CHEMICAL REACTION NETWORK THEORY

Contents

Date: December 9, 2016.

1. Notations

All operations (x^y, $ln(x)$), inequalities ($x \geq 0$), etc are to be understood **component-wise**. The support of a vector x is the set of indices $\text{supp}(x) = \{i\,, x_i > 0\}$.

2. Network definition

- **Species**: Finite set $\mathcal{E} = \{E^1\,, \cdots, E^d\}$. We identify $\mathbb{R}^{\mathcal{E}} \rightsquigarrow \mathbb{R}^d$
- **Complexes**: Finite set $\mathcal{C} = \{y^1\,, \cdots, y^n\}$. We identify $y \in \mathcal{C}$ as a vector in $\mathbb{R}^d$,
$$y = \begin{pmatrix} y_1 \\ \vdots \\ y_d \end{pmatrix}, \quad y_i = \text{stoichiometry of } E^i \text{ in } y.$$
Moreover, We identify $\mathbb{R}^{\mathcal{C}} \rightsquigarrow \mathbb{R}^n$, and $\{e_{y_1}\,, \cdots, e_{y_n}\} = \{e_1\,, \cdots, e_n\}$ as the canonical orthonormal basis.
- **Reaction**: Finite set $\mathcal{R} = \{y \to y'\}$. We identify $y \to y'$ with the vector $y' - y$ in $\mathbb{R}^n$. We denote the cardinal by $\mid \mathcal{R} \mid= r$.
- **Law of mass action**, kinetic rates: Finite set $\kappa = \{\kappa_{y \to y'}\,, y \to y' \in \mathcal{R}\}$

3. Deterministic mass-action CRN

The **deterministic** system associated to the CRN $(\mathcal{E}, \mathcal{C}, \mathcal{R}, \kappa)$ is given by an initial condition $x(0) = x_0 \in \mathbb{R}^d_+$ and
$$\frac{dx}{dt} = \sum_{y \to y' \in \mathcal{R}} \kappa_{y \to y'} x^y (y' - y)\,. \tag{1}$$

4. Stochastic mass-action CRN

The **stochastic** system associated to the CRN $(\mathcal{E}, \mathcal{C}, \mathcal{R}, \kappa)$ is given by an initial condition $X(0) = X_0 \in \mathbb{N}^d$ and
$$X(t) = X(0) + \sum_{y \to y' \in \mathcal{R}} P_{y \to y'} \left(\int_0^t \lambda_{y \to y'}(X(s))ds \right) (y' - y)\ , \tag{2}$$
where $\lambda_{y \to y'}(n) = \kappa_{y \to y'} \frac{n!}{(n-y)!} \mathbf{1}_{n \geq y}$, and $(P_{y \to y'}, y \to y' \in \mathcal{R})$ is a family of standard independent Poisson processes.

Remark 1. Other formulations

- Continuous Time Markov chain on $\mathbb{N}^d$ with transition
$$n \mapsto n + y' - y\,,\ \text{with rate } \lambda_{y \to y'}(n) \tag{3}$$
- Infinetesimal Generator
$$\mathcal{A}\varphi(n) = \sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(n) \left[\varphi(n + y' - y) - \varphi(n) \right] \tag{4}$$
- Chemical Master Equation
$$\frac{dp_t(n)}{dt} = \sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(n - y' + y) p_t(n - y' + y) - p_t(y) \sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(n) \tag{5}$$

5. Mapping

- **Complex composition matrix**: $Y : \mathbb{R}^n \to \mathbb{R}^d$ is the linear application defined by $Y(e_y) = y$, for all $y \in \mathcal{C}$.

  In particular, Y can be represented as a $\mathcal{M}_{d\times n}$ matrix, with

$$Y_{ij} = y_i^j \quad , 1 \leq i \leq d \, , 1 \leq j \leq n \, . \tag{6}$$

- **Complex graph matrix**: $A_\kappa : \mathbb{R}^n \to \mathbb{R}^n$ defined by

$$A_\kappa(z) = \sum_{y\to y' \in \mathcal{R}} \kappa_{y\to y'} z_y (e_{y'} - e_y) \, . \tag{7}$$

  In particular, A_κ can be represented as a $\mathcal{M}_{n\times n}$ matrix, with

$$A_\kappa^{ij} = \begin{cases} \kappa_{j\to i} \, , & \text{if } j \neq i \, , \\ -\sum_{l\neq j} \kappa_{j\to l} \, , & \text{if } j = i \, . \end{cases} \tag{8}$$

  We also have $A_\kappa = A - \mathrm{diag}(\mathbf{1}^T A)$, where

$$A_{ij} = \begin{cases} \kappa_{j\to i} \, , & \text{if } j \neq i \, , \\ 0 \, , & \text{if } j = i \, . \end{cases} \tag{9}$$

- **Propensity** vector: $\Psi : \mathbb{R}^d \to \mathbb{R}^n$ defined by

$$\Psi(x) = \sum_{y\in\mathcal{C}} x^y e_y \, . \tag{10}$$

  We identify $\Psi(x)$ as a vector in $\mathbb{R}^n$,

$$\Psi(x) = \begin{pmatrix} x^{y^1} \\ \vdots \\ x^{y^n} \end{pmatrix} \, .$$

Thus, the deterministic system can be re-written

$$\frac{dx}{dt} = f(x(t)) = \sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'} x^y (y' - y) = Y \circ A_\kappa \circ \Psi(x(t)) \, . \tag{11}$$

Also, we can notice that

$$\ln(\Psi(x)) = Y^T \ln(x) \, . \tag{12}$$

The last two relations are summarized with

$$\begin{array}{ccccccc} \mathbb{R}^{\mathcal{E}} = \mathbb{R}^d & \xrightarrow{\mathrm{f}} & \mathbb{R}^{\mathcal{E}} = \mathbb{R}^d & & \mathbb{R}^d_{>0} & \xrightarrow{\Psi} & \mathbb{R}^n_{>0} \\ \Psi \downarrow & & \uparrow Y & , & \ln \downarrow & & \uparrow \exp \\ \mathbb{R}^{\mathcal{C}} = \mathbb{R}^n & \xrightarrow{\mathrm{A}_\kappa} & \mathbb{R}^{\mathcal{C}} = \mathbb{R}^n & & \mathbb{R}^d & \xrightarrow{\mathrm{Y}^\mathrm{T}} & \mathbb{R}^n \end{array}$$

- **Reaction stoichiometry matrix** $\Gamma : \mathbb{R}^r \to \mathbb{R}^d$ is the linear application defined as a $\mathcal{M}_{d\times r}$ matrix, with

$$\Gamma_{ij} = y_i' - y_i \quad , 1 \leq i \leq d \, , 1 \leq j \leq r \, , \quad \text{where } y \to y' \in \mathcal{R} \text{is the j }^{th} \text{ reaction.} \tag{13}$$

- **Complex Incidence matrix** $I : \mathbb{R}^r \to \mathbb{R}^n$ is the linear application defined as a $\mathcal{M}_{n\times r}$ matrix, where columns are in one-to-one correspondence with the edges (reactions) and rows in one-to-one correspondence with the nodes (complexes), eg:

$$I_j = e_k - e_i \quad , 1 \leq j \leq r\,, \quad \text{where } y^i \to y^k \in \mathcal{R} \text{ is the j }^{th} \text{ reaction.} \tag{14}$$

- We verify that

$$\Gamma = Y I\,. \tag{15}$$

If we further define

$$k(x) := [k_1(x), \cdots, k_r(x)]\,, \tag{16}$$

with, for $1 \leq j \leq r$,

$$k_i(x) = \kappa_j x^y\,, \quad \text{where } y \to y' \in \mathcal{R} \text{ is the j }^{th} \text{ reaction}\,, \tag{17}$$

then Eq. (11) can be re-written

$$\frac{dx}{dt} = f(x(t)) = \sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'} x^y (y' - y) = \Gamma r(x(t)) = Y I r(x(t))\,. \tag{18}$$

Remark 2. Any non-zero row-vector $\nu \in \mathbb{R}^d$ that satisfies

$$\nu\Gamma = 0\,, \tag{19}$$

induces a conserved quantity, $\sum_{i=1}^d \nu_i E_i$. The network is said *conservative* if there exists a positive such row-vector ν.

Remark 3. The chemical reaction network is sometimes summarized by the set

$$\sum_{i=1}^d \alpha_{ij} E_i \to_{\kappa_j} \sum_{i=1}^d \beta_{ij} E_i\,, \quad j = 1\,, \cdots, r\,. \tag{20}$$

Then the reaction vectors have coordinates $(\beta_{ij} - \alpha_{ij})_{i=1,\cdots,d}$ and the matrix Γ is imply the matrix form of the reaction vectors, that is

$$\Gamma_{ij} = \beta_{ij} - \alpha_{ij}\,, \quad i = 1\,, \cdots, d\,, j = 1 \;\,, \cdots, r\,. \tag{21}$$

6. Network structure

- **Fixed point**: $x \in R^d_{\geq 0}$ such that $f(x) = 0$.
- **Positive Fixed point**: $x \in R^d_{>0}$ such that $f(x) = 0$.
- **Complex balanced equilibrium**: $x \in R^d_{>0}$ such that $A_\kappa \Psi(x) = 0$, e.g. such that for all $y \in \mathcal{C}$,

$$\text{(inflow into y)} \sum_{y'\to y\in\mathcal{R}} \kappa_{y'\to y} x^{y'} = \sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'} x^y \quad \text{(outflow from y)}\;\,. \tag{22}$$

- **Stoichiometric subspace**: $S = \operatorname{span}\{y' - y \mid y \to y' \in \mathcal{R}\}$. Dimension $s := \dim S$.
- **Stoichiometric compatibility class**: for all x$\in \mathbb{R}^d$, $S_x = (x + S) \cap \mathbb{R}^d_+$ (or $S_X = (X + S) \cap \mathbb{N}^d$).
- **Stoichiometric Complex subspace**: $T = \operatorname{span}\{e_{y'} - e_y \mid y \to y' \in \mathcal{R}\}$. Dimension: $\dim T = n - l$, where l is the number of linkage classes (see definition 1 and proposition 2).

Remark 4. It is clear that the dynamics of the dynamical system (1) or (2) is constrained to stay in a given stoichiometric compatibility class, $x(0) + S$ or $X(0) + S$, according to the initial condition. Thus the effective dimension of the system is at most $s \leq d$. A more sharper notion is given by the kinetic subspace (see [22, Appendix IV]) which is based on the observation that Eq. (1) can be re-written

$$\frac{dx}{dt} = \sum_{i=1}^{n} \left[\prod_{j=1}^{d} x_j^{y_j^i} \right] \sum_{y' :\, y^i \to y' \in \mathcal{R}} \kappa_{y^i \to y'} (y' - y_i) \,. \tag{23}$$

Thus, the effective dynamics lies inside the space generated by the linear combination of the vectors

$$d_i = \sum_{y' :\, y^i \to y' \in \mathcal{R}} \kappa_{y^i \to y'} (y' - y_i) \,. \tag{24}$$

It is clear however that the kinetic subspace depends on the precise value of the reaction rates

6.1. **Linkage classes.** We say y, y' are **directly linked**, denoted by $y \leftrightarrow y'$, if either $y \to y' \in \mathcal{R}$ or $y' \to y \in \mathcal{R}$. We define

Definition 1 (Linkage class)**.** The linkage relation is the equivalence relation on $\mathcal{C}$, denoted by $y \sim y'$, given by $y \sim y'$ if either $y = y'$ or if it exists $y^1, \cdots y^m$ such that $y = y^1 \leftrightarrow y^2 \leftrightarrow \cdots y^m = y'$. The linkage classes are the equivalence classes for the relation $\sim$, and are denoted by $L_1\,, \cdots, L_l$. Thus l is **the number of Linkage classes**.

The Linkage classes are the connected components of the non-directed graph $\mathcal{R}$.

Remark 5. Any two reaction networks with the same complexes and the same linkage classes (but not necessarily the same reactions) also have the same stoichiometric dimension s.

We also define characteristic vector associated to linkage classes,

$$e_{L_i} := \sum_{y \in L_i} = e_y. \tag{25}$$

We say that y **ultimately reacts** to y', denoted by $y \Rightarrow y'$, if either $y = y'$ or if it exists $y^1, \cdots y^m$ such that $y = y^1 \to y^2 \to \cdots y^m = y'$. We define

Definition 2 (strong Linkage class)**.** The strong Linkage relation is the equivalence relation on $\mathcal{C}$, denoted by $y \approx y'$, given by $y \approx y'$ if both $y \Rightarrow y'$ and $y' \Rightarrow y$. The strong Linkage classes are the equivalence classes for the relation $\approx$, and are denoted by $\overline{L}_1\,, \cdots, \overline{L}_p$. Thus p is **the number of strong Linkage classes**. If $i \in \overline{L}$, we also note $\overline{L} = [i]$.

Strong Linkage classes induces a sub-partition of the partition induced by the Linkage classes on the set of complexes. Thus, every Linkage class is a union of strong Linkage class (and then $p \geq l$).

Definition 3 (Terminal strong Linkage class)**.** The strong Linkage class $\overline{L}$ is **terminal** if no complex in $\overline{L}$ reacts to a complex outside $\overline{L}$. The Terminal strong Linkage classes are denoted by $T_1\,, \cdots, T_t$. Thus t is **the number of Terminal strong Linkage classes**.

Note that each linkage class necessarily contains at least one terminal strong linkage class (there is a finite number of reactions): in particular $t \geq l$. Hence,

$$p \geq t \geq l\,. \tag{26}$$

We also define the partial order on strong Linkage classes by

- $[i] \preccurlyeq [j]$ if, and only if, $i \Rightarrow j$ (this does not depend on the chosen element of each equivalent classes).
- We can re-order the strong Linkage classes and complexes such that, if $\overline{L}_u \preccurlyeq \overline{L}_v$, then $u \leq v$, and such that A_κ and A are block-wise triangular inferior,

$$A = \begin{pmatrix} A_1 & 0 & 0 & 0 \\ A(1,2) & \ddots & 0 & 0 \\ \vdots & \ddots & \ddots & 0 \\ A(1,p) & \cdots & A(p-1,p) & A_p \end{pmatrix} \tag{27}$$

6.2. **Reversibility.**

Definition 4 (Reversibility)**.** $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ is **reversible** if for any $y \to y' \in \mathcal{R}$, then $y' \to y \in \mathcal{R}$.
$(\mathcal{E}, \mathcal{C}, \mathcal{R})$ is **weakly reversible** if the strong linkage classes coincide with the linkage classes, or, equivalently,

$$\text{if } y \Rightarrow y' \text{ then } y' \Rightarrow y. \tag{28}$$

Remark 6. Weakly reversible networks are precisely those for which linkage classes, strong linkage classes and terminal strong Linkage classes coincide ($p = t = l$). For such networks, A and A_κ are block-wise diagonal. Similarly, one can show that networks such that each strong linkage class is a terminal strong linkage class ($p = t$), is a weakly reversible network. On the other hand, the networks for which $t = l$ is strictly larger than the set of weakly reversible networks (one may have $p > t = l$, see examples).

We will see when we will study the kernel of A_κ that

Proposition 1 ([21][Corollary 4.2)**.** *] Weak reversibility is equivalent to the existence of a strictly positive vector in the kernel of A_κ (or I).*

6.3. **Deficiency.**

Definition 5 (Deficiency)**.** The deficiency of a network is defined as

$$\delta = n - l - s\,. \tag{29}$$

Remark 7. Along with remark 5, one can show that a network composed with n complexes and l linkage classes have a stoichiometric subspace whose dimension cannot exceed $n - l$. Indeed, consider the minimal reaction network that connect complexes with a minimal number of reactions. It is not difficult to see that there is in such way only $n - l$ reactions, hence $\dim S = s \leq n - l$. Thus, $\delta \geq 0$. We will provide in Proposition 3 a more intuitive definition of the deficiency.

Remark 8. It also derives from remark 5 that the value of the deficiency of a network depends only of its complexes and the linkage classes (and not precisely on the nature of reactions within each linkage class).

7. Complex balanced

7.1. **Deterministic.** A complex balanced equilibrium is a concentration $c \in \mathbb{R}^d_{\geq 0}$ such that, for all $z \in \mathcal{C}$,

$$\underbrace{\sum_{y:\ y \to z \in \mathcal{R}} \kappa_{y \to z} c^y}_{\text{inflow}} = \underbrace{c^z \sum_{y':\ z \to y' \in \mathcal{R}} \kappa_{z \to y'}}_{\text{outflow}} \tag{30}$$

Note that complex balanced equilibrium might be located at the boundary of the state space.

A chemical reaction network $(\mathcal{E}, \mathcal{C}, \mathcal{R}, \kappa)$ is said complex balanced if there exists a *positive* complex balanced equilibrium. A chemical reaction network $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ is said undonditionnaly complex balanced if there exists a *positive* complex balanced equilibrium, whatever the choice of rate constants κ.

7.2. **Stochastic.** We need futher definition

Definition 6. Let $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ be a CRN.

a a reaction $y \to y'$ is active on $x \in \mathbb{N}^d$ if $x \geq y$.

b A stat u is accessible from x if there is $q \geq 0$ and a sequence $(y_j \to y'_j)_{j=1\ldots q})$ such that

$$u = x + \sum_{j=1}^{q} y'_j - y_j \tag{31}$$

and $y_h \to y'_h$ is active on $x + \sum_{j=1}^{h-1} y'_j - y_j$, for all $1 < h \leq q$.

c A nonempty set $\Gamma \subseteq \mathbb{N}^d$ is an irreducible component of $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ if for all $x \in \Gamma$, all $u \in \mathbb{N}^d$, u is accessible from x if, and only if, $u \in \Gamma$.

d A network is essential if the state space if the union of irreducible components, and almost essential if the state space if the union of irreducible components except for a finite number of states

e For an irreducible component Γ, the subnetwork $(\mathcal{E}_\Gamma, \mathcal{C}_\Gamma, \mathcal{R}_\Gamma)$ is the network composed of reactions that are active o some $x \in \Gamma$.

f An irreducible component Γ is said *positive* if $\mathcal{R}_\Gamma = \mathcal{R}$

Any irreducible component is contained in a stoichiometric compatibility class, and a stoichiometric compatibility class may contain several irreducible components. A weakly reversible network is essential [29].

The notion of complex balanced equilibrium has been adapted to stochastic network, by [11]

Definition 7. a A stationary distribution π_Γ on an irreducible component Γ is said to be complex balanced if, for all $z \in \mathcal{C}$,

$$\underbrace{\sum_{y \in \mathcal{C}: y \to z \in \mathcal{R}} \lambda_{y \to z}(x - z + y)\pi_\Gamma(x - z + y)}_{\text{inflow}} = \underbrace{\pi_\Gamma(x) \sum_{y' \in \mathcal{C}: z \to y' \in \mathcal{R}} \lambda_{z \to y'}(x)}_{\text{outflow}}, \quad \forall x \in \Gamma.$$

b A stochastic CRN $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ is said stochastically complex balanced if there exists a complex balanced distribution on a positive irreducible component.

8. Deficiency 0 theorem

8.1. **Deterministic.**

Theorem 1 (Horn, Jackson, Feinberg, 70$'$)**.** *Soit $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ un réseau qui vérifie les deux conditions suivantes:*

- *La déficience $\delta = 0$*
- *Faiblement réversible.*

Alors, le modèle déterministe associé vérifie:

- *Quelque soit les choix des constantes κ, à l'intérieur de chaque classe de compatibilité stoechiométrique, il y a exactement un point fixe strictement positif.*
- *Ce point fixe est localement asymptotiquement stable.*
- *Ce point est un point d'équilibre des complexes.*

Remark 9. For sharper conclusion on zero deficiency network, and information on which species might extinct, see [22, Section 6.1]. In particular, it is proven there that for zero deficiency network, if x^* is a steady state, then, for any complex y, $\mathrm{supp}(c^*)$ contains $\mathrm{supp}(y)$ only if y is a member of a terminal strong linkage class.

We also have a reciprocal property

Theorem 2 ([25]). *A chemical reaction network $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ is unconditionally complex balanced (e.g. there exists a positive complex balanced equilibrium, whatever the rate constants are) if, and only if,:*

- *The deficiency $\delta = 0$*
- *It is weakly-reversible.*

Furthermore, the following say that weakly-reversible non-zero deficiency network are somehow more intricate

Theorem 3 ([25]). *Let $x \in \mathbb{R}^d_{>0}$ be some positive concentration of the species space of a given weakly reversible chemical reaction network $(\mathcal{E}, \mathcal{C}, \mathcal{R})$. Then the following hold:*

a *There exists a set of reaction rates κ such that $(\mathcal{E}, \mathcal{C}, \mathcal{R}, \kappa)$ is complex balanced and for which x is an equilibrium concentration.*

b *In addition, if the network has non-zero deficiency, there is a set of reaction rates κ such that $(\mathcal{E}, \mathcal{C}, \mathcal{R}, \kappa)$ is not complex balanced and for which x is an equilibrium concentration.*

We also have a complete characterization of zero-deficiency network

Theorem 4 ([22]). *Let $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ be a zero-deficiency chemical reaction network. Then*

a *If the network is not weakly-reversible, then there exists no positive equilibria*

b *If the network is weakly-reversible, then there exists a unique positive equilibrium within each stoichiometric compatibility class (which is asymptotically stable).*

8.2. Stochastic.

Theorem 5 ([4]). *Soit $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ un réseau qui vérifie les deux conditions suivantes:*

- *La déficience $\delta = 0$*
- *Faiblement réversible.*

Alors, le modèle stochastique associé a pour distribution stationnaire le produit de loi de Poisson

$$\pi(x) = \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!} e^{-c_i}\,, x \in \mathbb{N}^d\,. \tag{32}$$

où c est un vecteur positif d'équilibre des complexes. De plus

- *Si $\mathbb{N}^d$ est irréductible, l'unique distribution est un produit de distribution de Poisson indépendante donné par (32).*
- *Si $\mathbb{N}^d$ n'est pas irréductible, alors chaque distribution stationnaire s'écrit*

$$\pi = \sum_{\Gamma} \alpha_\Gamma \pi_\Gamma\,, \tag{33}$$

où les π_Γ sont donnés par

$$\pi_\Gamma(x) = M_\Gamma \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!}\,, x \in \Gamma\,, \quad \pi_\Gamma(x) = 0 \text{ otherwise.} \tag{34}$$

avec M_Γ une constante positive de normalisation, et Γ une composante irréductible.

Dans le deuxième cas, la distribution est multinomiale (produit de Poisson indépendante dont la somme est contrainte) sur chaque composante irréductible.

The result in [4] is actually stronger:

Theorem 6. *If the network $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ is complex balanced, then there exists a unique stationary distribution on every irreducible component Γ, given by Eq. (34).*

In particular, the proof of this result only uses the existence of a *positive* complex balance equilibrium. The authors in [11] provide few additional interesting results

Theorem 7. *Let $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ be a CRN, and Γ an irreducible component. If there exists a complex balanced stationary distribution π_Γ on Γ, then $\mathcal{R}_\Gamma$ is weakly reversible. Morover, there exists such stationary distribution if, and only if, $(\mathcal{E}_\Gamma, \mathcal{C}_\Gamma, \mathcal{R}_\Gamma)$ is (deterministically) complex balanced.*

In particular, we deduce that stochastically complex balance and deterministically complex balance are equivalent notions for a CRN. They also provide a full characterization of zero deficiency network

Theorem 8. *Let $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ be a zero-deficiency CRN. Then*

- *if $\mathcal{R}$ is not weakly reversible, then there exist no positive irreducible component. Moreover, let Γ an irreducible component. Then $y \to y' \in \mathcal{R}$ is active on Γ only if $y \to y'$ is terminal, and the stationary distribution has the product form*

$$\pi_\Gamma(x) = M_\Gamma \prod_{i: E_i \in \mathcal{E}^*} \frac{c_i^{x_i}}{x_i!}\,, x \in \Gamma\,, \quad \pi_\Gamma(x) = 0 \text{ otherwise}, \tag{35}$$

  where $(\mathcal{E}^*, \mathcal{C}^*, \mathcal{R}^*)$ is the subnetwork composed by the set of terminal reactions.
- *if $\mathcal{R}$ is weakly reversible, then it is essential, and there exists a unique stationary distribution on every irreducible component (given by Eq. (34)).*

The characterization of network such that the stationary distribution is product-form on some or all irreducible components is partially provided by

Theorem 9 ([11])**.** *Let $(\mathcal{E}, \mathcal{C}, \mathcal{R})$ be an almost essential CRN, and $c \in \mathbb{R}^d_{>0}$. Then the probability distribution given by Eq. (34) is stationary on all irreducible components if, and only if c is a complex balanced equilibrium.*

However, it is shown in the examples that the class of network that has a product form stationary distribution is actually strictly bigger.

9. Exemple

9.1. Number of linkage classes and weak-reversibility.

$$\begin{array}{ccccc} A_1 \rightleftarrows A_2 + A_3 & \to & A_4 & \to & A_5 \\ & & & \nwarrow & \updownarrow \\ & & & & 2A_6 \\ A_4 + A_5 & \to & A_7 & & \end{array}$$

- $\mathcal{E} := \{A_1, \cdots, A_7\}$
- $\mid \mathcal{C} \mid = 7$
- $l = 2$, $p = 4$, $t = 2$
- Not weakly reversible

$$\begin{array}{ccccccc} A_1 \rightleftarrows A_2 + A_3 & \rightarrow & A_4 & \rightarrow & A_5 \\ & & & \searrow & \updownarrow \\ & & & & 2A_6 \\ A_4 + A_5 & \rightleftarrows & A_7 & & \end{array}$$

- $\mathcal{E} := \{A_1, \cdots, A_7\}$
- $\mid \mathcal{C} \mid = 7$
- $l = 2$, $p = 4$, $t = 2$
- Not weakly reversible

$$B \quad \leftarrow \quad A \quad \rightarrow \quad C$$

- $\mathcal{E} := \{A, B, C\}$
- $\mathcal{C} = \{A, B, C\}$
- $l = 1$, $p = 3$, $t = 2$
- Not weakly reversible. $\delta = 0$ $(n = 3, s = 2, l = 1)$.

$$\begin{array}{ccccc} B & \leftarrow & A & \rightarrow & C \\ B + C & \rightarrow & 2A & & \end{array}$$

- $\mathcal{E} := \{A, B, C\}$
- $\mathcal{C} = \{A, B, C, B + C, 2A\}$
- $l = 2$, $p = 5$, $t = 3$
- Not weakly reversible. $\delta = 1$ $(n = 5, s = 2, l = 2)$.
- Depending on the kinetic rates, there may be no steady states or an infinite number of positive steady states in each stoichiometric compatibility class, but a single one in each kinetic compatibility class (see [22, Appendix IV])

9.2. **Deficiency and weak-reversibility.**

$$\begin{array}{ccc} A & \rightleftarrows & 2B \\ A + C & \rightleftarrows & D \\ \nwarrow & & \swarrow \\ & B + E & \end{array}$$

- $\mathcal{E} := \{A, B, C, D, E\}$
- $\mathcal{C} := \{A, 2B, A + C, D, B + E\}$
- Weakly-reversible, $\delta = 0$ $(n = 5, l = 1, s = 2)$.

$$A + E \quad \rightleftarrows \quad AE \quad \rightarrow \quad B + E$$

- $\mathcal{E} := \{A, B, E\}$
- $\mathcal{C} := \{A + E, AE, B + E\}$
- Not weakly-reversible, $\delta = 0$ $(n = 3, l = 1, s = 2)$.

$$A + E \quad \rightleftarrows \quad AE \quad \rightleftarrows \quad B + E$$

- $\mathcal{E} := \{A, B, E\}$
- $\mathcal{C} := \{A + E, AE, B + E\}$
- Weakly-reversible, $\delta = 0$ $(n = 3, l = 1, s = 2)$.

$$A + B \quad \rightleftarrows \quad 2A$$

- $\mathcal{E} := \{A, B\}$

- $\mathcal{C} := \{A+B, 2A\}$
- $l=1$, $p=1$, $t=1$, Weakly-reversible
- $\delta = 0$ $(n=2, l=1, s=1)$.
- There exists boundary complex balanced equilibrium : $(0, x_2)$ for any $x_2 > 0$.

$$\begin{array}{ccc} A+B & \rightarrow & 3A \\ \uparrow & & \downarrow \\ 2B & \leftarrow & 2A+C \end{array}$$

- $\mathcal{E} := \{A, B, C\}$
- $\mathcal{C} := \{A+B, 3A, 2A+C, 2B\}$
- $l=1$, $p=1$, $t=1$, Weakly-reversible
- $\delta = 0$ $(n=4, l=1, s=3)$.
- There exists boundary complex balanced equilibrium : $(0, 0, x_3)$ for any $x_3 > 0$.

$$\begin{array}{ccccc} A+E & \rightleftarrows & AE & \rightleftarrows & B+E \\ B & \rightarrow & \emptyset & \rightarrow & A \end{array}$$

- $\mathcal{E} := \{A, B, E\}$
- $\mathcal{C} := \{A+E, AE, B+E, A, B, \emptyset\}$
- Not weakly-reversible, $\delta = 1$ $(n=6, l=t=2, s=3)$.
- but there exists a unique positive equilibrium point in each stoichiometric classes

$$\begin{array}{ccccc} A+E & \rightleftarrows & AE & \rightarrow & B+E \\ B+F & \rightleftarrows & BF & \rightarrow & A+F \end{array} \tag{36}$$

- $\mathcal{E} := \{A, B, E, F\}$
- $\mathcal{C} := \{A+E, AE, B+E, B+F, BF, A+F\}$
- Not Weakly-reversible
- $\delta = 1$ $(n=6, l=t=2, s=3)$.
- but there exists a unique positive equilibrium point in each stoichiometric classes

$$\begin{array}{ccc} 3A & \rightarrow & A+2B \\ \uparrow & & \downarrow \\ 2A+B & \leftarrow & 3A \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{3A, A+2B, 3B, 2A+B, 3A\}$
- Weakly-reversible $(l=t=p=1)$
- $\delta = 2$ $(n=4, l=1, s=1)$.
- It may admit three positive steady states in each stoichiometric compatibility classes. However, if all kinetic rates are equal to 1, then it is complex balanced.

$$\begin{array}{ccccc} A_1+A_2 \rightleftarrows A_3 & \rightarrow & A_4+A_5 & \rightleftarrows & A_6 \\ 2A_1 & \rightarrow & A_2+A_7 & & \\ & \nwarrow & \updownarrow & & \\ & & A_8 & & \end{array}$$

- $\mathcal{E} := \{A_1, \cdots, A_8\}$
- $\mid \mathcal{C} \mid = 8$
- $l=2$, $p=3$, $t=2$. Not weakly reversible.
- $\delta = 0$ $(n=7, s=5, l=2)$.
- No positive steady state nor sustained oscillations.

$$\begin{array}{ccccc} 0 & \rightleftarrows & A & \rightarrow & B \\ 2A+B & \rightarrow & 3A & & \end{array}$$

- "Brusselator"
- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{0, A, B, 2A+B, 3A\}$
- $l = 2$, $p = 4$, $t = 2$, Not weakly-reversible
- $\delta = 1$ $(n = 5, l = 2, s = 2)$.
- (for certain kinetic rates), it admits an unstable positive steady-state and a positive limit cycle.

$$\begin{array}{ccccc} A & \rightleftarrows & 2A & & \\ A+B & \rightleftarrows & C & \rightleftarrows & B \end{array}$$

- "Edelstein network"
- $\mathcal{E} := \{A, B, C\}$
- $\mathcal{C} := \{A, B, A+B, C, 2A\}$
- $l = 2$, $p = 2$, $t = 2$, Weakly-reversible
- $\delta = 1$ $(n = 5, l = 2, s = 2)$.
- (for certain kinetic rates), it admits three positive steady-states in a stoichiometric compatibility class, one of which is unstable.

$$\begin{array}{ccccc} A & \rightleftarrows & 2A & & \\ A+B & \rightleftarrows & C & \rightleftarrows & 2B \end{array}$$

- Modification of the "Edelstein network"
- $\mathcal{E} := \{A, B, C\}$
- $\mathcal{C} := \{A, B, A+B, C, 2B\}$
- $l = 2$, $p = 2$, $t = 2$, Weakly-reversible
- $\delta = 0$ $(n = 5, l = 2, s = 3)$.
- For any kinetic rates, it admits a unique positive steady-states in each stoichiometric compatibility class, which is asymptotically stable (Deficiency zero theorem).

$$\begin{array}{ccccc} & & A & \rightleftarrows & 2A \\ & & \updownarrow & & \\ A+B & \rightleftarrows & C & \rightleftarrows & 2B \end{array}$$

- Another Modification of the "Edelstein network"
- $\mathcal{E} := \{A, B, C\}$
- $\mathcal{C} := \{A, B, A+B, C, 2B\}$
- $l = 1$, $p = 1$, $t = 1$, Weakly-reversible
- $\delta = 1$ $(n = 5, l = 1, s = 3)$.
- For any kinetic rates, it admits a unique positive steady-states in each stoichiometric compatibility class, which is asymptotically stable (Deficiency one theorem).

9.3. **Detailed balance.**

$$A \rightleftarrows B \rightleftarrows C \rightleftarrows A$$

- $\mathcal{E} := \{A, B, C\}$
- $\mathcal{C} := \{A, B, C\}$
- (Weakly-)Reversible, $\delta = 0$ $(n = 3, l = 1, s = 2)$.

- Detailed balance equilibrium for

$$k_1 k_2 k_3 = k_{-1} k_{-2} k_{-3}\,. \tag{37}$$

9.4. **No complex balanced equilibrium but an equilibrium.**

$$\begin{array}{ccc} A & \to & B \\ 2B & \to & 2A \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{A, B, 2A, 2B\}$
- Not weakly-reversible, $\delta = 1$ ($n = 4, l = 2, s = 1$).
- No complex balanced equilibrium (as not weakly-reversible) but there is a positive equilibrium.

$$\emptyset \quad \rightleftarrows \quad A \quad \rightleftarrows \quad 2A \quad \rightleftarrows \quad \emptyset$$

- $\mathcal{E} := \{A\}$
- $\mathcal{C} := \{\emptyset, A, 2A\}$
- (Weakly-)reversible, $\delta = 1$ ($n = 3, l = 1, s = 1$).
- No complex balanced equilibrium but there is a positive equilibrium.

$$2A \quad \rightleftarrows \quad A+B \quad \rightleftarrows \quad 2B \quad \rightleftarrows \quad 2A$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{2A, 2B, A + B\}$
- (Weakly-)reversible, $\delta = 1$ ($n = 3, l = 1, s = 1$).
- No complex balanced equilibrium but there is a positive equilibrium.

9.5. **(positive) Oscillations.**

$$\begin{array}{ccc} A & \to & 2A \\ A+B & \to & 2B \\ B & \to & \emptyset \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{\emptyset, A, 2B, A + B, B\}$
- Not weakly-reversible, $\delta = 1$ ($n = 6, l = 3, s = 2$).
- There exists a positive equilibrium, but the long term behavior is a limit cycle.

9.6. **stochastic example.**

$$\begin{array}{ccc} 2A & \to & 2B \\ A+3B & \to & 3A+B \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{2A, 2B, A + 3B, 3A + B\}$
- Not weakly-reversible, $\delta = 1$ ($n = 4, l = 2, s = 1$).
- The stoichiometric compatibility class $\{x_A + x_B = 6\}$ contains two irreducible components ($\{(0, 6)\}$ and $\{(1, 5), (3, 3), (5, 1)\}$) and the three other states are transient (not in any irreducible class)
- Note that the behavior of the stochastically modeled system and the deterministic one can be quiet different, as extinction may occur for A in the stochastic case, while convergence to a positive equilibrium always hold in the deterministic case.

The following two examples have the same complex balance stationary distribution on $\Gamma_\theta = \{x_1 + x_2 = \theta\}$, for $\theta < 10$, but a deterministic behavior that differs substantially

$$\begin{array}{ccc} A & \rightleftarrows & B \\ 10A & \rightleftarrows & 10B \end{array}$$

And

$$\begin{array}{ccc} A & \rightleftarrows & B \\ 10A & \rightarrow & \emptyset \end{array}$$

in both cases, the Γ_θ subnetwork is deficiency weakly reversible network, given by

$$A \rightleftarrows B$$

and thus has a product form stationary distribution. Note that Γ_θ is not positive, and we cannot conclude that both network are stochastically complex balanced (and indeed, they are not for some choice of rate constants).

For $\rho > 0$ and $\theta \geq 2$, be an integer,

$$\begin{array}{ccc} A & \rightarrow^{\rho(\theta-1)} & B \\ 2B & \rightarrow^{\rho} & 2A \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{A, B, 2A, 2B\}$
- Not weakly-reversible, $\delta = 1$ $(n = 4, l = 2, s = 1)$.
- The stationary distribution on the irreducible component $\{x_1+x_2 = \theta\}$ has the product form with $c = (1, 1)$,
$$\pi_\theta(x) = M_\theta \frac{1}{x_1!x_2!} \tag{38}$$
- However, this CRN is not complex balance (it is not weakly reversible). It does not have a product-form stationary distribution on all irreducible components.

For $\rho_1, \rho_2, \rho_3 > 0$ and $\theta \geq 2$, be an integer,

$$\begin{array}{ccc} A & \rightleftarrows^{\rho(\theta-1)+\rho_2}_{\rho_2} & B \\ 2B & \rightleftarrows^{\rho_1+\rho_3}_{\rho_3} & 2A \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{A, B, 2A, 2B\}$
- Not weakly-reversible, $\delta = 1$ $(n = 4, l = 2, s = 1)$.
- The stationary distribution on the irreducible component $\{x_1+x_2 = \theta\}$ has the product form with $c = (1, 1)$,
$$\pi_\theta(x) = M_\theta \frac{1}{x_1!x_2!} \tag{39}$$
- However, this CRN is not complex balance (the deficiency is not 0). It does not have a product-form stationary distribution in any other irreducible components.

$$\begin{array}{ccc} A & \rightleftarrows & B \\ A + B & \rightleftarrows & 2A + B \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{A, B, A + B, 2A + B\}$
- Weakly-reversible, $\delta = 1$ $(n = 4, l = 2, s = 1)$.

- The stationary distribution everythe irreducible component $\Gamma_\theta = \{x_2 = \theta\}$ has the form with
$$\pi_\theta(x) = M_\theta \frac{1}{x!} \left(\frac{\kappa_2 + \kappa_4 \theta}{\kappa_1 + \kappa_3 \theta} \right)^x \tag{40}$$
- However, it is not a product form as in Eq. (34), as the rate of the Poisson distribution depends on θ (and thus on Γ).

9.7. **Absolute Concentration Robustesse.**

$$\begin{array}{ccc} A + B & \to^\alpha & 2B \\ B & \to^\beta & A \end{array}$$

- $\mathcal{E} := \{A, B\}$
- $\mathcal{C} := \{A, B, A + B, 2B\}$
- Not weakly-reversible, $\delta = 1$ ($n = 4, l = 2, s = 1$).
- The deterministic equilibrium is given by
$$x_A = \frac{\beta}{\alpha}\,, \quad x_B = M - \frac{\beta}{\alpha}\,, \quad M := x_A(0) + x_B(0)\,. \tag{41}$$
Thus x_A reaches the same equilibrium values *whatever is the initial condition* (provided $M > \frac{\beta}{\alpha}$)
- The stochastic system has a single accessible absorbing state, given by
$$(x_A, X_B) = (M, 0)\,. \tag{42}$$
- It is conjectured in [5] that in this setting, quasi-stationary distribution are of Poisson product-forms, and proved in [2] that appropriate scaling of the stochastic models yields a finite time distribution that converges towards a product-form Poisson distribution.

10. PROOF OF STOCHASTIC DEFICIENCY 0 THEOREM

D'après le théorème de la déficience 0 déterministe, il existe un point d'équilibre des complexes: $c \in \mathbb{R}^d_{>0}$, tel que, pour tout $z \in \mathcal{C}$,
$$\underbrace{\sum_{y:\ y \to z \in \mathcal{R}} \kappa_{y \to z} c^y}_{\text{inflow}} = \underbrace{\sum_{y':\ z \to y' \in \mathcal{R}} \kappa_{z \to y'} c^z}_{\text{outflow}} \tag{43}$$
π est stationnaire ssi, for all $x \in \mathbb{N}^d$,
$$\sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(x - y' + y) \pi(x - y' + y) = \pi(x) \sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(x)\,.$$
which is equivalent to
$$\sum_{y \to y' \in \mathcal{R}} \kappa_{y \to y'} \frac{(x - y' + y)!}{(x - y' + y - y)!} \mathbf{1}_{x - y' + y \geq y} \frac{c^{x - y' + y}}{(x - y' + y)!} = \frac{c^x}{x!} \sum_{y \to y' \in \mathcal{R}} \kappa_{y \to y'} \frac{x!}{(x - y)!} \mathbf{1}_{x \geq y}\,.$$
By simplification, we obtain
$$\sum_{y \to y' \in \mathcal{R}} \kappa_{y \to y'} \frac{c^{y - y'}}{(x - y')!} \mathbf{1}_{x \geq y'} = \sum_{y \to y' \in \mathcal{R}} \kappa_{y \to y'} \frac{\mathbf{1}_{x \geq y}}{(x - y)!}\,,$$
which can be re-written as
$$\sum_{z \in \mathcal{C}} \sum_{y:\ y \to z \in \mathcal{R}} \kappa_{y \to z} \frac{c^{y - z}}{(x - z)!} \mathbf{1}_{x \geq z} = \sum_{z \in \mathcal{C}} \sum_{y':\ z \to y' \in \mathcal{R}} \kappa_{z \to y'} \frac{\mathbf{1}_{x \geq z}}{(x - z)!}\,.$$

We finally obtain

$$\sum_{z\in\mathcal{C}} \frac{c^{-z}}{(x-z)!}\mathbf{1}_{x\geq z} \sum_{y:\ y\to z\in\mathcal{R}} \kappa_{y\to z} c^y = \sum_{z\in\mathcal{C}} \frac{\mathbf{1}_{x\geq z}}{(x-z)!} \sum_{y':\ z\to y'\in\mathcal{R}} \kappa_{z\to y'}\,.$$

The latter is clearly implied by Eq. (43)

Remark 10. We have shown that the stochastic deficiency 0 theorem actually holds with the only hypothesis that there exists a positive complex-balanced equilibrium for the deterministic system.

11. Proof of deterministic deficiency 0 theorem

11.1. Network structure and dimension.

Proposition 2. Dimension of the complex stoichiometric space. *We have*

$$\dim T = n - l\,. \tag{44}$$

Proof. We calculate the dimension of the orthogonal $T^{\perp}$. For all $i = 1\,,\cdots,l$, and any couple y, y' directly linked, we have

$$\langle e_{L_i}, e_{y'} - e_y\rangle = 0\,, \tag{45}$$

thus $\{e_{L_1}\,,\cdots,e_{L_l}\} \in T^{\perp}$, and these vectors are linearly independent (the linkage relation is an equivalence relation and induces a partition on the set of complexes). Reciprocally, let $z = \sum_{u\in\mathcal{C}} z_y e_y \in T^{\perp}$. For any couple y, y' directly linked, $\langle e_{y'} - e_y, z\rangle = 0$ implies that $z'_y = z_y$. Hence, z is constant on any linkage classes. Thus, $z \in \mathrm{span}\{e_{L_1}\,,\cdots,e_{L_l}\}$. We conclude that

$$T^{\perp} = \mathrm{span}\{e_{L_1}\,,\cdots,e_{L_l}\} \tag{46}$$

□

Remark 11. Note also that we may write T as the direct sum

$$T = \mathrm{span}(U_1) \oplus \cdots \oplus \mathrm{span}(U_l)\,, \quad U_i := \{e_{y'} - e_y \mid y, y' \in L_i\} \tag{47}$$

let n_i be the number of complexes in L_i, and $y_1, \cdots, y_{n_i}$ the elements of L_i. Then any element of $\mathrm{span}(U_i)$ can be written as the linear combinaison of the independent vector

$$e_{y_2} - e_{y_1}, \cdots e_{y_{n_i}} - e_{y_1}\,. \tag{48}$$

Thus, $\dim\mathrm{span}(U_i) = n_i - 1$ and $\dim T = \displaystyle\sum_{i=1}^{l} n_i - 1 = n - l$.

Proposition 3. Deficiency Lemma. *We have*

$$0 \leq \dim\left(\ker Y \cap ImA_\kappa\right) \leq \delta = \dim\ker Y_{|T} \tag{49}$$

Proof. We use

$$\dim T = \dim\ker Y_{|T} + \dim\mathrm{Im}Y_{|T}\,, \tag{50}$$

and, due to its definition, for all complexes y, we have $Y(e_y) = y$, thus $Y_{|T}$ is clearly a surjection from $T = \mathrm{span}\{e_{y'} - e_y \mid y \to y' \in \mathcal{R}\}$ to $S = \mathrm{span}\{y' - y \mid y \to y' \in \mathcal{R}\}$. Thus,

$$\dim\mathrm{Im}Y_{|T} = s\,, \Rightarrow \dim\ker Y_{|T} = \dim T - \dim\mathrm{Im}Y_{|T} = n - l - s\,,$$

thanks to proposition 2. Finally, it is clear from the definition of $A_\kappa(z) = \sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'} z_y (e_{y'} - e_y)$ that $\mathrm{Im}A_\kappa \subseteq T$, so that $\ker Y \cap \mathrm{Im}A_\kappa \subseteq \ker Y_{|T}$. □

Corollary 1. *$Y_{|T}$ is an isomorphism if, and only if, $\delta = 0$.*

Remark 12. Note that $\delta = 0$ is equivalent to $n - l = s$, which, thanks to proposition 2, is equivalent to $\dim T = \dim S$. If $\delta > 0$, then T is "bigger" than S.

Remark 13. We will show in the next subsection that $\dim \ker A_\kappa = t$. As a side consequence, it turns out that the second inequality in (49) is an equality if the network is weakly-reversible. Indeed, in such case, $t = l$, and $\dim \mathrm{Im} A_\kappa = n - l = \dim T$.

Remark 14. It is easy to see that

$$\ker(Y A_\kappa) = \ker A_\kappa \oplus \Delta\,, \quad \Delta = \{\nu \in \mathbb{R}^n\,,\, A_\kappa \nu \in \ker(Y) \setminus \{0\}\} \cup \{0\}\,, \tag{51}$$

and clearly

$$\dim \Delta = \dim(\ker Y \cap \mathrm{Im} A_\kappa) \tag{52}$$

Thus the deficiency δ provides an upper bound on the dimension of the set of fixed point that are not complex balanced.

Remark 15. It is clear that if $\ker Y = \{0\}$, then all equilibrium are necessarily complex balanced equilibrium. The latter condition is valid if all complex vectors are linearly independent, which is trivially true for mono-molecular reaction systems. Note that $\delta = 0$ for mono-molecular reaction systems.

11.2. **Kernel of A_κ.**

Proposition 4. Block structure *Up to a re-ordering of complexes, we may write A_κ and A as block-wise triangular inferior matrices, with*

$$A = \begin{pmatrix} A_1 & 0 & 0 & 0 \\ A(2,1) & \ddots & 0 & 0 \\ \vdots & \ddots & \ddots & 0 \\ A(p,1) & \cdots & A(p,p-1) & A_p \end{pmatrix} \tag{53}$$

and

$$diag(\mathbf{1}^\perp A) = \begin{pmatrix} \Delta_1 & 0 & 0 & 0 \\ 0 & \ddots & 0 & 0 \\ 0 & 0 & \ddots & 0 \\ 0 & 0 & 0 & \Delta_p \end{pmatrix} \tag{54}$$

For a vector $z \in \mathbb{R}^n$, we denote by $z(i)$, $i = 1, \cdots, p$ the block that corresponds to the strong linkage class $\overline{L}_1$. Note that $\Delta_i = diag(\mathbf{1}^\perp A)(i)$.

Lemma 1. *We have the following assertions:*

1. $(A_\kappa z \geq 0) \Rightarrow (A_\kappa z = 0)$
2. $(z \in ker A_\kappa) \Rightarrow (\mid z \mid \in ker A_\kappa)$
3. *If $z \in \ker A_\kappa$, then $(z_i = 0) \Rightarrow (z_j = 0\,, \forall j \to i)$*

Proof. For the first point, multiplying by the left by $\mathbf{1}^\perp$, we get $\mathbf{1}^\perp A_\kappa z = \left(\mathbf{1}^\perp A - \mathbf{1}^\perp diag(\mathbf{1}^\perp A)\right) z = 0$. Thus, $\mathbf{1}^\perp A_\kappa z$ is a sum of non negative term which is equal to zero, so that each term is zero and $A_\kappa z = 0$.

For the second point, $A_\kappa z = 0$ implies $\mid Az \mid = \mid diag(\mathbf{1}^\perp A) z \mid = diag(\mathbf{1}^\perp A) \mid z \mid$. By the triangular inequality, $\mid Az \mid \leq A \mid z \mid$, so that $A_\kappa \mid z \mid \geq 0$, hence $\mid z \mid \in \ker A_\kappa$ by the first point.

Finally, for the last point, we may assume $z \geq 0$. Then $A_\kappa z = 0$ implies

$$\sum_{j \neq i} \kappa_{j \to i} z_j = \left(\sum_{j \neq i} \kappa_{i \to j} \right) z_i \tag{55}$$

Then $z_i = 0$ implies each term on the left hand-side is zero, e.g. $z_j = 0$ for each $j \to i$. □

Lemma 2. *Let $z \in \ker A_\kappa$. If $\overline{L}_1$ is not terminal, then $z(1) = 0$. Else there exists a vector $\chi_1 \geq 0$ with $\mathrm{supp}(\chi_1) = \overline{L}_1$ such that on $z(1) = \lambda\chi_1(1)$.*

Proof. Thanks to lemma 1, we may assume $z \geq 0$. Assume $z(1) > 0$ and that $\overline{L}_1$ is not terminal. As $z \in \ker A_\kappa$, we have

$$A_1 z(1) = \Delta_1 z(1) = diag(\mathbf{1}^\perp A) z(1) > diag(\mathbf{1}^\perp A_1) z(1)\,, \tag{56}$$

where the last inequality comes from the non-terminal assumption, that implies that there exists a non-diagonal non-zero block $A(j,1)$, for a given $j \geq 2$. Now, considering $\overline{L}_1$ as a sub-network (that is only the complexes that belongs to $\overline{L}_1$ and the reactions between them) in its own right. The matrix corresponding to the labelled, directed graph is A_1. But then, we have exhibited a vector for which $\left(A_1 - diag(\mathbf{1}^\perp A_1)\right) z(1) > 0$, which is in contradiction to the first point of lemma 1.

Now, if $\overline{L}_1$ is terminal. If the cardinal of $\overline{L}_1$ is one, we do not have anything to prove. Else, by the strong linkage relationship, there must be non-zero elements in each column of A_1, so that $diag(\mathbf{1}^\perp A_1)$ is invertible. Then $z \in \ker A_\kappa$ implies

$$A_1 z(1) = diag(\mathbf{1}^\perp A_)z(1) = diag(\mathbf{1}^\perp A_1) z(1)\,, \tag{57}$$

so that

$$A_1 \left(diag(\mathbf{1}^\perp A_1)\right)^{-1} z(1) = z(1)\,, \tag{58}$$

e.g. $z(1)$ is an eigenvector of $M = A_1 \left(diag(\mathbf{1}^\perp A_1)\right)$, associated to the eigenvalue 1. Clearly, M is irreducible (by the strong linkage relationship), and as $\mathbf{1}^\perp M = \mathbf{1}^\perp$, its spectral radius is one. We conclude by the Perron-Frobenius theorem. □

We may now proceed by recurrence to prove the following proposition

Proposition 5. $\ker A_\kappa = span\{\chi_1, \cdots, \chi_t\}$*, où* $supp(\chi_i) = T_i$

Proof. it remains to prove that the lemma 2 can be applied repeatedly. Indeed, if $z \in \ker A_\kappa$, then, for any i,

$$A_i z(i) + \sum_{1_l eqj<i} A(i,j) z(j) = \Delta_i z(i) \tag{59}$$

But either $\overline{L}_j$ is terminal, so that $A(i,j) = 0$, or $\overline{L}_j$ is not terminal, so that $z(j) = 0$. Then, by induction, we prove that necessarily, $z(i)$ is solution of

$$A_i z(i) = \Delta_i z(i)\,, \tag{60}$$

and we are lead to the same dichotomy as in the case $i = 1$ (see lemma 2). □

11.3. **Complex-balanced Fixed points** $A_\kappa \Psi(x) = 0$.

Proposition 6. *Si $\exists x \in R^d_{>0}$ tel que $A_\kappa \Psi(x) = 0$ alors $\mathcal{R}$ est faiblement réversible.*

Proof. Thanks to Proposition 5, if x is a positive complex-balanced fixed point, then $\Psi(x) = \sum_{i=1}^t \lambda_i \chi_i$, with $\lambda_i > 0$. thus $z = \sum_{i=1}^t \lambda_i \chi_i$ is an element of $\ker A_\kappa$, with $\mathrm{supp}(z) = \{1, \cdots, d\}$. Then, by lemma 2 each strong linkage classes are terminal. Now, let two complexes i, j be in the same linkage class, $i \sim j$, and suppose that they are not in the same strong linkage class, $[i] \neq [j]$. Then either $[i]$ or $[j]$ is not terminal, which is in contradiction with the above statement. Then $[i] = [j]$ and each linkage class is also a strong linkage class. Thus, $\mathcal{R}$ is weakly reversible. □

We can also now prove the characterization of weak reversibility:

Proof of the proposition 1. Suppose the network is not weakly reversible. Then there is a complex $y \in \mathcal{C}$ that is not any terminal strong linkage class. Since by Proposition 5, every vector in $\ker A_\kappa$ is a linear combination of vectors with support in the terminal strong linkage classes, then $x_y = 0$ for every $x \in \ker A_\kappa$. Thus, there is no strictly positive vector in $\ker A_\kappa$.

On the other hand, if the network is weakly reversible, then every complex is a member of some terminal strong linkage class. In such case, $x = \sum_{i=1}^{t} \chi_i \in \ker A_\kappa$ is strictly positive. $\square$

Proposition 7. *Soit $Z = \{x \in R^d_{>0}\,,\, A_\kappa \Psi(x) = 0\}$. Soit $Z = \emptyset$, soit $\ln Z = \ln(x) + S^\perp$. Dans ce dernier cas, Z rencontre chaque classe de compatibilité $S_x = (x + S) \cap \mathbb{R}^d_+$ une et une seule fois.*

Proof. We will use the basis of the kernel of A_κ, as obtained by proposition 5. First, if $Z \neq \emptyset$, by Proposition 6, $\mathcal{R}$ is weakly reversible so that each linkage class is a terminal strong linkage class. Hence, by proposition 5, $\ker A_\kappa = \operatorname{span}\{\chi_1, \cdots, \chi_l\}$,, with $\operatorname{supp}(\chi_i) = L_i$.

Let $x^* \in Z$. Then $\Psi(x^*) \in \ker A_\kappa$, so that

$$\Psi(x^*) = \sum_{i=1}^{l} \lambda_i(x^*)\chi_i\,, \quad \lambda_i(x^*) > 0\,. \tag{61}$$

On the other hand,

$$\Psi(x^*) = \sum_{i=1}^{d} (x^*)^y e_y = \sum_{i=1}^{l} \sum_{y \in Li} (x^*)^y e_y = \sum_{i=1}^{l} \lambda_i(x^*)\chi_i\,, \tag{62}$$

which implies that, for all $i = 1, \cdots l$,

$$\sum_{y \in Li} (x^*)^y e_y = \lambda_i(x^*)\chi_i\,. \tag{63}$$

For any $x \in Z$, we may repeat the same argument, hence, for all $i = 1, \cdots l$,

$$\chi_i = \sum_{y \in Li} \frac{(x^*)^y}{\lambda_i(x^*)} e_y = \sum_{y \in Li} \frac{x^y}{\lambda_i(x)} e_y\,. \tag{64}$$

As $\{e_y\}$ is an orthonormal basis, we deduce

$$\frac{(x^*)^y}{\lambda_i(x^*)} = \frac{x^y}{\lambda_i(x)}\,, \quad \forall i = 1, \cdots, l\,, \forall y \in L_i\,. \tag{65}$$

Finally, we conclude that, for any $x \in Z$, $\frac{x^y}{(x^*)^y}$ is constant on each linkage class.

Reciprocally, if x is such that $\frac{x^y}{(x^*)^y}$ is constant on each linkage class, then, for all $i = 1, \cdots l$,

$$\sum_{y \in L_i} x^y e_y = \mu_i \sum_{y \in Li} (x^*)^y e_y = \mu_i \lambda_i(x^*)\chi_i\,, \tag{66}$$

and

$$\Psi(x) = \sum_{i=1}^{l} \mu_i \lambda_i(x^*)\chi_i \in \ker A_\kappa\,. \tag{67}$$

Thus,

$$Z = \{x > 0\,, \frac{x^y}{(x^*)^y} \text{ is constant on each linkage class }\}\,. \tag{68}$$

For any $x \in Z$, $\ln\left(\frac{x^y}{(x^*)^y}\right) = \langle y, \ln(x) - \ln(x^*)\rangle$ is constant on each linkage class, so that

$$\langle y' - y, \ln(x) - \ln(x^*)\rangle = 0\,, \forall y \to y'\,. \tag{69}$$

Then, $\ln(x)-\ln(x^*)\in S^{\perp}$. Reciprocally, if $\ln(x)-\ln(x^*)\in S^{\perp}$, we verify that $\frac{x^y}{(x^*)^y}$ is constant on each linkage class.

For the last part of the proposition, notice that we may write Z as

$$Z=\{x^*e^u\,,u\in S^{\perp}\}\,. \tag{70}$$

Using Hahn-Banach theorem, for any $x>0$, we prove that there exists a unique $\overline{u}\in S^{\perp}$ such that $x^*e^{\overline{u}}-x\in S$. Thus $Z\cap(x+S)=\{x^*e^{\overline{u}}\}$ □

Proposition 8. *Si $Z\neq\emptyset$, $x^*\in Z$, alors tout point fixe positif vérifie $A_\kappa\Psi(x)=0$, et $f(x)=\sum_{y\to y'\in\mathcal{R}}\kappa_{y\to y'}x^y(y'-y)$ vérifie*

$$\langle f(x),\ln(x)-\ln(x^*)\rangle\leq 0\,, \tag{71}$$

avec égalité si, et seulement si, $x\in Z$.

Proof. Let $x^*\in Z$, and $x>0$, we define $u:=\ln(x)-\ln(x^*)$. Thus, $x^y=e^{\langle y,u+\ln(x^*)\rangle}$. Then

$$f(x)=\sum_{y\to y'\in\mathcal{R}}\kappa_{y\to y'}x^y(y'-y)=\sum_{y\to y'\in\mathcal{R}}\kappa_{y\to y'}(x^*)^y e^{\langle y,u\rangle}(y'-y)\,,. \tag{72}$$

Thus, by convexity,

$$\begin{aligned}\langle f(x),u\rangle=\sum_{y\to y'\in\mathcal{R}}&\kappa_{y\to y'}(x^*)^y e^{\langle y,u\rangle}(\langle y',u\rangle-\langle y,u\rangle)\\ &\leq\sum_{y\to y'\in\mathcal{R}}\kappa_{y\to y'}(x^*)^y(e^{\langle y',u\rangle}-e^{\langle y,u\rangle})\\ &\qquad\leq\langle\sum_{y\to y'\in\mathcal{R}}\kappa_{y\to y'}(x^*)^y(e_{y'}-e_y),\sum_{y\in\mathcal{C}}e^{\langle y,u\rangle}e_y\rangle\,,\end{aligned} \tag{73}$$

where the inequality is an equality if, and only if, $\langle y'-y,u\rangle=0$ for any $y\to y'$, e.g. if, and only if $u\in S^{\perp}$, e.g. if, and only if $x\in Z$. In particular, we proved that

$$\langle f(x),\ln(x)-\ln(x^*)\rangle\leq 0\,, \tag{74}$$

with equality if, and only if, $x\in Z$. □

Corollary 2. *$h(x)=\langle x\ln(x)-x-x\ln(x^*)+x^*,\mathbf{1}\rangle$ est une fonction de Lyapounov stricte pour x^*, au sein de classe de compatibilité $S_{x^*}=(x^*+S)\cap\mathbb{R}^d_+$.*

Proof. It is immediate that $\nabla h=\ln(x)-\ln(x^*)$, so that

$$\langle f(x),\nabla h\rangle\leq 0\,, \tag{75}$$

with equality if an only i $x\in Z$. By proposition 7, the inequality is strict in S_{x^*} except in x^*. Moreover, is is immediate that $h(x)\geq 0$ with $h(x)=0$ if, and only if, $x=x^*$. □

Before continuing, we summarize all Propositions 6-7-8 in the following

Theorem 10 (Horn and Jackson)**.** *Si il existe un point d'équilibre des complexes $x_*\in\mathbb{R}^d_{>0}$ (tel que $A_\kappa(\Psi(x_*))=0$), alors*

- *Il n'existe pas de point fixe $x_*\in\mathbb{R}^d_{>0}$ tel que $A_\kappa(\Psi(x_*))\neq 0$.*
- *Le réseau est faiblement réversible.*
- *Chaque classe de compatibilité stoechiométrique a exactement un point fixe positif (tel que $A_\kappa(\Psi(x_*))=0$).*
- *Un tel point fixe est localement asymptotiquement stable.*

Deficiency theorem can now be obtained with the last

Proposition 9. *Si $\mathcal{R}$ a une déficience nulle, alors $\exists x \in Z$ si, et seulement si, $\mathcal{R}$ est faiblement réversible.*

Proof. We are looking for an element $x > 0$ such that $\Psi(x) \in \ker A_\kappa$. Finding such element is greatly simplified by the following observation. If there exists $u > 0$, $u \in \ker A_\kappa$, and $\ln(u) \in \mathrm{Im} Y^T$, then there is an element in Z. Indeed, for such u, there exists x, such that $\ln(u) = Y^T x$. Now define $z = e^x$. We have

$$\ln(u) = Y^T \ln(z) = \ln(\Psi(z))\,, \tag{76}$$

so that $u = \Psi(z)$ and $z \in Z$. Hence,

$$\left(\ln\left(\ker A_\kappa\right)^+ \cap \mathrm{Im}Y^T \neq \emptyset\right) \Rightarrow (Z \neq \emptyset)\,.$$

By Proposition 5, $\ln\left(\ker A_\kappa\right)^+$ is a coset of span $\{e_{T_1}, \cdots, e_{T_t}\}$. Indeed, define for all $i = 1, \cdots, t$, all $y \in T_i$, $p_{i,y} = \langle \chi_i, e_y\rangle$. then $\chi_i = \sum_{y\in T_i} p_{i,y} e_y$. It is clear that $(\ker A_\kappa)^+ = \{\sum_{i=1}^t \lambda_i \chi_i\,, \lambda_i > 0\}$. Then

$$\begin{aligned}\ln\left(\sum_{i=1}^t \lambda_i \chi_i\right) = \ln\left(\sum_{i=1}^t \sum_{y\in T_i} \lambda_i p_{i,y} e_y\right) &= \sum_{i=1}^t \ln(\lambda_i) \sum_{y\in T_i} e_y + \sum_{i=1}^t \sum_{y\in T_i} \ln(p_{i,y}) e_y \\ &= \sum_{i=1}^t \ln(\lambda_i) e_{T_i} + \sum_{i=1}^t \sum_{y\in T_i} \ln(p_{i,y}) e_y\,. \end{aligned}\tag{77}$$

Let

$$U = \mathrm{Im}Y^T + \mathrm{span}\{e_{T_1}, \cdots, e_{T_t}\}\,,$$

If $\mathcal{R}$ is weakly reversible, each linkage class is a strong linkage class, so that by Proposition 2,

$$T^\perp = \mathrm{span}\{e_{T_1}, \cdots, e_{T_t}\}\,.$$

We have $\mathrm{Im}A_\kappa \subseteq T$, and by Proposition 5, $\dim \mathrm{Im}A_\kappa = n - t$, while by Proposition 2, $\dim T = n - l$. Then, as $\mathcal{R}$ is weakly reversible, each linkage class is a terminal strong linkage class, so that $l = t$ and

$$T = \mathrm{Im}A_\kappa\,. \tag{78}$$

Hence,

$$U = \ker(Y)^\perp + (\mathrm{Im}A_\kappa)^\perp = \left(\ker(Y) \cap \mathrm{Im}A_\kappa\right)^\perp\,. \tag{79}$$

For a deficiency 0 network, by Proposition 3, $\dim\left(\ker(Y) \cap \mathrm{Im}A_\kappa\right) = 0$, so that $U = \mathbb{R}^n$. Finally, $\ln\left(\ker A_\kappa\right)^+ \subseteq U$, and as $\ln\left(\ker A_\kappa\right)^+$ is a coset of $\mathrm{span}\{e_{T_1}, \cdots, e_{T_t}\}$,

$$\ln\left(\ker A_\kappa\right)^+ \cap \mathrm{Im}Y^T \neq \emptyset\,. \tag{80}$$

□

Note that we actually proved that

Theorem 11 (Deficiency Zero Theorem - Feinberg)**.** *Si le réseau a une déficience nulle, alors il a un point fixe $x_* \in \mathbb{R}^d_{>0}$ tel que $A_\kappa(\Psi(x_*)) = 0$ si, et seulement si, il est faiblement réversible.*

12. Miscellaneous

12.1. **Detailed balance equilibrium.** In the case of reversible networks, it may be possible to look for detailed balance equilibrium, which are in general dependent of the kinetic rates. See the general results in [31]. In particular, the same Lyapounov function as in holds Corollary 2 in the case of existence of a detailed balance equilibrium.

12.2. **Persistence.** We denote $w(x)$ the orbit of the solution of Eq. (1) associated to the initial condition $x(0) = x$.

Definition 8 (persistence)**.** A network is called persistent if

$$w(x) \subset (0,\infty)^d\,, \quad \forall x \in (0,\infty)^d \tag{81}$$

Definition 9 (Siphon)**.** A set $\Sigma \subset \mathcal{E}$ is called a siphon if for each reaction that has some species of Σ as a product, there exists at least one of its reactant which is in Σ.

Remark 16. Clearly, if all the species of a siphon starts at 0, they stay at 0 for ever.

Theorem 12 ([9])**.** *Let $(\mathcal{E},\mathcal{C},\mathcal{R})$ be a conservative network, such that each siphon contains the support of a strictly positive conserved quantity. Then, the network is persistent.*

Remark 17. Example (36) satisfies the hypothesis of the above theorem.

Theorem 13 ([9])**.** *Let $(\mathcal{E},\mathcal{C},\mathcal{R})$ and $x_0 \in (0,\infty)^d$ giving rise to bounded solution such that $w(x_0) \subset (0,\infty)^d$. Then there exists a positive $\nu \in (0,\infty)^r$ such that*

$$\Gamma\nu = 0\,. \tag{82}$$

These results are in particular important in light of the following characterization of ω-limit set for complex balanced network.

Theorem 14 ([21], [34])**.** *Let $(\mathcal{E},\mathcal{C},\mathcal{R},\kappa)$ be a complex balanced network, and $x_0 \in \mathbb{R}^d_{\geq 0}$. Then the ω-limit set $\omega(x_0)$ consists either of boundary points of complex balanced equilibria, or of a single positive point of complex balanced equilibrium.*

Thus the only missing gap towards a full characterization of the long term dynamics of complex balanced CRN is the possibility or not to reach the boundary. This has been names the Global attractor conjecture, and is thus related to persistence properties. More results on persistence for special cases are contained in [1, 8, 34], and a general proof of the Global Attractor Conjecture is contained in [15]

12.3. **Existence of unique positive equilibria (Deficiency 1 theorem).** Deficiency one theorem guarantees the existence of a unique positive equilibrium (that might not be complex balanced)

Theorem 15 ([22])**.** *Let $(\mathcal{E},\mathcal{C},\mathcal{R})$ a CRN with l linkage classes, each containing a single strong linkage class. Assume that the deficiency of the network δ, and the deficiency of each linkage class δ_i, $i = 1..l$, satisfies*

a $\delta_i \leq 1\,, \quad i = 1, 2, \cdots, i$
b $\sum_{i=1}^{l} \delta_i = \delta$.

Then, for any choice of the kinetic rate κ, there can not be more than one positive steady-states in each stoichiometric compatibility classes. If the network is weakly-reversible, there is precisely one such steady-states.

12.4. **Multiple equilibria.** Results for a particular class of networks, called CFSTR are contained in [12–14, 16], using the notion of the species-reaction graph (SR graph, close to petri nets formalism).

Using the notion of toric steady states, see [20].

12.5. **Monotone systems.** See [9].

12.6. **Algebraic geometry and multi-stationarity.** Sign conditions to preclude multi-stationarity have a long history in the study of polynomial equations, which goes back at least to Descartes' rule of signs. Among recent results going towards generalization to a multivariate Descartes' rule of signs, see [20,27].

Let us denote by V the kinetic order matrix, $V \in \mathcal{M}_{r\times n}$, such that the row of V are composed of the stoichiometries of the reactant species of each reaction. For a vector $x \in \mathbb{R}^n$, we denote by $\sigma(x) \in \{-,0,+\}^n$ its sign vector, and by

$$\sigma(S) = \{\sigma(x) \mid x \in S\}\,, \quad \Sigma(S) = \sigma^{-1}(\sigma(S))\,. \tag{83}$$

As a particular result in [27], we write

Theorem 16. *Let $(\mathcal{E},\mathcal{C},\mathcal{R})$ be a reaction network, and f given by (11). Then, the following statements are equivalent*

1. *f is injective on every stoichiometric compatibility classes, for all kinetic rates $\kappa > 0$.*
2. *$\sigma(\ker\Gamma) \cap \sigma\left(V(\Sigma(S^*))\right) = \emptyset$*

Further results in [27] guarantee the existence of multiple steady states.

12.7. **Laplacian matrix.** $L = -A_\kappa$ is a weighted Laplacian matrix. If there exists a complex balanced equilibrium $x^* \in \mathbb{R}^d_{>0}$, satisfying

$$A_\kappa \Psi(x^*) = -L \exp\left(Y^\top \ln(x^*)\right) = 0\,, \tag{84}$$

then

$$\mathcal{L}(x^*) = L \ \mathrm{diag}\left(\exp(Y_i^\top \ln(x^*))\right)_{i=1,\dots,d}\,, \tag{85}$$

is a balanced Laplacian matrix, $\mathbf{1}^\perp \mathcal{L}(x^*) = \mathcal{L}(x^*)\mathbf{1} = 0$, and the dynamics (11) can be re-written

$$\dot{x} = -Y\mathcal{L}(x^*)\exp\left(Y^\top \ln(\frac{x}{x^*})\right) \tag{86}$$

See [35] for a link between complex balancedness and Kirchoff's Matrix tree theorem and relation with consensus dynamics.

12.8. **Stationary distributions and Lyapounov functions.** A systematic link is drawn between scaling limit of non-equilibrium potential of stationary distributions of a complex balance network, and its Lyapounov functions, in [3]. In particular, it shown that, within the classical "Kurtz's scaling",

$$\lim_{V\to\infty} -\frac{1}{V}\ln\left(\pi^V(x^V)\right) = h(x)\,, \quad \text{as } x^V \to x\,, \quad V \to \infty\,. \tag{87}$$

Such relationship is also proved for non complex balanced birth-and-death models.

This relationship may suggest a general large deviation result may holds for complex balanced networks, as in [26,28].

12.9. **other.**

- Results on possibility of oscillations, extinction of species, higher deficiency networks, behavior of subnetworks, are contained in [22]
- Toric dynamical systems and computational algebraic geometry [15]
- Necessary conditions for multi-stationarity, cycle limite [12–14,16]
- Absolute robustesse (steady-state of some species are independent of the total mass, extinction in stochastic) [32,33], [2,5]
- Parameter identifiability [17]
- Generalized mass-action systems
- Computional approaches

- Mutiscale networks, slow-fast reduction, hybrid limit [6, 7, 10, 18]
- Model reduction, dynamical equivalence and linear conjugacy
- Reaction-diffusion models [30], [19, 23, 24]

References

[1] David F. Anderson. A Proof of the Global Attractor Conjecture in the Single Linkage Class Case. *SIAM Journal on Applied Mathematics*, 71(4):1487–1508, January 2011.

[2] David F. Anderson, Daniele Cappelletti, and Thomas G. Kurtz. Finite time distributions of stochastically modeled chemical systems with absolute concentration robustness. *arXiv:1604.03388 [math, q-bio]*, April 2016. arXiv: 1604.03388.

[3] David F. Anderson, Gheorghe Craciun, Manoj Gopalkrishnan, and Carsten Wiuf. Lyapunov Functions, Stationary Distributions, and Non-equilibrium Potential for Reaction Networks. *Bulletin of Mathematical Biology*, 77(9):1744–1767, September 2015.

[4] David F. Anderson, Gheorghe Craciun, and Thomas G. Kurtz. Product-Form Stationary Distributions for Deficiency Zero Chemical Reaction Networks. *Bulletin of Mathematical Biology*, 72(8):1947–1970, November 2010.

[5] David F. Anderson, Germán A. Enciso, and Matthew D. Johnston. Stochastic analysis of biochemical reaction networks with absolute concentration robustness. *Journal of the Royal Society Interface*, 11(93), April 2014.

[6] David F. Anderson and Thomas G. Kurtz. Continuous time Markov chain models for chemical reaction networks. In *Design and Analysis of Biomolecular Circuits*, pages 3–42. Springer, 2011.

[7] David F. Anderson and Thomas G. Kurtz. Models of biochemical reaction systems. In *Stochastic Analysis of Biochemical Systems*, number 1.2 in Mathematical Biosciences Institute Lecture Series, pages 19–31. Springer International Publishing, 2015.

[8] D. Angeli, P. De Leenheer, and E. Sontag. Persistence Results for Chemical Reaction Networks with Time-Dependent Kinetics and No Global Conservation Laws. *SIAM Journal on Applied Mathematics*, 71(1):128–146, January 2011.

[9] David Angeli. A Tutorial on Chemical Reaction Network Dynamics. *European Journal of Control*, 15(3):398–406, January 2009.

[10] Karen Ball, Thomas G. Kurtz, Lea Popovic, and Greg Rempala. Asymptotic analysis of multiscale approximations to reaction networks. *The Annals of Applied Probability*, 16(4):1925–1961, November 2006.

[11] Daniele Cappelletti and Carsten Wiuf. Product-Form Poisson-Like Distributions and Complex Balanced Reaction Systems. *SIAM Journal on Applied Mathematics*, 76(1):411–432, January 2016.

[12] G. Craciun and M. Feinberg. Multiple Equilibria in Complex Chemical Reaction Networks: I. The Injectivity Property. *SIAM Journal on Applied Mathematics*, 65(5):1526–1546, January 2005.

[13] G. Craciun and M. Feinberg. Multiple equilibria in complex chemical reaction networks: extensions to entrapped species models. *IEE Proceedings - Systems Biology*, 153(4):179, 2006.

[14] G. Craciun and M. Feinberg. Multiple Equilibria in Complex Chemical Reaction Networks: II. The Species-Reaction Graph. *SIAM Journal on Applied Mathematics*, 66(4):1321–1338, January 2006.

[15] Gheorghe Craciun. Toric Differential Inclusions and a Proof of the Global Attractor Conjecture. *arXiv:1501.02860 [math]*, January 2015. arXiv: 1501.02860.

[16] GHEORGHE CRACIUN and MARTIN FEINBERG. MULTIPLE EQUILIBRIA IN COMPLEX CHEMICAL REACTION NETWORKS: SEMIOPEN MASS ACTION SYSTEMS. *SIAM Journal on Applied Mathematics*, 70(6):1859–1877, 2010.

[17] Gheorghe Craciun and Casian Pantea. Identifiability of chemical reaction networks. *Journal of Mathematical Chemistry*, 44(1):244–259, September 2007.

[18] A Crudu, A Debussche, A Muller, and O Radulescu. Convergence of stochastic gene networks to hybrid piecewise deterministic processes. *Annals of Applied Probability*, 22:1822–1859, 2012.

[19] Laurent Desvillettes, Klemens Fellner, and Bao Quoc Tang. Trend to equilibrium for reaction-diffusion systems arising from complex balanced chemical reaction networks. *arXiv preprint arXiv:1604.04536*, 2016.

[20] Alicia Dickenstein. Biochemical Reaction Networks: An Invitation for Algebraic Geometers. In *MCA 2013*, volume 65-83, 2016.

[21] Martin Feinberg. Lectures on Chemical reaction Networks. 1979.

[22] Martin Feinberg. Chemical reaction network structure and the stability of complex isothermal reactors—I. The deficiency zero and deficiency one theorems. *Chemical Engineering Science*, 42(10):2229–2268, 1987.

[23] Klemens Fellner, Wolfgang Prager, and Bao Q. Tang. The entropy method for reaction-diffusion systems without detailed balance: first order chemical reaction networks. *arXiv:1504.08221 [math]*, April 2015. arXiv: 1504.08221.

[24] Klemens Fellner and Bao Quoc Tang. Explicit exponential convergence to equilibrium for nonlinear reaction-diffusion systems with detailed balance condition. *arXiv preprint arXiv:1601.05992*, 2016.

[25] F. Horn. Necessary and sufficient conditions for complex balancing in chemical kinetics. *Archive for Rational Mechanics and Analysis*, 49(3):172–186, January 1972.

[26] Alexander Mielke, R. I. Patterson, Mark A. Peletier, and M. Renger. Non-equilibrium thermodynamical principles for chemical reactions with mass-action kinetics. *WIAS Preprint No. 2165*, 2015.

[27] Stefan Müller, Elisenda Feliu, Georg Regensburger, Carsten Conradi, Anne Shiu, and Alicia Dickenstein. Sign Conditions for Injectivity of Generalized Polynomial Maps with Applications to Chemical Reaction Networks and Real Algebraic Geometry. *Foundations of Computational Mathematics*, 16(1):69–97, February 2016.

[28] Robert I. A. Patterson and D. R. Michiel Renger. Dynamical large deviations of countable reaction networks under a weak reversibility condition. *Weierstrass Institute for Applied Analysis and Stochastics: Preprint 2273*, July 2016.

[29] Loïc Paulevé, Gheorghe Craciun, and Heinz Koeppl. Dynamical Properties of Discrete Reaction Networks. *Journal of mathematical biology*, 69(1):55–72, July 2014.

[30] Peter Pfaffelhuber and Lea Popovic. Scaling limits of spatial compartment models for chemical reaction networks. *The Annals of Applied Probability*, 25(6):3162–3208, December 2015.

[31] Stefan Schuster and Ronny Schuster. A generalization of Wegscheider's condition. Implications for properties of steady states and for quasi-steady-state approximation. *Journal of Mathematical Chemistry*, 3(1):25–42, 1989.

[32] Guy Shinar, Uri Alon, and Martin Feinberg. Sensitivity and Robustness in Chemical Reaction Networks. *SIAM Journal on Applied Mathematics*, 69(4):977–998, January 2009.

[33] Guy Shinar and Martin Feinberg. Structural Sources of Robustness in Biochemical Reaction Networks. *Science*, 327(5971):1389–1391, March 2010.

[34] D. Siegel and D. MacLean. Global stability of complex balanced mechanisms. *Journal of Mathematical Chemistry*, 27(1-2):89–110, October 2000.

[35] Arjan van der Schaft, Shodhan Rao, and Bayu Jayawardhana. A network dynamics approach to chemical reaction networks. *arXiv preprint arXiv:1502.02247*, 2015.