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

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Society for Industrial and Applied Mathematics
Conference on the Life Sciences
Minisymposium on the Long-Term Dynamical Properties of Biochemical Reaction Networks

San Diego, California, USA
7-10 August 2012

Outline

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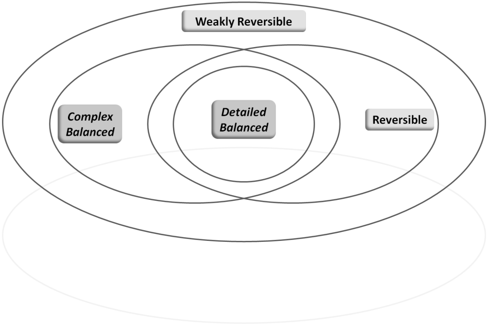
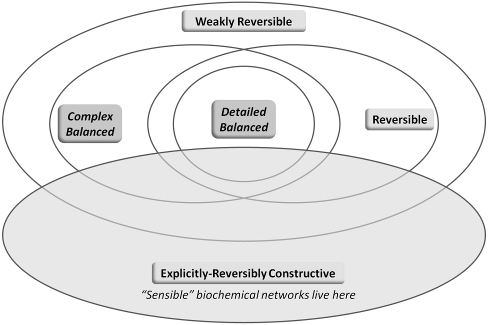
The Two Usual Notions of Reversibility in CRNT



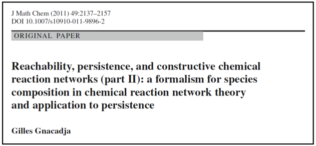
- **Weakly reversible network:** Each reaction lies in at least one cycle.
- **Reversible network:** Each reaction is reversible.
- **Complex-balanced equilibrium:** Reaction nodes are flux-neutral: at each node, $\sum$(rates of incoming reactions) $=$ $\sum$(rates of outgoing reactions).
- **Detailed-balanced 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 <u>or</u> is consumed by a dissociation reaction, and
   - Each elementary species is consumed by a binding reaction <u>or</u> is produced by a dissociation reaction.
3. **Explicitly-reversibly constructive:** Replace <u>or</u> with <u>and</u>.

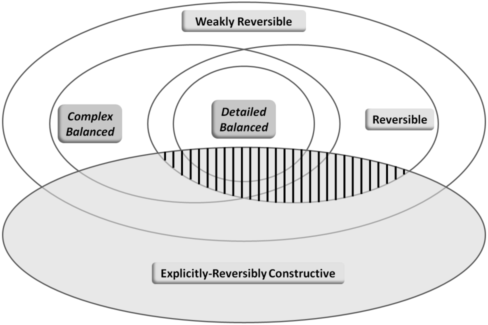

J Math Chem (2011) 49:2137–2157
DOI 10.1007/s10910-011-9896-2

ORIGINAL PAPER

Reachability, persistence, and constructive chemical reaction networks (part II): a formalism for species composition in chemical reaction network theory and application to persistence

Gilles Gnacadja

Where the Particular Network in this Presentation Lives



Outline

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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All This Well Known in Physics or Chemistry?

Uniqueness of chemical equilibria in ideal mixtures of ideal gases

Joseph M. Powers and Samuel Paolucci
Department of Aerospace and Mechanical Engineering, University of Notre Dame, Notre Dame, Indiana 46556-5637

(Received 7 June 2007; accepted 14 April 2008)

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-O_2-O_3 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.*
[DOI: 10.1119/1.2919742]

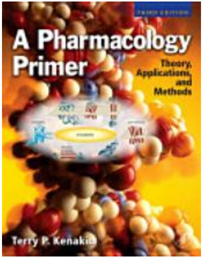
Am. J. Phys. **76** (9), September 2008 http://aapt.org/ajp

Outline

Structure

$$
\begin{array}{ccc}
R + A & \rightleftharpoons & RA \\
+ & & + \\
B & & B \\
\downharpoonleft\upharpoonright & & \downharpoonleft\upharpoonright \\
RB + A & \rightleftharpoons & RAB
\end{array}
$$

$$
\begin{aligned}
R + A &\rightleftharpoons RA \\
R + B &\rightleftharpoons RB \\
RA + B &\rightleftharpoons RAB \\
RB + A &\rightleftharpoons RAB
\end{aligned}
$$



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

$$x = \begin{bmatrix} x_R \\ x_A \\ x_B \\ x_{RA} \\ x_{RB} \\ x_{RAB} \end{bmatrix} \qquad k = \begin{bmatrix} k_{R+A\to RA} \\ k_{RA\to R+A} \\ k_{R+B\to RB} \\ k_{RB\to R+B} \\ k_{RA+B\to RAB} \\ k_{RAB\to RA+B} \\ k_{RB+A\to RAB} \\ k_{RAB\to RB+A} \end{bmatrix}$$

Stoichiometric Matrix S

$$\begin{array}{cc} & \begin{array}{cccc} R+A \rightleftharpoons RA & RA+B \rightleftharpoons RAB & RAB \rightleftharpoons RB+A & RB \rightleftharpoons R+B \end{array} \\ S = & \left(\begin{array}{rrrr} -1 & 0 & 0 & 1 \\ -1 & 0 & 1 & 0 \\ 0 & -1 & 0 & 1 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \\ 0 & 1 & -1 & 0 \end{array}\right) \begin{array}{l} R \\ A \\ B \\ RA \\ RB \\ RAB \end{array} \end{array}$$

Vector $w(k,x)$ of (Differences of) Reaction Rates

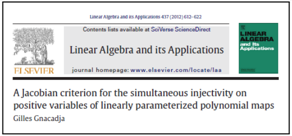
$$w(k,x) = \begin{pmatrix} k_{RA\to R+A} & x_{RA} & - & k_{R+A\to RA} & x_R x_A \\ k_{RAB\to RA+B} & x_{RAB} & - & k_{RA+B\to RAB} & x_{RA} x_B \\ k_{RB+A\to RAB} & x_{RB} x_A & - & k_{RAB\to RB+A} & x_{RAB} \\ k_{R+B\to RB} & x_R x_B & - & k_{RB\to R+B} & x_{RB} \end{pmatrix} \qquad \begin{array}{l} R + A \rightleftharpoons RA \\ RA + B \rightleftharpoons RAB \\ RAB \rightleftharpoons RB + A \\ RB \rightleftharpoons R + B \end{array}$$

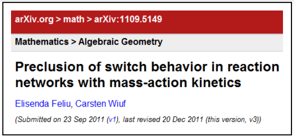
Outline

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.


Linear Algebra and its Applications 437 (2012) 612–622
Contents lists available at SciVerse ScienceDirect
Linear Algebra and its Applications
journal homepage: www.elsevier.com/locate/laa
A Jacobian criterion for the simultaneous injectivity on positive variables of linearly parameterized polynomial maps
Gilles Gnacadja


arXiv.org > math > arXiv:1109.5149
Mathematics > Algebraic Geometry
Preclusion of switch behavior in reaction networks with mass-action kinetics
Elisenda Feliu, Carsten Wiuf
(Submitted on 23 Sep 2011 (v1), last revised 20 Dec 2011 (this version, v3))

- 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.

Outline

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.**
- $n + \mathtt{multiplicity}(0, AB) = m + \mathtt{multiplicity}(0, BA)$

Theorem (Classic in Linear Algebra and Graph Theory)

Consider a square real nonnegative matrix M and its Laplacian matrix $\mathscr{L}(M)$. Let $\lambda \in \mathbb{C}$ be an eigenvalue of $\mathscr{L}(M)$.
Either $\boldsymbol{\lambda} = 0$ or $\mathtt{Re}(\boldsymbol{\lambda}) > 0$.

A Matrix Isospectral with the Jacobian Matrix

$$\begin{aligned} f(k,x) &= -S \cdot w(k,x) \\ J(f,k,x) &= -S \cdot J(w,k,x) \\ L(k,x) &:= J(w,k,x) \cdot S \end{aligned}$$

- The matrices $J(f,k,x)$ and $-L(k,x)$ have the same nonzero eigenvalues with same multiplicities.
- $\texttt{multiplicity}\big(0, J(f,k,x)\big) = \texttt{multiplicity}\big(0, L(k,x)\big) + 2$

Spectrum of Jacobian Matrix

$$M(k,x) := \begin{pmatrix} 0 & k_{RA\to R+A} & k_{R+A\to RA}x_R & k_{R+A\to RA}x_A \\ k_{RA+B\to RAB}x_B & 0 & k_{RAB\to RA+B} & k_{RA+B\to RAB}x_{RA} \\ k_{RB+A\to RAB}x_{RB} & k_{RAB\to RB+A} & 0 & k_{RB+A\to RAB}x_A \\ k_{R+B\to RB}x_B & k_{R+B\to RB}x_R & k_{RB\to R+B} & 0 \end{pmatrix}$$

Result

$$L(k,x) = \mathscr{L}\left(M(k,x)\right)$$

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 $\mathtt{Re}(\lambda) < 0$.

Note: The vector x is not required to be an equilibrium state.

Conservation of Total Concentrations of Elementary Species

Elementary species: R, A, B. Composite species: RA, RB, RAB.

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

$$\begin{aligned} x_R + x_{RA} + x_{RB} + x_{RAB} &= T_R \\ x_A + x_{RA} \phantom{{}+x_{RB}} + x_{RAB} &= T_A \\ x_B \phantom{{}+x_{RA}} + x_{RB} + x_{RAB} &= T_B \end{aligned}$$

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

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

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

System reduction

$$\dot{x} = f(k, x) \quad \cong \quad \dot{x}_{\text{Comp}} = g(k, x_{\text{Comp}})$$

(dimension 6) (dimension 3)

$$P := \begin{pmatrix} \mathrm{Id}_3 & -E \\ E^{\mathsf{T}} & \mathrm{Id}_3 \end{pmatrix}$$

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 $\mathtt{Re}(\lambda) < 0$.

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.