Global Attractors in Biochemical Dynamics

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Example

\[
\begin{aligned}
A & \iff 2B \\
A + C & \iff D \\
& \iff B + E
\end{aligned}
\]

\[
\begin{align*}
dc_A/\text{dt} &= -(\kappa_{A\rightarrow 2B})c_A + (\kappa_{2B\rightarrow A})c_B^2 - (\kappa_{A+C\rightarrow D})c_Ac_C + (\kappa_{D\rightarrow A+C})c_D + (\kappa_{B+E\rightarrow A+C})c_{BCE} \\
dc_B/\text{dt} &= 2(\kappa_{A\rightarrow 2B})c_A - 2(\kappa_{2B\rightarrow A})c_B^2 + (\kappa_{D\rightarrow B+E})c_D - (\kappa_{B+E\rightarrow A+C})c_{BCE} \\
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dc_E/\text{dt} &= (\kappa_{D\rightarrow B+E})c_D - (\kappa_{B+E\rightarrow A+C})c_{BCE}.
\end{align*}
\]
The Lorenz equations

\[
\begin{align*}
\frac{dx}{dt} &= ay - ax \\
\frac{dy}{dt} &= cx - y - xz \\
\frac{dz}{dt} &= xy - bz
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\]
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\]

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

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\[ A + C \leftrightarrow D \]
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\begin{align*}
\frac{dc_A}{dt} &= -\left(\kappa_{A \to 2B}\right)c_A + \left(\kappa_{2B \to A}\right)c_B^2 - \left(\kappa_{A+C \to D}\right)c_{AC}c_C + \left(\kappa_{D \to A+C}\right)c_D + \left(\kappa_{B+E \to A+C}\right)c_{BC}c_E \\
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\frac{dc_D}{dt} &= \left(\kappa_{A+C \to D}\right)c_{AC}c_C - \left(\kappa_{D \to A+C}\right)c_D - \left(\kappa_{D \to B+E}\right)c_D \\
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**Notation:** \[ c^y = \prod_{s \in S} (c_s)^{y_s} \]
Vector equations for mass action kinetics

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Vector representation of differential equations:

\[ \frac{dc}{dt} = \sum_{y \to y' \in \mathcal{R}} (\kappa_{y \to y'}) c^y (y' - y) \]
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\end{align*}
\]
Stoichiometric Subspace

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

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>$A + C \leftrightarrow D$</td>
<td>Since $B + E - A - C = (B + E - D) - (A + C - D)$, this simplifies further to give $S = \text{span}{2B - A, A + C - D, B + E - D}$.</td>
</tr>
<tr>
<td>$\downarrow$</td>
<td></td>
</tr>
<tr>
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<td></td>
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Decomposition of the reaction rate function

\[ \frac{dc}{dt} = \sum_{y \rightarrow y' \in \mathcal{R}} (\kappa_{y \rightarrow y'}) c^y (y' - y) \]

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\omega_U(y) = \begin{cases} 
1 & \text{if } y \in U \\
0 & \text{otherwise}
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For a given kinetics, \( \kappa : \mathcal{R} \rightarrow \mathbb{P} \), define the map \( A_\kappa : \mathbb{R}^C \rightarrow \mathbb{R}^C \) by

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

\[ \Psi(c) = \sum_{y \in \mathcal{C}} c^y \omega_y \]
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\Psi(c) = \sum_{y \in \mathcal{C}} c^y \omega_y
\]
Deficiency of a reaction network

\[ \frac{dc}{dt} = f(c) \]

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

**Definition 3.2** The **deficiency** of a chemical reaction network is \( \dim(\ker Y \cap \text{Im} A) \)

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

\[ \ker Y \cap \text{Im} A \subseteq \ker Y|_T \quad (13) \]

and so \( \delta \leq \dim \ker Y|_T \). Let \( s = \dim S \). Since \( \dim T = \dim \ker Y|_T + \dim \text{Im} Y|_T \) 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 \( y_1, \ldots, y_m \in \mathcal{C} \) 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 \( L_1, \ldots, L_l \subseteq \mathcal{C} \) be the linkage classes.

Lemma  The following statements hold for any chemical reaction network:

\[
\text{span}\{\omega_{y'} - \omega_y \mid y \to y'\} = \text{span}\{\omega_{y'} - \omega_y \mid y \sim y'\},
\]

\[
\text{span}\{\omega_{y'} - \omega_y \mid y \to y'\}^\perp = \text{span}\{\omega_{L_1}, \ldots, \omega_{L_l}\},
\]

\[
\dim \text{span}\{\omega_{y'} - \omega_y \mid y \to y'\} = n - l.
\]

Proposition  The deficiency, \( \delta \), 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.

\[
\begin{align*}
A & \iff 2B \\
A + C & \iff D \\
B + E & \iff \\
\end{align*}
\]

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 $M$ be 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 $\text{span}(u)$, with $u \in \mathbb{P}^m$.

Proposition Suppose that $x \in \ker A_k$. 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 $\chi_i \in \overline{\mathbb{P}^C}$ such that $\text{supp}(\chi_i) = T_i$ for $1 \leq i \leq t$.
2. $\ker A_\kappa = \text{span}\{\chi_1, \cdots, \chi_t\}$ 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, $\delta$, 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 $i, j \in C$.

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 $Z = \{ c \in \mathbb{P}^\Sigma | A_\kappa \Psi(c) = 0 \}$. Suppose that $Z \neq \emptyset$. For any $c^* \in Z$, $Z = \{ c \in \mathbb{P}^\Sigma | \ln c - \ln c^* \in S^\perp \}$. 

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

Proposition 6.4 In any chemical reaction network let $Z = \{ c \in \mathbb{P}^\Sigma | A_\kappa \Psi(c) = 0 \}$. 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 $c^* \in \mathbb{P}^\Sigma$ for which $A_\kappa \Psi(c^*) = 0$ then, for any $c \in \mathbb{P}^\Sigma$, $\langle f(c), \ln c - \ln c^* \rangle \leq 0$, 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 $c^* \in \mathbb{P}^\Sigma$ for which $A_\kappa \Psi(c^*) = 0$ then any fixed point, $c \in \mathbb{P}^\Sigma$ 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 \( c^* \in \mathcal{P}^S \) for which \( A_K \Psi(c^*) = 0 \). The following statements hold.

1. The network is weakly reversible.

2. Every fixed point, \( c \in \mathcal{P}^S \) with \( f(c) = 0 \), satisfies \( A_K \Psi(c) = 0 \).

3. If \( Z \) is the set of all fixed points, \( Z = \{c \in \mathcal{P}^S | f(c) = 0\} \), 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 \( \text{span}\{\omega_{T_1}, \cdots, \omega_{T_t}\} \). 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 \( c \in \mathbb{P}^C \) such that \( A_\kappa \Psi(c) = 0 \).

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