Notes on Chemical Reaction Networks

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These notes are shamelessly cribbed from the extremely helpful online notes [2]. Even most of the notation is the same. I wrote them because, like Goethe's Frenchman, I wanted to translate Gunawardena's notes 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 nonnegative integers are denoted respectively by

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

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**

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

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 α by

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

2. Definition. A **chemical reaction network** is a quadruple $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ where $\mathcal{S}$, $\mathcal{C}$, $\mathcal{R}$ are finite sets with

$$\mathcal{C} \subset \mathbb{N}^{\mathcal{S}}, \qquad \text{and} \qquad \mathcal{R} \subset \mathbb{N}^{\mathcal{S}}$$

and $\kappa : \mathcal{R} \to \mathbb{P}$, i.e. $\kappa \in \mathbb{P}^{\mathcal{R}}$. The $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ determines a system of polynomial differential equations on $\mathbb{R}^{\mathcal{S}}$

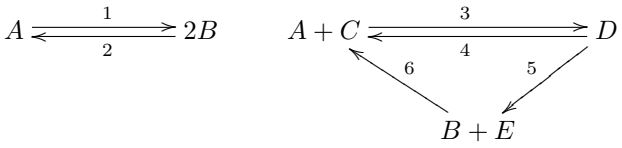
$$\dot{x} = \sum_{(\alpha,\beta) \in \mathcal{R}} \kappa_{\alpha\beta} x^{\alpha} (\beta - \alpha). \tag{1}$$

The finite set $\mathcal{S}$ is called the set of **species**, the finite set $\mathcal{C}$ of multi-indices 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. Thus a complex is a multi-set of species and each reaction is between a pair of complexes. 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 $\alpha \to \beta$ instead of $(\alpha, \beta) \in \mathcal{R}$, i.e.

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

The idea behind equation (1) is that whenever a chemical reaction $\alpha \to \beta$ occurs, β_i molecules of species i are created, α_i molecules of species i are destroyed, and the reaction occurs at a rate proportional to x^α where x_i is the amount of species i present.

3. Example. Engineers represent a chemical reaction network as in the following example:



Here $\mathcal{S} = \{A, B, C, D, E\}$, $\mathcal{C} = \{A, 2B, A+C, D, B+E\}$, $\mathcal{R} = \{A \to 2B, 2B \to A, A+C \to D, D \to A+C, D \to B+E, B+E \to A+C\}$, and $X \to Y$ means (X, Y). Thus $A, B, \ldots$ are indeterminates, and the expressions $A, 2B, A+C, \ldots$ represent multi-indices. The corresponding ODE is

$$\begin{aligned}
\dot{x}_A &= -(\kappa_{A\to 2B})x_A + (\kappa_{2B\to A})x_B^2 - (\kappa_{A+C\to D})x_A x_C + (\kappa_{D\to A+C})x_D + (\kappa_{B+E\to A+C})x_B x_E \\
\dot{x}_B &= 2(\kappa_{A\to 2B})x_A - 2(\kappa_{2B\to A})x_B^2 + (\kappa_{D\to B+E})x_D - (\kappa_{B+E\to A+C})x_B x_E \\
\dot{x}_C &= -(\kappa_{A+C\to D})x_A x_C + (\kappa_{D\to A+C})x_D + (\kappa_{B+C\to A+C})x_B x_E \\
\dot{x}_D &= +(\kappa_{A+C\to D})x_A x_C - (\kappa_{D\to A+C})x_D - (\kappa_{D\to B+E})x_D \\
\dot{x}_E &= +(\kappa_{D\to B_E})x_D - (\kappa_{B+E\to A+C})x_B x_E
\end{aligned}$$

Replacing the subscripts by numerals gives

$$\begin{aligned}
\dot{x}_1 &= -\kappa_1 x_1 + \kappa_2 x_2^2 - \kappa_3 x_1 x_3 + \kappa_4 x_4 + \kappa_5 x_2 x_5 \\
\dot{x}_2 &= 2\kappa_1 x_1 - 2\kappa_2 x_2^2 + \kappa_5 x_4 - \kappa_6 x_2 x_5 \\
\dot{x}_3 &= -\kappa_3 x_1 x_3 + \kappa_4 x_4 + \kappa_6 x_2 x_5 \\
\dot{x}_4 &= \kappa_3 x_1 x_3 - \kappa_4 x_4 - \kappa_5 x_4 \\
\dot{x}_5 &= \kappa_5 x_4 - \kappa_6 x_2 x_5
\end{aligned}$$

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

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

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

$$p_i(x) = b_i(x) + x_i a_i(x) \tag{3}$$

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 $\beta_i = \alpha_i - 1$. □

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

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

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.

6. Corollary. 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 $\varepsilon \to 0$ we conclude (by the continuity of the solution of the differential equation with respect to ε) 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 $u : I \to \mathbb{R}^{\mathcal{S}}$ 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 $u(t) \in \mathbb{P}^{\mathcal{S}}$ (i.e. $u_j(t) > 0$ for all $j \in \mathcal{S}$) and all $0 \leq t < \bar{t}$ and $x(\bar{t}) \notin \mathbb{P}^{\mathcal{S}}$. Define

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

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 $t = \bar{t}$ if 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 $u(\bar{t}) \in \mathbf{X}$. □

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

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

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

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

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

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

and $\Psi : \mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{C}}$ 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 $K, D : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ are defined by

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

8. Definition. 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 γ is destroyed equals the rate at which it is produced.

9. Conjecture. [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.)

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

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

of $\mathcal{C}$ (without repetitions) determines a one-one correspondence between the standard basis vectors ω_{α} 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 $A, K, D : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$. The (α, β) 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 (α, β) of indices, some positive power of P has a positive (α, β) entry. The following lemma holds for any square matrix K with nonnegative entries.

11. Lemma. 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 1×1 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 $\gamma_0, \ldots, \gamma_m \in \mathcal{C}$ such that $\gamma_0 = \alpha$, $\gamma_m = \beta$ and $\gamma_{i-1} \to \gamma_i$ for $i = 1, \ldots m$. Equivalently $\alpha \Rightarrow \beta$ iff either $\alpha = \beta$ or the (α, β) entry in K^m is nonzero for some $m > 0$. We say that α and β are **linked** iff both $\alpha \Rightarrow \beta$ and $\beta \Rightarrow \alpha$. The equivalence classes of this equivalence relation are called the **linkage classes**.

Let $\mathcal{C}_1, \mathcal{C}_2, \ldots, \mathcal{C}_k$ 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 (α, β) 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 α, so $\alpha \Rightarrow \beta$ and $\beta \Rightarrow \alpha$ and hence some positive power of K_{aa} has a positive (α, β) entry and some other positive power has a positive (β, α) entry. The product of these two powers has a positive (α, α) 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 1×1 and irreducible. □

12. Definition. Continue the notation and terminology of Lemma 11 and its proof. The network is said to be **strongly reversible** iff $\beta \to \alpha$ whenever $\alpha \to \beta$. 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 $(\mathcal{C}, \mathcal{R})$.

13. Proposition. 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 β. Then (6) implies that $\sum_\alpha c^\alpha \kappa_{\alpha\gamma} = 0$, so $\kappa_{\alpha\gamma} = 0$ for all α (as $c^\alpha > 0$). But this contradicts $\gamma \in \mathcal{C}$ as $\mathcal{C}$ is the set of $\gamma \in \mathbb{N}^{\mathcal{S}}$ such that either $\gamma \to \beta$ for some β or $\alpha \to \gamma$ for some α.

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. □

14. The subspaces

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

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 $Y : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{S}}$ defined above.) The intersection of a translate of $\mathbf{S}$ with the positive cone $\mathbb{P}^{\mathcal{S}}$ is called (if it is nonempty) a **positive stoichiometric compatibility class**.

15. A vector $\xi \in \mathbb{R}^{\mathcal{C}}$ 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 $\xi \in \mathbb{R}^{\mathcal{C}}$ such that $\xi_\beta = \xi_\alpha$ whenever $\kappa_{\alpha\beta} > 0$. A vector $u \in \mathbb{R}^{\mathcal{S}}$ lies the orthogonal complement $\mathbf{S}^\perp$ to the stoichiometric subspace $\mathbf{S}$ if and only if $\langle \alpha - \beta, u\rangle = 0$ whenever $\kappa_{\alpha\beta} > 0$.

16. Proposition. The image $A(\mathbb{R}^{\mathcal{C}})$ 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 $\mathbf{F} \subseteq \mathbb{R}^{\mathcal{C}}$. By the part (iii) of definition 12 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 $A(\mathbb{R}^{\mathcal{C}})$ of A is the same as the dimension of the kernel of A so it suffices to a basis $\zeta_1, \zeta_2, \ldots, \zeta_k$ for the kernel. The number k of linkage classes is also the number of diagonal blocks in the block decomposition of K in Lemma 11. 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 $\mathbb{R}^{\mathcal{C}}$ by setting the components indexed by the complement to $\mathcal{C}_a$ to zero. Denote the product of this vector with D by ζ_a. Then $A\zeta_a = K\zeta_a - D\zeta_a = 0$ and the vectors ζ_n form a basis for the kernel of A. □

17. Proposition. 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 6. □

18. Choose $c \in \mathbb{P}^{\mathcal{S}}$ and define a diffeomorphism $\Phi : \mathbb{R}^{\mathcal{S}} \to \mathbb{P}^{\mathcal{S}}$ via the formula

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

We denote the set of balanced equilibria by

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

19. Theorem. 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 Φ 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 satisifes (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^{α} and also the row vector with components x^{α} 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 α to $\mathcal{C}_a$ we see that 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 $\alpha \to \beta$, 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 $\phi : \mathbb{R}^{\mathcal{S}} \to \mathbb{R}$ defined by

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

The gradient of ϕ is $\Phi(u) - b$. It is enough to show that the restriction of ϕ 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.

$\Phi(u) - b \in \left(\mathbf{S}^{\perp}\right)^{\perp} = \mathbf{S}$ and so $\Phi(u) \in b + \mathbf{S}$. The function ϕ 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 ϕ 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 ϕ 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 $\phi(w + sv) \to \infty$ as $s \to \infty$. 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 $\phi(w + sv) \to \infty$ as $s \to \infty$. Now on the boundary of a sufficiently large ball ϕ takes values strictly greater than its value at the center of that ball. Therefore ϕ must have an interior minimum which is the desired critical point. (Since ϕ has a positive definite Hessian, Morse theory tells us that it has only one critical point; this provides an alternate proof of Step 3.) □

20. Theorem. If the system (1) has a balanced equilibrium c, then the function $V : \mathbb{P}^{\mathcal{S}} \to \mathbb{R}$ 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 Φ to rewrite (1) as a differential equation on $\mathbb{R}^{\mathcal{S}}$. 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

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

so

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

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 α, β 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 $\Omega = \sum_{\alpha} e^{\langle \alpha, u\rangle} \omega_{\alpha} \in \mathbb{R}^{\mathcal{C}}$. 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. □

21. Remark. 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 20 does not prove that every integral curve converges to an equilibrium.

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

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

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

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

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

$$\lambda(\xi)_{\alpha} = \ln(\xi_{\alpha}), \qquad \lambda(x)_i = \ln(x_i)$$

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

$$\Lambda \circ \Psi(c) = Y^{\mathsf{T}} \lambda(c).$$

Introduce the abbreviation

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

Our goal is to find $c \in \mathbb{P}^{\mathcal{S}}$ 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 16. 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 16 the vectors $\omega_{\mathcal{C}_a}$ form a basis for $\mathbf{F}^\perp$ so this shows that Λ sends K^+ onto a translate of $\mathbf{F}^\perp$. Since the system is weakly reversible we have $A(\mathbb{R}^{\mathcal{C}}) = \mathbf{F}$ by Proposition 16 so since the deficiency is zero we have

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

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

25. Conjecture.[Feinberg 1987] If the network is weakly reversible, then the kinetics are **persistent**, i.e. the ω limit set of every orbit starting in $\mathbb{P}^{\mathcal{S}}$ avoids $\partial \mathbb{P}^{\mathcal{S}}$.

References

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