Uniqueness and Asymptotic Stability of Equilibria in a Reversible, Non-Complex-Balanced Reaction Network

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Outline

1. Kinds of Reversibility and Equilibria
   - Three Notions of Reversibility
   - Complex Balance: Why and Why Not

2. The Allosteric Ternary Complex Model
   - Structure and Kinetics
   - Existence and Uniqueness of Equilibrium
   - Asymptotic Stability
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The Two Usual Notions of Reversibility in CRNT

- **Weakly reversible network:** Each reaction lies in at least one cycle.
- **Reversible network:** Each reaction is reversible.
- **Complex-balanced equilibrium:** Reaction nodes are flux-neutral: at each node, \( \sum (\text{rates of incoming reactions}) = \sum (\text{rates of outgoing reactions}) \).
- **Detailed-balanced equilibrium:** Any two reverse reactions have same rate.
A Third Notion of Reversibility

“Aren’t All Networks Like That?”

Explicitly-reversibly constructive network:

1. Constructive: Sensible notions of species composition, elementary species, composite species, isomers, etc.

2. Explicitly constructive:
   - Each composite species is produced by a binding reaction or is consumed by a dissociation reaction, and
   - Each elementary species is consumed by a binding reaction or is produced by a dissociation reaction.

3. Explicitly-reversibly constructive: Replace or with and.
Kinds of Reversibility and Equilibria
The Allosteric Ternary Complex Model

Three Notions of Reversibility
Complex Balance: Why and Why Not

Where the Particular Network in this Presentation Lives
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Complex-Balanced (aka Toric) Networks

- **Known Results** on positive equilibria in stoichiometric compatibility classes
  - Uniqueness
  - Local asymptotic stability via entropy-like Lyapunov function

- **Open Conjectures**
  - Persistence
  - Global asymptotic stability

- **Restrictions**
  - Weakly reversible networks
  - Often, algebraic conditions on (mass action) rate constants
Explicitly-Reversibly Constructive Networks

- **My Observations on Reversibility**
  - "Sensible" biochemical networks are explicitly-reversibly constructive.
  - Those that are weakly reversible are actually reversible.

- **Algebraic Constraints for Complex Balance**
  - Justified or verifiable in physics or chemistry?
  - Not enforceable in finite-precision computations.
  - Are mathematical results robust w.r.t. constraints algebraic variety?
    - Can unique equilibria become multiple?
    - Can stable equilibria become unstable?

- **Guiding intuition**: Properties of biochemical reaction networks should not depend on conditions on rate constants that are "stiff", i.e. easy to break, e.g. complement is open and dense; codimension > 0; measure = 0; etc.
  - Uniqueness or quantified multiplicity.
  - Asymptotic stability via quadratic Lyapunov function.
  - Focus on explicitly-reversibly constructive networks.
  - Hope: Better structural conditions on networks will eliminate need for "stiff" algebraic conditions on rate constants.
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Uniqueness of chemical equilibria in ideal mixtures of ideal gases

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We prove the uniqueness of chemical equilibrium for an ideal mixture of ideal gases in a closed, spatially homogeneous volume. Uniqueness, a fundamental issue of chemical physics, is incompletely justified in textbooks and much of the scientific literature. We first reproduce a little known proof by Zel’dovich and show in a more direct fashion than originally presented that a unique equilibrium exists for isothermal reactions. Zel’dovich’s approach is then extended to the adiabatic case, and a more complete exposition than that of Aris is provided. The example of an isothermal, isochoric O-O2-O3 system provides an illustration of uniqueness. The discussion should be useful for students and instructors of graduate level thermal physics, as well as for researchers in macroscale reaction dynamics. © 2008 American Association of Physics Teachers.

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Kinds of Reversibility and Equilibria
The Allosteric Ternary Complex Model

Structure and Kinetics
Existence and Uniqueness of Equilibrium
Asymptotic Stability

Structure

\[ \begin{align*}
R + A & \rightleftharpoons RA \\
B + & \\
\uparrow & \\
RB + A & \rightleftharpoons RAB
\end{align*} \]

\[ \begin{align*}
R + A & \rightleftharpoons RA \\
R + B & \rightleftharpoons RB \\
RA + B & \rightleftharpoons RAB \\
RB + A & \rightleftharpoons RAB
\end{align*} \]
Mass-Action Kinetics

\[ \dot{x} = f(k, x) = -S \cdot w(k, x) \]

- \( x \): Vector of species concentrations
- \( k \): Vector of mass-action rate constants
- \( S \): Stoichiometric matrix
- \( w(k, x) \): Vector of reaction rates

\[
\begin{align*}
    x &= \begin{pmatrix}
        x_R \\
        x_A \\
        x_B \\
        x_{RA} \\
        x_{RB} \\
        x_{RAB}
    \end{pmatrix} \\
    k &= \begin{pmatrix}
        k_{R+A \rightarrow RA} \\
        k_{RA \rightarrow R+A} \\
        k_{R+B \rightarrow RB} \\
        k_{RB \rightarrow R+B} \\
        k_{RAB \rightarrow RA+B} \\
        k_{RB+A \rightarrow RAB} \\
        k_{RAB \rightarrow RB+A}
    \end{pmatrix}
\end{align*}
\]
### Stoichiometric Matrix $S$

The stoichiometric matrix $S$ is given by:

$$
S = \begin{pmatrix}
-1 & 0 & 0 & 1 \\
-1 & 0 & 1 & 0 \\
0 & -1 & 0 & 1 \\
1 & -1 & 0 & 0 \\
0 & 0 & 1 & -1 \\
0 & 1 & -1 & 0
\end{pmatrix}
$$

The reactions are represented as:

- $R + A \leftrightarrow RA$
- $RA + B \leftrightarrow RAB$
- $RAB \leftrightarrow RB + A$
- $RB \leftrightarrow R + B$

The states are denoted as:

- $R$
- $A$
- $B$
- $RA$
- $RB$
- $RAB$
Vector $w(k, x)$ of (Differences of) Reaction Rates

$$w(k, x) = \begin{pmatrix}
    k_{RA \rightarrow RA + A} x_{RA} - k_{R + A \rightarrow RA} x_R x_A \\
    k_{RAB \rightarrow RA + B} x_{RAB} - k_{RA + B \rightarrow RAB} x_R x_A x_B \\
    k_{RB + A \rightarrow RAB} x_{RB} x_A - k_{RAB \rightarrow RB + A} x_{RAB} x_A \\
    k_{R + B \rightarrow RB} x_R x_B - k_{RB \rightarrow R + B} x_{RB}
\end{pmatrix}$$

$$R + A \Leftrightarrow RA$$
$$RA + B \Leftrightarrow RAB$$
$$RAB \Leftrightarrow RB + A$$
$$RB \Leftrightarrow R + B$$
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Existence and Uniqueness of Equilibrium

**Result**

*For the Allosteric Ternary Complex Model, regardless of (positive) rate constants, each stoichiometric compatibility class contains a unique equilibrium state.*

- The unique equilibrium is detailed/complex-balanced only provided a “stiff” algebraic condition on rate constants.
- The network has deficiency one. The Deficiency-Zero Theorem is not applicable.
- The three linkage classes have deficiency zero. The Deficiency-One Theorem is not applicable.
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Two Tools to Study Spectrum of Jacobian Matrix

**Theorem (Classic in Linear Algebra)**

Let $A$ and $B$ be matrices of size $m \times n$ and $n \times m$.

- $\lambda^n p_{AB}(\lambda) = \lambda^m p_{BA}(\lambda)$
- The $m \times m$ matrix $AB$ and the $n \times n$ matrix $BA$ have the same nonzero eigenvalues with the same multiplicities.
- $n + \text{multiplicity}(0, AB) = m + \text{multiplicity}(0, BA)$

**Theorem (Classic in Linear Algebra and Graph Theory)**

Consider a square real nonnegative matrix $M$ and its Laplacian matrix $\mathcal{L}(M)$. Let $\lambda \in \mathbb{C}$ be an eigenvalue of $\mathcal{L}(M)$.

Either $\lambda = 0$ or $\Re(\lambda) > 0$. 
A Matrix Isospectral with the Jacobian Matrix

\[
\begin{align*}
  f(k, x) &= -S \cdot w(k, x) \\
  J(f, k, x) &= -S \cdot J(w, k, x) \\
  L(k, x) &:= J(w, k, x) \cdot S
\end{align*}
\]

- The matrices \( J(f, k, x) \) and \( -L(k, x) \) have the same nonzero eigenvalues with the same multiplicities.
- \( \text{multiplicity}(0, J(f, k, x)) = \text{multiplicity}(0, L(k, x)) + 2 \)
Spectrum of Jacobian Matrix

\[ M(k, x) := \begin{pmatrix}
0 & k_{RA \rightarrow R+A} & k_{R+A \rightarrow RA \times_R} & k_{R+A \rightarrow RA \times_A} \\
k_{RA+B \rightarrow RAB \times_B} & 0 & k_{RAB \rightarrow RA+B} & k_{RA+B \rightarrow RAB \times_RA} \\
k_{RB+A \rightarrow RAB \times_RB} & k_{RAB \rightarrow RB+A} & 0 & k_{RB+A \rightarrow RAB \times_A} \\
k_{R+B \rightarrow RB \times_B} & k_{R+B \rightarrow RB \times_R} & k_{RB \rightarrow R+B} & 0
\end{pmatrix} \]

Result

\[ L(k, x) = \mathcal{L}(M(k, x)) \]

Corollary

Given arbitrary nonnegative vectors \( k \) and \( x \), if \( \lambda \in \mathbb{C} \) is an eigenvalue of the Jacobian matrix \( J(f, k, x) \), then either \( \lambda = 0 \) or \( \text{Re}(\lambda) < 0 \).

Note: The vector \( x \) is not required to be an equilibrium state.
Conservation of Total Concentrations of Elementary Species


$$x_{\text{Elem}} := \begin{pmatrix} x_R \\ x_A \\ x_B \end{pmatrix} \quad x_{\text{Comp}} := \begin{pmatrix} x_{RA} \\ x_{RB} \\ x_{RAB} \end{pmatrix} \quad x = \begin{pmatrix} x_{\text{Elem}} \\ x_{\text{Comp}} \end{pmatrix}$$

$$x_R + x_{RA} + x_{RB} + x_{RAB} = T_R$$
$$x_A + x_{RA} + x_{RAB} = T_A$$
$$x_B + x_{RB} + x_{RAB} = T_B$$

Composition matrix: $E := \begin{pmatrix} 1 & 1 & 1 \\ 1 & 0 & 1 \\ 0 & 1 & 1 \end{pmatrix}$

$$\left( \text{Id}_3 \mid E \right) \cdot x = T \quad x_{\text{Elem}} = T - E \cdot x_{\text{Comp}}$$

(Taking advantage of absence of isomers among elementary species.)
System reduction

\[ \dot{x} = f(k, x) \cong \dot{x}_{\text{Comp}} = g(k, x_{\text{Comp}}) \]  
(dimension 6)  
(dimension 3)

\[ P := \begin{pmatrix} \text{Id}_3 & -E \\ E^T & \text{Id}_3 \end{pmatrix} \]

First three columns of \( P \) span conservation space.  
Last three columns of \( P \) span stoichiometric space.

\[ P^{-1} \cdot J(f, k, x) \cdot P = \begin{pmatrix} O_{3,3} & O_{3,3} \\ * & J(g, k, x_{\text{Comp}}) \end{pmatrix} \]

The nonzero eigenvalues of \( J(f, k, x) \) are  
the nonzero eigenvalues of \( J(g, k, x_{\text{Comp}}) \) with same multiplicities.
Stability

- **Reuse result that justified uniqueness of equilibrium:**
  The matrix $J(g, k, x_{\text{Comp}})$ is nonsingular.

- **Corollary:**
  If $\lambda \in \mathbb{C}$ is an eigenvalue of $J(g, k, x_{\text{Comp}})$, then $\Re(\lambda) < 0$.

**Result**

*For the Allosteric Ternary Complex Model, regardless of (positive) rate constants, the unique equilibrium state in each stoichiometric compatibility class is asymptotically stable via a quadratic Lyapunov function.*