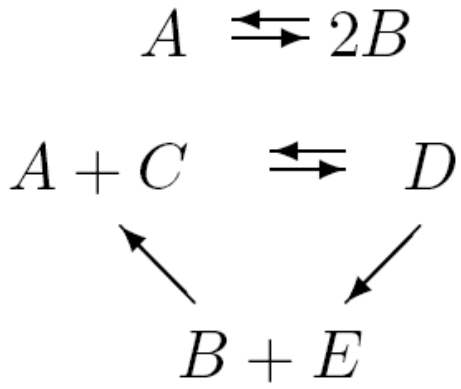
Global Attractors in Biochemical Dynamics

Gheorghe Craciun
Department of Mathematics and
Department of Biomolecular Chemistry
University of Wisconsin-Madison

Example

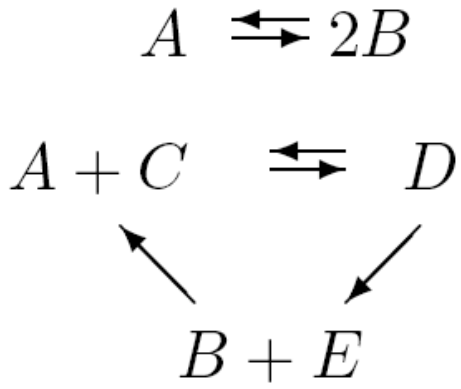


$$
\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \ .
\end{aligned}
$$

The Lorenz equations

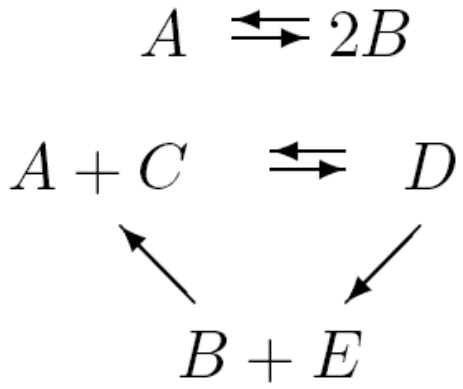
$$\begin{aligned} dx/dt &= ay - ax \\ dy/dt &= cx - y - xz \\ dz/dt &= xy - bz \end{aligned}$$

Example



$$
\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \ .
\end{aligned}
$$

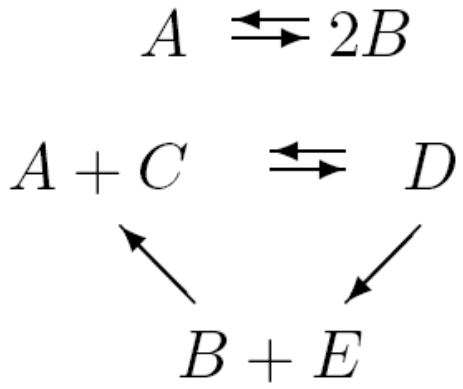
Example



$$
\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \ .
\end{aligned}
$$

Definition 2.1 *A chemical reaction network is a quadruple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa\}$ where $\mathcal{S}$ is a finite set of species; $\mathcal{C}$ is a finite set of multisets of species, called complexes; $\mathcal{R}$ is a relation on $\mathcal{C}$, denoted $y \to y'$ for $y, y' \in \mathcal{C}$, which represents a reaction converting y to y'; and $\kappa : \mathcal{R} \to \mathbb{P}$ associates a positive rate constant to each reaction.*

Example

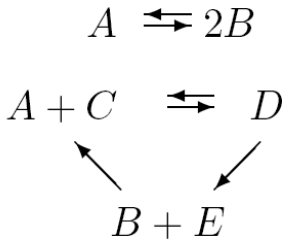


$$
\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \ .
\end{aligned}
$$

Definition 2.1 *A chemical reaction network is a quadruple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa\}$ where $\mathcal{S}$ is a finite set of species; $\mathcal{C}$ is a finite set of multisets of species, called complexes; $\mathcal{R}$ is a relation on $\mathcal{C}$, denoted $y \to y'$ for $y, y' \in \mathcal{C}$, which represents a reaction converting y to y'; and $\kappa : \mathcal{R} \to \mathbb{P}$ associates a positive rate constant to each reaction.*

Notation: $$c^y = \prod_{s\in\mathcal{S}} (c_s)^{y_s}$$

Vector equations for mass action kinetics

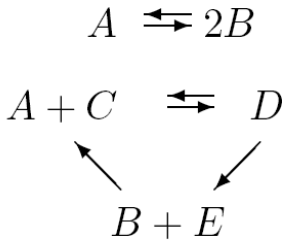


Definition 2.1 *A chemical reaction network is a quadruple* $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa\}$ *where* $\mathcal{S}$ *is a finite set of species;* $\mathcal{C}$ *is a finite set of multisets of species, called complexes;* $\mathcal{R}$ *is a relation on* $\mathcal{C}$*, denoted* $y \to y'$ *for* $y, y' \in \mathcal{C}$*, which represents a reaction converting* y *to* y'*; and* $\kappa : \mathcal{R} \to \mathbb{P}$ *associates a positive rate constant to each reaction.*

Notation: $$c^y = \prod_{s \in \mathcal{S}} (c_s)^{y_s}$$

$$\mathcal{R} = \{A \to 2B, 2B \to A, A + C \to D, D \to A + C, D \to B + E, B + E \to A + C\}$$

Vector equations for mass action kinetics



Definition 2.1 *A chemical reaction network is a quadruple* $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa\}$ *where* $\mathcal{S}$ *is a finite set of species;* $\mathcal{C}$ *is a finite set of multisets of species, called complexes;* $\mathcal{R}$ *is a relation on* $\mathcal{C}$*, denoted* $y \to y'$ *for* $y, y' \in \mathcal{C}$*, which represents a reaction converting* y *to* y'*; and* $\kappa : \mathcal{R} \to \mathbb{P}$ *associates a positive rate constant to each reaction.*

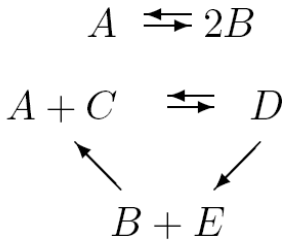
Notation: $$c^y = \prod_{s \in \mathcal{S}} (c_s)^{y_s}$$

$$\mathcal{R} = \{A \to 2B, 2B \to A, A + C \to D, D \to A + C, D \to B + E, B + E \to A + C\}$$

Vector representation of differential equations:

$$\frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y)$$

Vector equations for mass action kinetics



Definition 2.1 *A chemical reaction network is a quadruple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa\}$ where $\mathcal{S}$ is a finite set of species; $\mathcal{C}$ is a finite set of multisets of species, called complexes; $\mathcal{R}$ is a relation on $\mathcal{C}$, denoted $y \to y'$ for $y, y' \in \mathcal{C}$, which represents a reaction converting y to y'; and $\kappa : \mathcal{R} \to \mathbb{P}$ associates a positive rate constant to each reaction.*

Notation: $$c^y = \prod_{s \in \mathcal{S}} (c_s)^{y_s}$$

$$\mathcal{R} = \{A \to 2B, 2B \to A, A + C \to D, D \to A + C, D \to B + E, B + E \to A + C\}$$

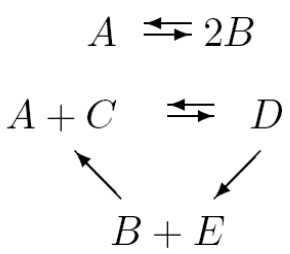
Vector representation of differential equations:

$$\frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y)$$

$$\begin{aligned}
dc_A/dt &= -(\kappa_{A\to 2B})c_A + (\kappa_{2B\to A})c_B^2 - (\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_B/dt &= 2(\kappa_{A\to 2B})c_A - 2(\kappa_{2B\to A})c_B^2 + (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \\
dc_C/dt &= -(\kappa_{A+C\to D})c_A c_C + (\kappa_{D\to A+C})c_D + (\kappa_{B+E\to A+C})c_B c_E \\
dc_D/dt &= (\kappa_{A+C\to D})c_A c_C - (\kappa_{D\to A+C})c_D - (\kappa_{D\to B+E})c_D \\
dc_E/dt &= (\kappa_{D\to B+E})c_D - (\kappa_{B+E\to A+C})c_B c_E \ .
\end{aligned}$$

Stoichiometric Subspace

Definition 2.2 *The stoichiometric subspace, S, of a chemical reaction network is the vector subspace of $\mathbb{R}^{\mathcal{S}}$ defined by* $S = \text{span}\{y' - y \mid y \to y' \in \mathcal{R}\}$.



Example: $S = \text{span}\{2B - A, A + C - D, B + E - D, B + E - A - C\}$.

Since $B + E - A - C = (B + E - D) - (A + C - D)$, this simplifies further to give

$$S = \text{span}\{2B - A, A + C - D, B + E - D\}$$

Decomposition of the reaction rate function

$$\frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y)$$

$$dc/dt = f(c) \qquad f : \mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$$

Decomposition of the reaction rate function

$$\frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y)$$

$$dc/dt = f(c) \qquad f : \mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$$

$$\omega_U(y) = \begin{cases} 1 & \text{if } y \in U \\ 0 & \text{otherwise} \end{cases} \qquad Y : \mathbb{R}^{\mathcal{C}} \longrightarrow \mathbb{R}^{\mathcal{S}} \qquad Y(\omega_y) = y$$

Decomposition of the reaction rate function

$$\frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y)$$

$$dc/dt = f(c) \qquad f : \mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$$

$$\omega_U(y) = \begin{cases} 1 & \text{if } y \in U \\ 0 & \text{otherwise} \end{cases} \qquad Y : \mathbb{R}^{\mathcal{C}} \longrightarrow \mathbb{R}^{\mathcal{S}} \qquad Y(\omega_y) = y$$

For a given kinetics, $\kappa : \mathcal{R} \to \mathbb{P}$, define the map $A_\kappa : \mathbb{R}^{\mathcal{C}} \to \mathbb{R}^{\mathcal{C}}$ by

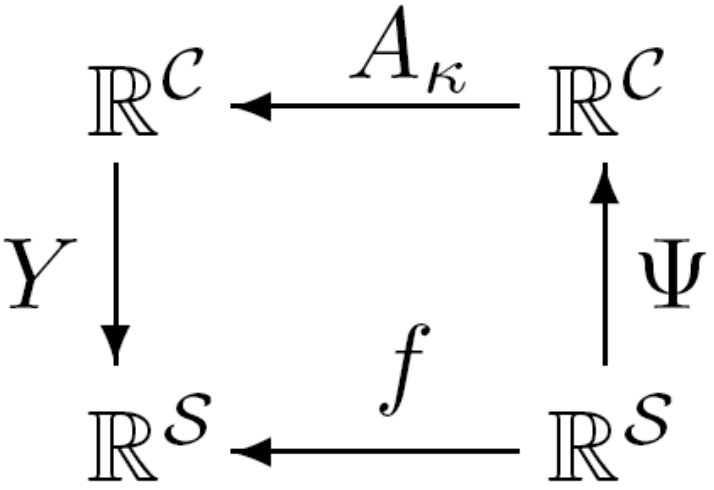
$$A_\kappa(x) = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) x_y (\omega_{y'} - \omega_y) \ .$$

$$\Psi(c) = \sum_{y \in \mathcal{C}} c^y \omega_y$$

Decomposition of the reaction rate function

$$\frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y)$$

$$dc/dt = f(c) \qquad f : \mathbb{R}^{\mathcal{S}} \to \mathbb{R}^{\mathcal{S}}$$

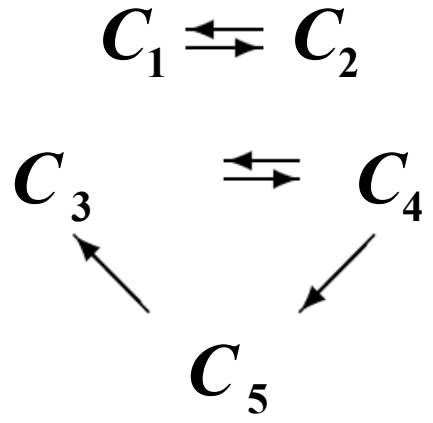


$$\omega_U(y) = \begin{cases} 1 & \text{if } y \in U \\ 0 & \text{otherwise} \end{cases} \qquad Y : \mathbb{R}^{\mathcal{C}} \longrightarrow \mathbb{R}^{\mathcal{S}} \qquad Y(\omega_y) = y$$

For a given kinetics, $\kappa : \mathcal{R} \to \mathbb{P}$, define the map A_κ

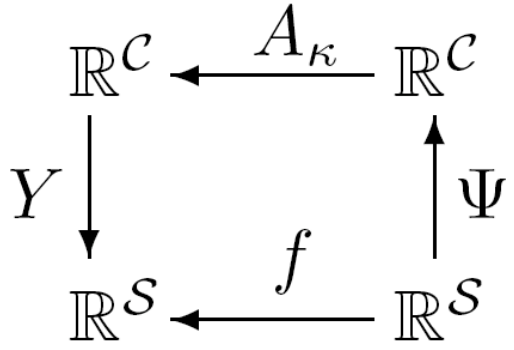
$$A_\kappa(x) = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) x_y (\omega_{y'} - \omega_y)$$

$$\Psi(c) = \sum_{y \in \mathcal{C}} c^y \omega_y$$



Deficiency of a reaction network

$$dc/dt = f(c)$$



Definition 3.1 *A fixed point of a chemical reaction network is a state $c \in \mathbb{P}^{\mathcal{S}}$ for which $dc/dt = 0$.*

Definition 3.2 *The deficiency of a chemical reaction network is* $\dim(\ker Y \cap \mathrm{Im} A_\kappa)$

A simple estimate for the deficiency, δ, of a network can be obtained as follows. Let $T = \mathrm{span}\{\omega_{y'} - \omega_y \mid y \to y'\}$. The map Y is evidently a surjection from T to the stoichiometric subspace, S. From the definition of A_κ in (10) we see that $\mathrm{Im} A_\kappa \subseteq T$. It follows that

$$\ker Y \cap \mathrm{Im} A_\kappa \subseteq \ker Y|_T \tag{13}$$

and so $\delta \leq \dim \ker Y|_T$. Let $s = \dim S$. Since $\dim T = \dim \ker Y|_T + \dim \mathrm{Im} Y|_T$ we see that $\delta \leq \dim T - s$.

Definition *If $y, y' \in \mathcal{C}$ then y is said to be linked to y', denoted $y \sim y'$, if either $y = y'$ or there are $y_1, \cdots, y_m \in \mathcal{C}$ such that $y = y_1 \leftrightarrow y_2 \leftrightarrow \cdots \leftrightarrow y_m = y'$.*

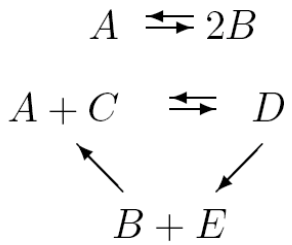
The equivalence classes of complexes under $\sim$ are termed *linkage classes.*

Let $L_1, \cdots, L_l \subseteq \mathcal{C}$ be the linkage classes.

Lemma *The following statements hold for any chemical reaction network:*

$$\begin{aligned}
&\operatorname{span}\{\omega_{y'} - \omega_y \mid y \to y'\} = \operatorname{span}\{\omega_{y'} - \omega_y \mid y \sim y'\},\\
&\operatorname{span}\{\omega_{y'} - \omega_y \mid y \to y'\}^{\perp} = \operatorname{span}\{\omega_{L_1}, \cdots, \omega_{L_l}\},\\
&\dim \operatorname{span}\{\omega_{y'} - \omega_y \mid y \to y'\} = n - l.
\end{aligned}$$

Proposition *The deficiency, δ, of any chemical reaction network satisfies $0 \leq \delta \leq n - l - s$, where n is the number of complexes, l is the number of linkage classes and s is the dimension of the stoichiometric subspace.*



(1)

Example (1) has $n = 5$, $l = 2$ and $s = 3$ so that $\delta = 0$.

Remark: *If* $x \in \ker A_\kappa$ *then* $|x| \in \ker A_\kappa$.

Remark: *If* $x \in \ker A_\kappa$ *and* $x_j = 0$ *then* $x_i = 0$ *whenever* $i \to j$.

Theorem (The Perron-Frobenius theorem) *Let M by any irreducible nonnegative $m \times m$ matrix. Any two eigenvectors in $\mathbb{P}^m$ have the same eigenvalue, which is the spectral radius of M, and are the same up to a positive scalar multiple. In particular, the eigenspace for the spectral radius is 1 dimensional and can always be represented as* $\operatorname{span}(u)$, *with* $u \in \mathbb{P}^m$.

Proposition *Suppose that $x \in \ker A_\kappa$. If L_i is not terminal then $x(i) = 0$, while if L_i is terminal then $x(i) = \lambda_i u_i$, for some $\lambda_i \in \mathbb{R}$.*

Theorem *(description of the kernel of A_k)* *Let t be the number of terminal strong linkage classes in a chemical reaction network and suppose that these classes are $T_1, \cdots, T_t \subseteq \mathcal{C}$, in any order. The following statements hold.*

1. *There exist $\chi_i \in \overline{\mathbb{P}}^{\mathcal{C}}$ such that $\operatorname{supp}(\chi_i) = T_i$ for $1 \leq i \leq t$.*
2. $\ker A_\kappa = \operatorname{span}\{\chi_1, \cdots, \chi_t\}$ *and these are linearly independent.*
3. $\dim \ker A_\kappa = t$.

Proposition *If each linkage class has precisely one terminal strong linkage class then the deficiency, δ, of the network is given by $\delta = n - l - s$.*

Weakly reversible networks

Definition *A chemical reaction network is said to be* weakly reversible *if it satisfies any of the conclusions of the following Lemma.*

Lemma *For any chemical reaction network, the following statements are equivalent, where* $i, j \in \mathcal{C}$.

1. *Each complex lies in a terminal strong linkage class.*
2. *Every strong linkage class is terminal.*
3. *The terminal strong linkage classes coincide with the linkage classes.*
4. *If* $[i] \preceq [j]$ *then* $[i] = [j]$.
5. *If* $i \Rightarrow j$ *then* $j \Rightarrow i$.

Proposition 6.1 *In any chemical reaction network, if* $A_\kappa \Psi(c) = 0$ *then the network is weakly reversible.*

Proposition 6.2 ([11, Proposition 5.3 (ii) and (iii)]) *In any chemical reaction network let* $Z = \{c \in \mathbb{P}^{\mathcal{S}} \mid A_\kappa \Psi(c) = 0\}$. *Suppose that* $Z \neq \emptyset$. *For any* $c^* \in Z$, $Z = \{c \in \mathbb{P}^{\mathcal{S}} \mid \ln c - \ln c^* \in S^\perp\}$.

Definition 6.2 *A* (positive) stoichiometric compatibility class *of the network (8) is a nonempty set of the form* $\mathbb{P}^{\mathcal{S}} \cap (S + c)$ *for some* $c \in \mathbb{P}^{\mathcal{S}}$.

Proposition 6.4 *In any chemical reaction network let* $Z = \{c \in \mathbb{P}^{\mathcal{S}} \mid A_\kappa \Psi(c) = 0\}$. *Then, either* $Z = \emptyset$ *or* $\ln Z$ *is a coset of* $S^\perp$ *and* Z *meets each stoichiometric compatibility class in one and only one point.*

Proposition 6.5 *If a chemical reaction network has a fixed point* $c^* \in \mathbb{P}^{\mathcal{S}}$ *for which* $A_\kappa \Psi(c^*) = 0$ *then, for any* $c \in \mathbb{P}^{\mathcal{S}}$, $\langle f(c), \ln c - \ln c^* \rangle \leq 0$, *with equality if, and only if,* $\ln c - \ln c^* \in S^\perp$

Theorem 6.2 ([11, Proposition 5.3 (iii) and (iv)]) *In any chemical reaction network, if there exists some fixed point* $c^* \in \mathbb{P}^{\mathcal{S}}$ *for which* $A_\kappa \Psi(c^*) = 0$ *then any fixed point,* $c \in \mathbb{P}^{\mathcal{S}}$ *with* $f(c) = 0$, *must satisfy the same condition* $A_\kappa \Psi(c) = 0$.

Definition 6.3 *A function $h : \mathbb{R}^m \to \mathbb{R}$ is a* Lyapunov function *for the fixed point c^* if*

1. *$h(c) \geq 0$, for all $c \in \mathbb{R}^m$, with equality if, and only if, $c = c^*$*
2. *$dh(c(t))/dt \leq 0$ along any trajectory, $t \to c(t)$.*

If, furthermore, $dh(c(t))/dt = 0$ if, and only if, $c(t) = c^*$, then the Lyapunov function is strict.

Theorem 6.3 (Lyapunov's Theorem, [20, Chapter 9, §3, Theorem 1]) *If h is a Lyapunov function then c^* is stable. That is, given any neighbourhood $U \ni c^*$, there exists some neighbourhood $U_1 \ni c^*$ in U such that any trajectory $c(t)$ with $c(0) \in U_1$ satisfies $c(t) \in U$ for all $t \geq 0$. If, furthermore, the Lyapunov function is strict then c^* is asymptotically stable. That is, U_1 can always be chosen so that $u(t) \to c^*$ as $t \to \infty$.*

Theorem 6.4 *In any chemical reaction network, suppose there exists a fixed point $c^* \in \mathbb{P}^{\mathcal{S}}$ for which $A_\kappa \Psi(c^*) = 0$. The following statements hold.*

1. *The network is weakly reversible.*
2. *Every fixed point, $c \in \mathbb{P}^{\mathcal{S}}$ with $f(c) = 0$, satisfies $A_\kappa \Psi(c) = 0$.*
3. *If Z is the set of all fixed points, $Z = \{c \in \mathbb{P}^{\mathcal{S}} \mid f(c) = 0\}$, then $\ln Z$ is a coset of $S^\perp$.*
4. *There is one, and only one, fixed point in each stoichiometric compatibility class.*
5. *Each fixed point has a strict Lyapunov function defined on its stoichiometric compatibility class and is asymptotically stable relative to that class.*

Existence of positive fixed points

Lemma 7.1 $\ln(\ker A_\kappa)^+$ *is a coset of* $\mathrm{span}\{\omega_{T_1}, \cdots, \omega_{T_t}\}$. *Furthermore, either* $\ln(\ker A_\kappa)^+ \cap U = \emptyset$ *or* $\ln(\ker A_\kappa)^+ \subseteq U$. *The latter case holds if, and only if, there exists* $c \in \mathbb{P}^{\mathcal{C}}$ *such that* $A_\kappa \Psi(c) = 0$.

Theorem 7.1 *If a chemical reaction network has deficiency 0 then it has a fixed point* $c \in \mathbb{P}^{\mathcal{S}}$ *for which* $A_\kappa \Psi(c) = 0$ *if, and only if, it is weakly reversible.*