# Reachability Approach to the Persistence of Reaction Networks

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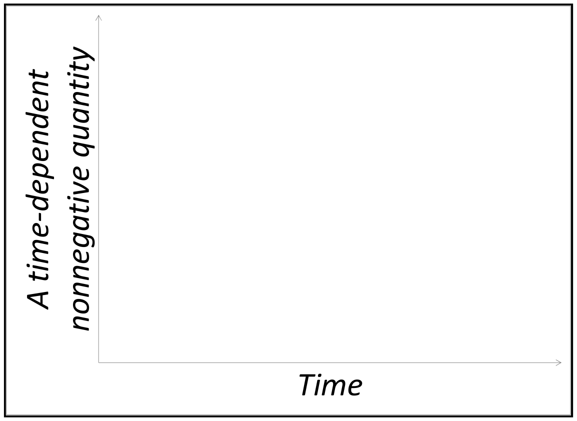
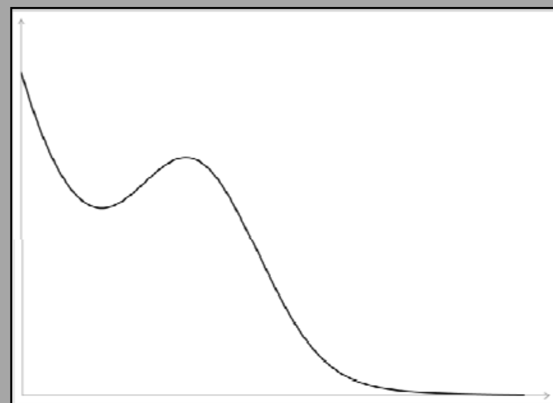
# The Idea of Persistence

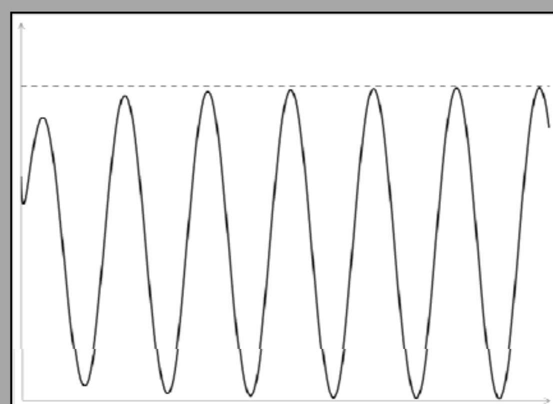



Non-persistence: Trend toward extinction, either continuously or discretely.

## *Non-persistence*

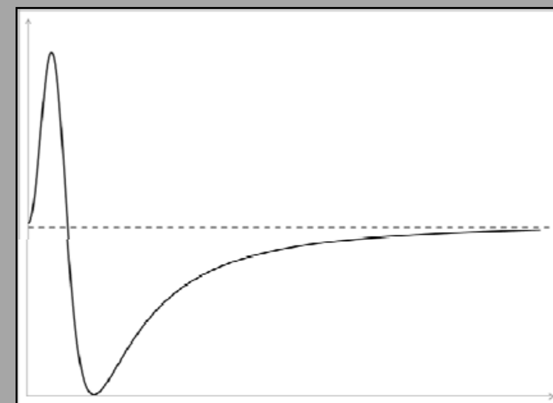


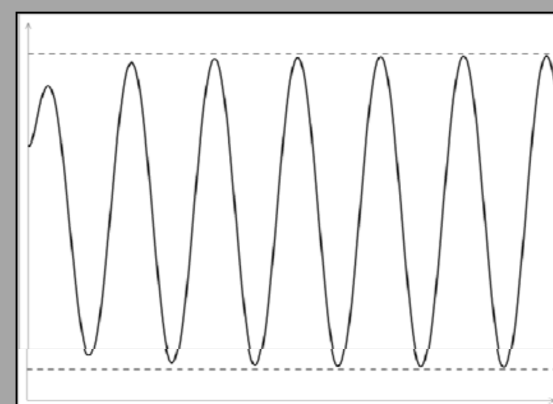
Zero is the limit at infinity



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

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

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.

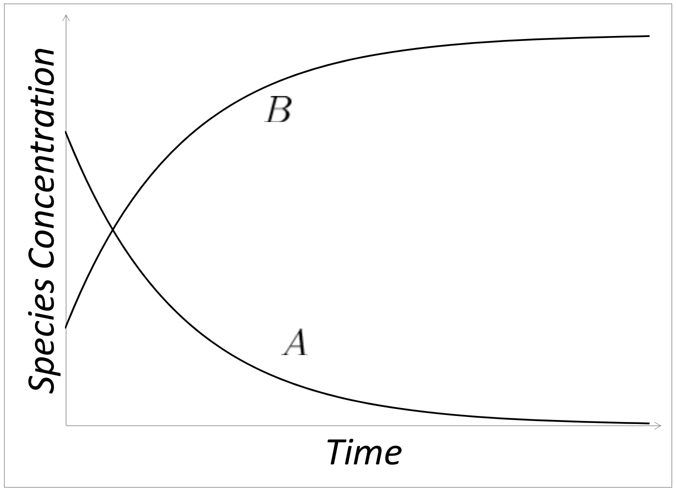
# Persistence and Reaction Networks

**Persistence:**

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

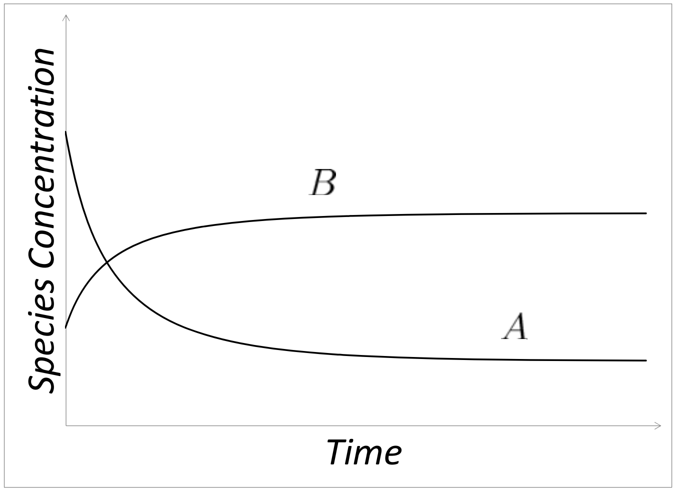
A non-persistent network:

$$A \rightarrow B$$




A persistent network:

$$2A \rightleftharpoons B$$



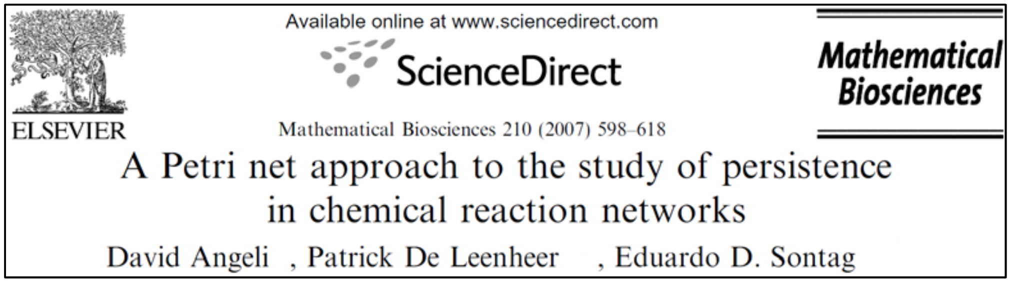
# Persistence and Reaction Networks

## 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 (not exhaustive, 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, M. Johnston, etc.
- For a large class of networks:

***Persistence*** $\Longrightarrow$ ***Global asymptotic stability of positive equilibria***

# ADS Sufficient Condition for Persistence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Mathematical Biosciences
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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, Patrick De Leenheer, Eduardo D. Sontag

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

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

Siphon in hydraulics; probable inspiration.

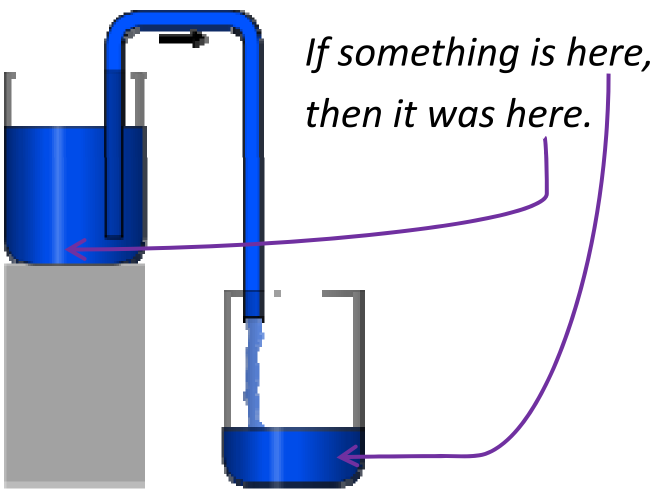


Image retrieved 16 June 2010 from http://en.wikipedia.org/wiki/Siphon.

**Definition:** *In a reaction network, a siphon is a 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.

# ADS Sufficient Condition for Persistence

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

The simple futile enzymatic cycle is persistent.

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

# New Contribution

## Motivations

– Incorporate ***<u>vacuous persistence</u>***:
Persistence when at initial state, all species are implicitly present but need not be explicitly present. Reflects actual experimental settings.

– Have a **necessary and sufficient condition**.

– Be able to tell **by visual inspection** whether networks of interest in biochemistry or pharmacology are 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), http://dx.doi.org/10.1007/s11538-010-9502-y.

# 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.

J Math Chem (2011) 49:2117–2136
DOI 10.1007/s10910-011-9894-4

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A structural necessary and sufficient condition for vacuous persistence.

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

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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"?** *(Too late for better terminology)*

- 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**

(E. D. Sontag, private communication, January 2010)

If stoichiometric compatibility classes are bounded, then vacuous persistence is persistence together with the absence of degenerate equilibrium states (resp. degenerate trajectories).

# Preparation for Main Result 1

- Vacuous Persistence
- Reachability
- Stoichiometric Admissibility

# Reachability

For a set $\mathcal{Z}$ of species:

$$
\begin{aligned}
\text{Prod}(\mathcal{Z}) \quad &: \quad \text{Set of species that can be produced from } \mathcal{Z} \\
&\phantom{:} \quad \text{and are not already is } \mathcal{Z} \\[1em]
\text{Reach}_0(\mathcal{Z}) \quad &= \quad \mathcal{Z} \\
\text{Reach}_1(\mathcal{Z}) \quad &= \quad \text{Prod}(\mathcal{Z}) \\
\text{Reach}_2(\mathcal{Z}) \quad &= \quad \text{Prod}(\mathcal{Z} \cup \text{Reach}_1(\mathcal{Z})) \\
\text{Reach}_3(\mathcal{Z}) \quad &= \quad \text{Prod}(\mathcal{Z} \cup \text{Reach}_1(\mathcal{Z}) \cup \text{Reach}_2(\mathcal{Z})) \\
&\vdots \\
\text{Reach}(\mathcal{Z}) \quad &= \quad \bigsqcup_{r=0}^{\infty} \text{Reach}_r(\mathcal{Z}) \\[1em]
\text{NonReach}(\mathcal{Z}) \quad &: \quad \text{Complement of Reach}(\mathcal{Z})
\end{aligned}
$$

# 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 $r$ w.r.t. $\mathcal{Z}$.
- $\text{Reach}(\mathcal{Z})$ 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.
- A set $\mathcal{Z}$ of species is **stoichiometrically admissible** if it is stoichiometrically compatible with the full set of species.

$$\mathrm{Reach}(\mathcal{Z}) = \mathrm{full} \quad \overrightarrow{\not\leftarrow} \quad \mathcal{Z} \text{ is stoichiometrically admissible}$$

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

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

$\mathcal{Z}$ has full reach

$\mathcal{Z}$ is stoichiometrically admissible

$$\begin{tikzcd} 2A + B \arrow[r] & C \arrow[d] \\ D \arrow[u] & A + 2B \arrow[l] \end{tikzcd}$$

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

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

$\mathcal{Z}$ is stoichiometrically admissible

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

# Preparation for Main Result 1

- Vacuous Persistence
- Reachability
- Stoichiometric Admissibility

# 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.

## Main result 3

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

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# Types of Reactions

– Binding/association reaction:

(Many species) $\rightarrow$ (One species)

– Unbinding/dissociation reaction:

(One species) $\rightarrow$ (Many species)

– Isomerization reaction:

(One species) $\rightarrow$ (One species)

- In actuality, spontaneous, non-catalyzed isomerization reactions probably do not exist.

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

(Many species) $\rightarrow$ (Many species)

# Constructive Reaction Networks

**Constructive network**:

(Terminology: Shinar, Alon, Feinberg; SIAM J. Appl. Math. 69 (2009); http://dx.doi.org/10.1137/080719820)

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.*

$$\begin{array}{ccccc}
R & + A & \rightleftharpoons & RA \\
+ & & & + \\
B & & & B \\
\downarrow\!\uparrow & & & \downarrow\!\uparrow \\
RB & + A & \rightleftharpoons & RAB
\end{array}$$

☺

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.

# 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**

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# Enzymatic Reactions

Isomerization

$$S \rightarrow P$$

Isomerization of substrate $S$ into product $P$ catalysed by enzyme $E$

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

Futile cycle (a simple illustrative example)

$$\begin{aligned} &E + S \rightarrow ES \rightarrow E + P \\ &F + P \rightarrow FP \rightarrow F + S \end{aligned}$$

Enzyme cascade (a simple illustrative example)

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

# Background for Main Result 3

– *Binary enzymatic network*
– *Initial substrates* of a given enzyme:
  Every product is ultimately produced from any initial substrate.
– *Terminal products* of a given enzyme:
  Every substrate ultimately produces any terminal product.
– *Reversing enzyme*:
  The initial substrates of a reversing enzyme are the terminal products of a reversed enzyme.
– *Futile network*:
  Every enzyme is a reversing enzyme.
    – *Futility involution*: Often in practice, enzymes occur in pairs of mutually reversing enzymes.
– *Cascadedness* and *cascade index*

# Background for Main Result 3

Example

$$
\begin{array}{ccccccccc}
E+S_0 & \rightleftharpoons & ES_0 & \rightarrow & E+S_1 & \rightleftharpoons & ES_1 & \rightarrow & E+E^\star \\
F+E^\star & \rightleftharpoons & FS_2 & \rightarrow & F+S_1 & \rightleftharpoons & FS_1 & \rightarrow & F+S_0 \\
E^\star+S_0^\star & \rightleftharpoons & ES_0^\star & \rightarrow & E^\star+S_1^\star & \rightleftharpoons & ES_1^\star & \rightarrow & E^\star+S_2^\star \\
F^\star+S_2^\star & \rightleftharpoons & FS_2^\star & \rightarrow & F^\star+S_1^\star & \rightleftharpoons & FS_1^\star & \rightarrow & F^\star+S_0^\star
\end{array}
$$

| $X \in$ Enz | par$(X)$ | int$(X)$ | isub$(X)$ | tpro$(X)$ | $\varphi(X)$ | $\gamma(X)$ |
|---|---|---|---|---|---|---|
| $E$ | $\{S_0, S_1, E^\star\}$ | $\{ES_0, ES_1\}$ | $\{S_0\}$ | $\{E^\star\}$ | $F$ | $0$ |
| $F$ | $\{S_0, S_1, E^\star\}$ | $\{FS_1, FS_2\}$ | $\{E^\star\}$ | $\{S_0\}$ | $E$ | $0$ |
| $E^\star$ | $\{S_0^\star, S_1^\star, S_2^\star\}$ | $\{ES_0^\star, ES_1^\star\}$ | $\{S_0^\star\}$ | $\{S_2^\star\}$ | $F^\star$ | $1$ |
| $F^\star$ | $\{S_0^\star, S_1^\star, S_2^\star\}$ | $\{FS_1^\star, FS_2^\star\}$ | $\{S_2^\star\}$ | $\{S_0^\star\}$ | $E^\star$ | $0$ |

# Main Result 3

**Theorem:**

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

$$\begin{aligned} E + S &\rightleftharpoons ES \rightarrow E + P \\ F + P &\rightleftharpoons FP \rightarrow F + S \end{aligned}$$

$$\begin{array}{ccccccccc} E + S_0 & \rightleftharpoons & ES_0 & \rightarrow & E + S_1 & \rightleftharpoons & ES_1 & \rightarrow & E + S_2 \\ F + S_2 & \rightleftharpoons & FS_2 & \rightarrow & F + S_1 & \rightleftharpoons & FS_1 & \rightarrow & F + S_0 \end{array}$$

$$\begin{array}{ccccccccc} E + S_0 & \rightleftharpoons & ES_0 & \rightarrow & E + S_1 & \rightleftharpoons & ES_1 & \rightarrow & E + E^\star \\ F + E^\star & \rightleftharpoons & FS_2 & \rightarrow & F + S_1 & \rightleftharpoons & FS_1 & \rightarrow & F + S_0 \\ E^\star + S_0^\star & \rightleftharpoons & ES_0^\star & \rightarrow & E^\star + S_1^\star & \rightleftharpoons & ES_1^\star & \rightarrow & E^\star + S_2^\star \\ F^\star + S_2^\star & \rightleftharpoons & FS_2^\star & \rightarrow & F^\star + S_1^\star & \rightleftharpoons & FS_1^\star & \rightarrow & F^\star + S_0^\star \end{array}$$

☺

These networks are all vacuously persistent, just by visual inspection.

$$\begin{array}{ccccccccc} M + E & \rightleftharpoons & ME & \rightarrow & M_y + E & \rightleftharpoons & M_yE & \rightarrow & M_2 + E \\ M + E & \rightleftharpoons & ME^\star & \rightarrow & M_t + E & \rightleftharpoons & M_tE & \rightarrow & M_2 + E \\ M_2 + F & \rightleftharpoons & M_2F & \rightarrow & M_y + F & \rightleftharpoons & M_yF & \rightarrow & M + F \\ M_2 + F & \rightleftharpoons & M_2F^\star & \rightarrow & M_t + F & \rightleftharpoons & M_tF & \rightarrow & M + F \end{array}$$

# *** 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.

J Math Chem (2011) 49:2117–2136
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ORIGINAL PAPER

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**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

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**Reachability, persistence, and constructive chemical reaction networks (part III): a mathematical formalism for binary enzymatic networks and application to persistence**

Gilles Gnacadja

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