Persistence in Chemical Reaction Network Theory

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Recent Developments in Nonlinear Analysis and Applications
Cotonou, Benin
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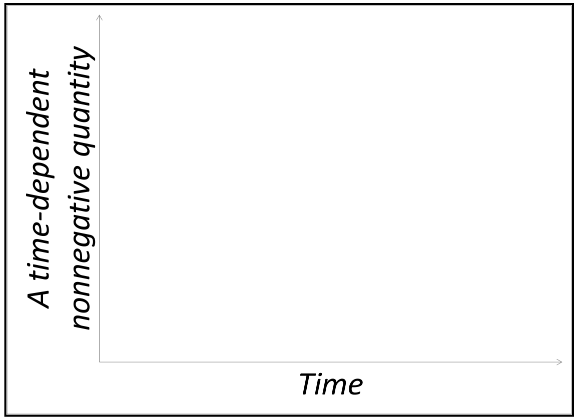
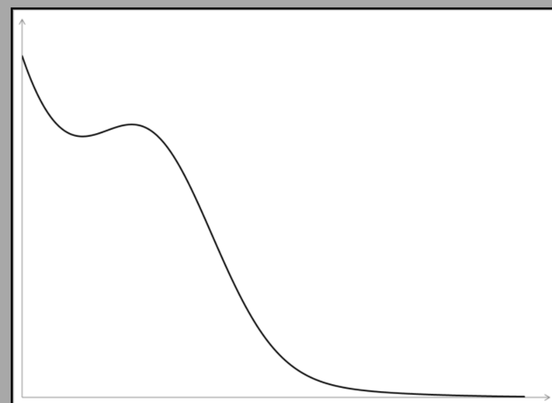
The Idea of Persistence

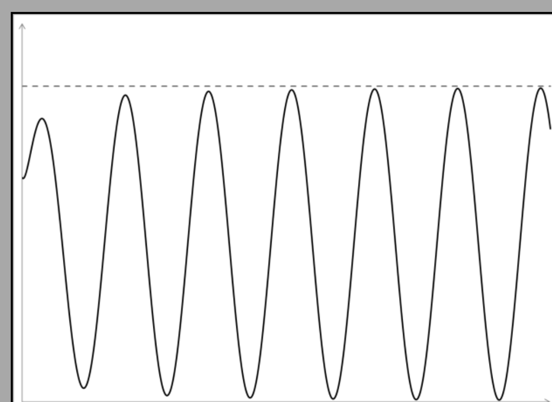


Non-persistence: Trend toward extinction, either in a steady fashion or in recurring and worsening episodes.

Non-persistence

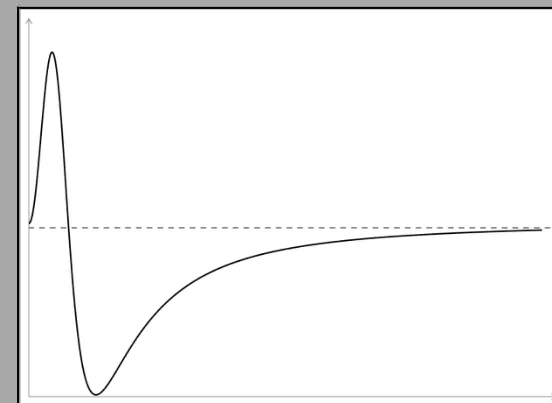


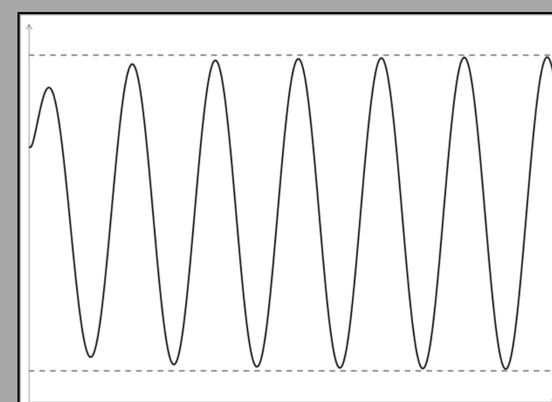
Zero is the limit at infinity



Zero is an ω-limit point

Persistence





Examples of (Chemical) Reaction Networks

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

The Ternary Complex Model,
a basic model in pharmacology

$$E + S \rightleftharpoons ES \rightarrow E + P$$
$$F + P \rightleftharpoons FP \rightarrow F + S$$

A simple futile enzymatic cycle

$$\begin{aligned} \mathrm{Prey} &\rightarrow 2\,\mathrm{Prey} \\ \mathrm{Prey} + \mathrm{Predator} &\rightarrow 2\,\mathrm{Predator} \\ \mathrm{Predator} &\rightarrow 0 \end{aligned}$$

A crude ecological model

Chemical Reaction Network Theory

- A typical question:

  Infer qualitative features of dynamics from structure alone, independently of kinetic parameters.

  (Kinetic parameters are rarely known precisely, if at all.)

- Some qualitative features of interest:
  - Existence of nonnegative/positive equilibrium states
  - Uniqueness of equilibrium state or multistability
  - Local/global asymptotic stability of equilibrium state
  - Periodicity
  - **Persistence**

- Mass-action kinetics assumed throughout.

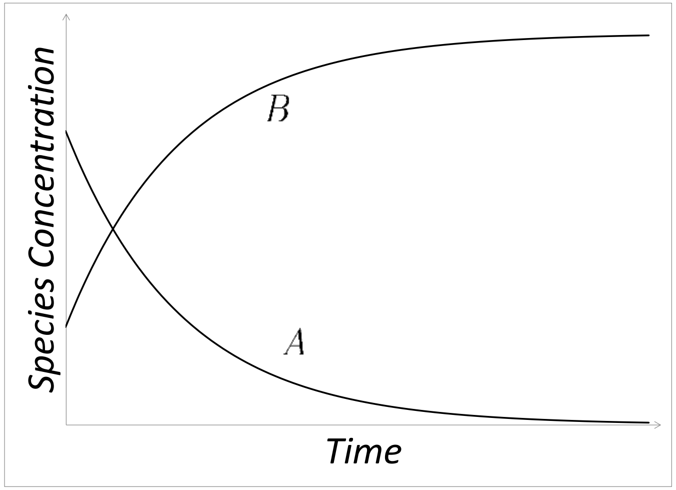
Persistence and Reaction Networks

Persistence:

If all species are present at the initial state, then all species are present at any ω-limit point.

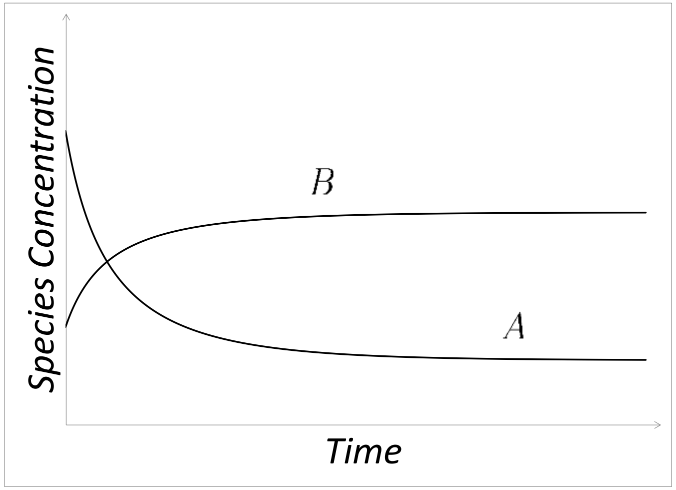
A non-persistent network:

$$A \to B$$



A persistent network:

$$2A \rightleftharpoons B$$



Persistence and Reaction Networks

Why bother about persistence of reaction networks?

- Inherent interest: Can a species disappear?
- Extensively studied in population dynamics.
- In chemical/biochemical models:
  - An early consideration, including a conjecture still open:
    M. Feinberg, Chemical Engineering Science 42 (1987).
  - More recent work: (order more or less chronological)
    D. Siegel, Y. F. Chen, D. MacLean, D. Angeli, P. De Leenheer, E. D. Sontag,
    D. F. Anderson, A. Shiu, B. Sturmfels, G. Craciun, F. Nazarov, C. Pantea, etc.
- Seems to be taken for granted in biochemistry,
  yet the supporting mathematics is not obvious.
- For a large class of networks, persistence is the hurdle to ascertaining global asymptotic stability of positive equilibrium states.

Necessary Condition for Persistence

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Mathematical Biosciences 210 (2007) 598–618

A Petri net approach to the study of persistence in chemical reaction networks

David Angeli [a], Patrick De Leenheer [b,1], Eduardo D. Sontag [c,*,2]

http://dx.doi.org/10.1016/j.mbs.2007.07.003

Theorem: *If a reaction network is persistent, then the reaction vectors are positively dependent.*

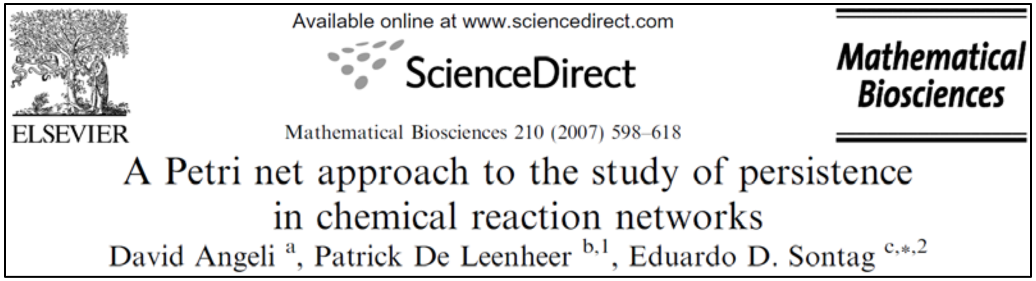
The reaction vectors of the simple futile enzymatic cycle are positively dependent.

$$E + S \rightleftharpoons ES \rightarrow E + P$$
$$F + P \rightleftharpoons FP \rightarrow F + S$$

$$\begin{aligned} & 2\cdot(ES - (E+S)) \;+ 1\cdot((E+S) - ES) \;+ 1\cdot((E+P) - ES) \\ + & \,2\cdot(FP - (F+P)) + 1\cdot((F+P) - FP) + 1\cdot((F+S) - FP) \;=\; 0 \end{aligned}$$

Positive dependence of reaction vectors is a network reversibility condition.

Sufficient Condition for Persistence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Theorem: *A reaction network is persistent provided every nonempty siphon contains the support of some conserved positive combination.*

Siphon in hydraulics; probable inspiration.

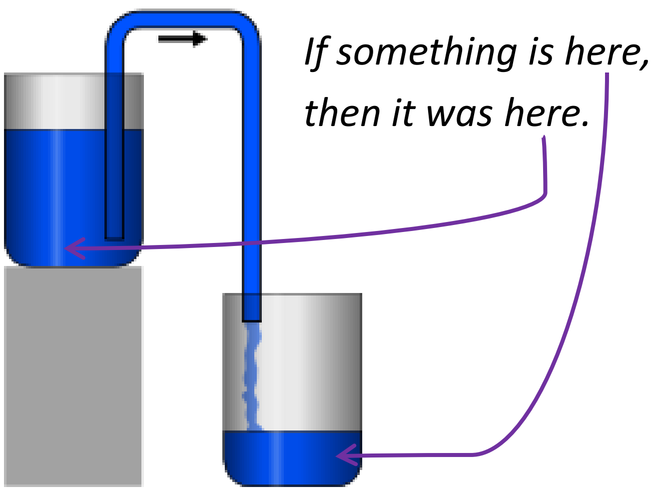

Image retrieved 16 June 2010 from http://en.wikipedia.org/wiki/Siphon.

Definition: *In a reaction network, a siphon is any set $\mathcal{Z}$ of species which satisfies this property:*
If a reaction produces a species in $\mathcal{Z}$,
then it consumes a species in $\mathcal{Z}$.

Intuition in the theorem: If a nonempty siphon has no positive conserved combinations, then it could be depleted and cause non-persistence.

Sufficient Condition for Persistence

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Theorem: *A reaction network is persistent provided every nonempty siphon supports a positive conserved combination.*

$$E + S \rightleftharpoons ES \to E + P$$
$$F + P \rightleftharpoons FP \to F + S$$

The simple futile enzymatic cycle is persistent.

Siphon (minimal, $\neq \emptyset$)	Positive conserved combination
$\{E, ES\}$	$E + ES$
$\{F, FP\}$	$F + FP$
$\{S, P, ES, FP\}$	$S + P + ES + FP$

New Contribution

Motivations

– Incorporate *vacuous persistence*:
Persistence when initial state is *stoichiometrically compatible* with a state where all species are present.
(Stoichiometric compatibility = "matching counts")

– Have a necessary and sufficient condition.

– Be able to tell by visual inspection whether a network of interest is persistent:
  - What a biochemist would do (if they explicitly cared).
  - Computing siphons is easy ...
    with the proper algebraic baggage and/or computational tools
    (e.g. A. Shiu and B. Sturmfels, Bull. Math. Biol. (2010)).

New Contribution

Main result 1

A structural necessary and sufficient condition for vacuous persistence.

Main result 2

For *explicitly-reversibly constructive* networks, the absence of *isomerism* among the elementary species implies vacuous persistence.

Main result 3

For *binary enzymatic* networks, *futility* and *cascadedness* imply vacuous persistence.

Reachability, Persistence, and
Constructive Chemical Reaction Networks
Gilles Gnacadja
Revision D.18 23 April 2010

http://math.GillesGnacadja.info/files/ConstructiveCRNT.html

New Contribution

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Preparation for Main Result 1

- Vacuous Persistence
- Reachability
- Stoichiometric Admissibility

Vacuous Persistence

Persistence:

If all species are present at the initial state, then all species are present at any ω-limit points.

Vacuous Persistence:

If the initial state is stoichiometrically compatible with a state where all species are present, then all species are present at any ω-limit points.

Vacuous Persistence

Why "vacuous"? *(Better terminology most welcome!)*

- Ordinary persistence can occur with opportunities for non-persistence: ω-limit points of degenerate trajectories.
- Vacuous persistence is persistence with the absence of such opportunities.

Equivalent formulation of vacuous persistence

(Eduardo Sontag, private communication, January 2010)

Provided a boundedness condition, vacuous persistence is persistence with the absence of degenerate equilibrium states (resp. degenerate trajectories).

Preparation for Main Result 1

- Vacuous Persistence
- Reachability
- Stoichiometric Admissibility

Reachability

Illustrative examples for the simple futile enzymatic cycle

$$E + S \rightleftharpoons ES \rightarrow E + P \qquad F + P \rightleftharpoons FP \rightarrow F + S$$

$\mathcal{Z} = \{ES, F\}$

r	$\text{Reach}_r(\mathcal{Z})$
0	$\{ES, F\}$
1	$\{E, S, P\}$
2	$\{FP\}$

$\text{Reach}(\mathcal{Z}) = \text{full}$
$\text{NonReach}(\mathcal{Z}) = \varnothing$

$\mathcal{Z} = \{E, S\}$

r	$\text{Reach}_r(\mathcal{Z})$
0	$\{E, S\}$
1	$\{ES\}$
2	$\{P\}$

$\text{Reach}(\mathcal{Z}) = \{E, S, P, ES\}$
$\text{NonReach}(\mathcal{Z}) = \{F, FP\}$

$\mathcal{Z} = \{S, P\}$

r	$\text{Reach}_r(\mathcal{Z})$
0	$\{S, P\}$

$\text{Reach}(\mathcal{Z}) = \{S, P\} = \mathcal{Z}$
$\text{NonReach}(\mathcal{Z}) = \{E, F, ES, FP\}$

General definitions and properties:

- The species in $\text{Reach}_r(\mathcal{Z})$ have reachability index r.
- $\text{Reach}(\mathcal{Z})$ is the reach-closure of $\mathcal{Z}$.
- $\mathcal{Z}$ is reach-closed provided $\text{Reach}(\mathcal{Z}) = \mathcal{Z}$.
- $\text{Reach}(\mathcal{Z})$ is reach-closed.
- $\mathcal{Z}$ is reach-closed if and only if its complement is a siphon.

Reachability

Aizik Isaakovich Vol'pert

*c.*1923-2006

Image retrieved 17 June 2010 from http://www.math.technion.ac.il/~shafrir/volpert.html.

Selected reference
Book title: Analysis in Classes of Discontinuous Functions and Equations of Mathematical Physics
Authors: A. I. Vol'pert and S. I. Hudjaev
Info online: http://www.google.com/books?isbn=9789024731091
Relevant results: Theorem 1 on page 617 and Theorem 2 on page 618

Theorem: (Special form of much more general results on "differential equations on graphs")

Consider a concentration trajectory for time $t \geq 0$.
Let $\mathcal{Z}$ be the set of species present at $t = 0$.

- *If a species is non-reachable from $\mathcal{Z}$, then its concentration is $= 0$ for $t \geq 0$.*
- *If a species is reachable from $\mathcal{Z}$, then its concentration is > 0 for $t > 0$.*

Preparation for Main Result 1

- Vacuous Persistence
- Reachability
- Stoichiometric Admissibility

Stoichiometric Admissibility

Definitions:

- Two sets of species are stoichiometrically compatible if they are the supports of two stoichiometrically compatible states.
  (Reminder: Stoichiometric compatibility = "matching counts")
- A set $\mathcal{Z}$ of species is **stoichiometrically admissible** if it is stoichiometrically compatible with the full set of species.

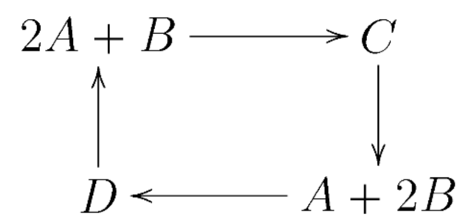
$$\mathrm{Reach}(\mathcal{Z}) = \text{full} \quad \overset{\Rightarrow}{\not\Leftarrow} \quad \mathcal{Z} \text{ is admissible}$$

$$E + S \rightleftharpoons ES \rightarrow E + P$$
$$F + P \rightleftharpoons FP \rightarrow F + S$$

$\mathcal{Z} = \{ES, F\}$

$\mathcal{Z}$ has full reach

$\mathcal{Z}$ is admissible



$\mathcal{Z} = \{A\}$

$\mathcal{Z}$ does not have full reach
($\mathcal{Z}$ is reach-closed)

$\mathcal{Z}$ is admissible

$$(A + B + C + D) - 8A = 4(B - A) + (C - (2A + B)) - ((A + 2B) - D)$$

Main Result 1

Theorem:

Suppose that all concentration trajectories are bounded. The following are equivalent:

– *The reaction network is vacuously persistent.*
– *Among the subsets of the set of all species, only the full set is both reach-closed and stoichiometrically admissible.*

Main tool in proof:
Theorem of A. I. Vol'pert on nullity and positivity of species concentration.

☺ Structural necessary and sufficient condition for vacuous persistence.

☹ Can't tell vacuous persistence just by looking at network.

New Contribution

Main result 1

A structural necessary and sufficient condition for vacuous persistence.

Main result 2

For *explicitly-reversibly constructive* networks, the absence of *isomerism* among the elementary species implies vacuous persistence.

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For *binary enzymatic* networks, *futility* and *cascadedness* imply vacuous persistence.

Types of Reactions

– Binding/association reaction:

(Many species) → (One species)

– Unbinding/dissociation reaction:

(One species) → (Many species)

– Isomerization reaction:

(One species) → (One species)

– Do these really exist? Do they have a name?

(Many species) → (Many species)

Constructive Reaction Networks

Constructive network: (Terminology: Shinar, Alon, Feinberg; SIAM J. Appl. Math. 69 (2009))

There are sensible notions of species composition, elementary species, composite species, etc.
(Think atoms and molecules.)
Isomers = species with same composition.

Explicitly constructive / *Explicitly-reversibly constructive* :

– Constructive;
– Each composite species is produced by a binding reaction **or / *and*** is consumed by a dissociation reaction;
– Each elementary species is consumed by a binding reaction **or / *and*** is produced by a dissociation reaction.

Main Result 2

Theorem:

If a network is explicitly-reversibly constructive and if there is no isomerism among the elementary species, then the network is vacuously persistent.

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

☺

The Ternary Complex Model
is vacuously persistent,
just by visual inspection.

$$E + S \rightleftharpoons ES \rightarrow E + P$$

$$F + P \rightleftharpoons FP \rightarrow F + S$$

☹

The theorem can't tell whether
the simple futile enzymatic cycle
is vacuously persistent;
the species S and P
are elementary and isomeric.

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Enzymatic Reactions

Isomerization

$$S \to P$$

Isomerization of substrate S into product P catalysed by enzyme E

$$E + S \to ES \to E + P$$

Futile cycle (a simple illustrative example)

$$E + S \to ES \to E + P$$
$$F + P \to FP \to F + S$$

Enzyme cascade (a simple illustrative example)

$$\begin{array}{l} E_1 + S_1 \rightleftharpoons E_1S_1 \to E_1 + P_1 \\ \qquad\qquad\qquad\qquad\quad \| \\ \qquad\qquad\qquad\qquad\quad E_2 + S_2 \rightleftharpoons E_2S_2 \to E_2 + P_2 \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \| \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad E_3 + S_3 \rightleftharpoons E_3S_3 \to E_3 + P_3 \end{array}$$

Main Result 3

Theorem:

If a binary enzymatic network is futile and cascaded, then it is vacuously persistent.

Key tools: Mathematical definitions and properties of:

- Binary enzymatic network
- Initial substrate and terminal product
- Reversing enzyme
- Futile network and futility involution
- Cascadedness and cascade index

*** THE END ***

Main result 1

A structural necessary and sufficient condition for vacuous persistence.

Main result 2

For explicitly-reversibly constructive networks, the absence of isomerism among the elementary species implies vacuous persistence.

Main result 3

For binary enzymatic networks, futility and cascadedness imply vacuous persistence.

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