thus  $\Lambda = \Phi^{-1}$  where  $\Phi$  is as in (7) with  $c_i = 1$ .) Then with the notation used in Equation (5) we have for  $\xi \in \mathbb{R}^C$  and  $c \in \mathbb{P}^S$  that

$$\langle \Lambda \circ \Psi(c), \xi \rangle = \sum_{\alpha} \ln(c^\alpha) \xi_\alpha = \sum_{\alpha} \langle \alpha, \lambda(c) \rangle \xi_\alpha = \left\langle \sum_{\alpha} \xi_\alpha Y \omega_\alpha, \lambda(c) \right\rangle = \langle Y\xi, \lambda(c) \rangle$$

so

$$\Lambda \circ \Psi(c) = Y^\top \lambda(c).$$

Introduce the abbreviation

$$K^+ := \ker(A) \cap \mathbb{P}^C.$$

Our goal is to find  $c \in \mathbb{P}^S$  with  $\Psi(c) \in K^+$ . Let

$$\zeta_a = \sum_{\alpha \in \mathcal{C}_a} \zeta_{a,\alpha} \omega_\alpha$$

be the basis vector for  $\ker(A)$  constructed in the proof of Proposition 15. Then for any vector  $\zeta = \sum_{a=1}^k \mu_a \zeta_a$  in  $K^+$  we have

$$\Lambda(\zeta) = \sum_{a=1}^k \ln(\mu_a) \omega_{\mathcal{C}_a} + \sum_{a=1}^k \sum_{\alpha \in \mathcal{C}_a} \ln(\zeta_{a,\alpha}) \omega_\alpha$$

where we used the definition  $\omega_{\mathcal{C}_a} = \sum_{\alpha \in \mathcal{C}_a} \omega_\alpha$ . As we noted in the proof of Proposition 15 the vectors  $\omega_{\mathcal{C}_a}$  form a basis for  $\mathbf{F}^\perp$  so this shows that  $\Lambda$  sends  $K^+$  onto a translate of  $\mathbf{F}^\perp$ . Since the system is weakly reversible we have  $A(\mathbb{R}^C) = \mathbf{F}$  by Proposition 15 so since the deficiency is zero we have

$$\mathbb{R}^C = (\ker(Y) \cap A(\mathbb{R}^C))^\perp = \ker(Y)^\perp + A(\mathbb{R}^C)^\perp = Y^\top(\mathbb{R}^S) + \mathbf{F}^\perp.$$

Hence  $\Lambda(K^+) = Y^\top u + \mathbf{F}^\perp$  for some  $u \in \mathbb{R}^S$  so  $Y^\top v \in \Lambda(K^+)$  for some  $v \in \mathbb{R}^S$  so with  $c = \lambda^{-1}(v)$  we have  $\Lambda(\Psi(c)) = Y^\top \lambda(c) \in \Lambda(K^+)$  and hence  $\Psi(c) \in K^+$  as required.  $\square$

**Conjecture 24** (Feinberg 1987). *If the network is weakly reversible, then the kinetics are **persistent**, i.e. the  $\omega$  limit set of every orbit starting in  $\mathbb{P}^S$  avoids  $\partial\mathbb{P}^S$ .*

## References

- [1] Martin Feinberg: *Lectures on Chemical Reaction Networks*, Lectures delivered at the Mathematics Research Center, University of Wisconsin Madison, Fall 1979. <http://www.chbmeng.ohio-state.edu/~FEINBERG/LecturesOnReactionNetworks/>
- [2] Jeremy Gunawardena: *Chemical reaction network theory for in-silico biologists*, <http://www.jeremy-gunawardena.com/papers/crnt.pdf>