An Algebraic Framework for Describing and Studying Binary Enzymatic Networks

Gilles Gnacadja
http://math.GillesGnacadja.info/

AMGEN
Thousand Oaks, California, USA

Society for Industrial and Applied Mathematics

Conference on the Life Sciences

Minisymposium on the Algebraic Aspects of Biochemical Reaction Networks

Charlotte, North Carolina, USA
4-7 August 2014

An Algebra for Binary Enzymatic Networks

An Algebra for Binary Enzymatic Networks

Enzymes and Enzymatic Reactions (oversimplified)

$A \rightarrow B$ ✗

$E + A \rightarrow E + B$ ✔

Enzyme E catalyzes (enables or accelerates) the conversion of substrate A into product B.

Simple Futile Cycle

$$
\begin{array}{ccccc}
E + A & \rightleftharpoons & EA & \rightarrow & E + B \\
F + A & \leftarrow & FB & \leftrightharpoons & F + B
\end{array}
$$

Species A and B are converted one into the other.

- Enzyme E catalyzes the conversion of A into B.
- Enzyme F catalyzes the reverse conversion.

Simple Cascade

$$
\begin{array}{ccccccccccc}
E_0 + A_0 & \rightleftharpoons & Y_0 & \rightarrow & E_0 + E_1 & & & & & & \\
 & & & & + & & & & & & \\
 & & & & A_1 & & & & & & \\
 & & & & \upharpoonleft\downharpoonright & & & & & & \\
 & & & & Y_1 & & & & & & \\
 & & & & \downarrow & & & & & & \\
 & & & & E_1 & & & & & & \\
 & & & & + & & & & & & \\
 & & & & E_2 + A_2 & \rightleftharpoons & Y_2 & \rightarrow & E_2 + B_2 & &
\end{array}
$$

- E_1 is product in first conversion and enzyme in second.
- E_2 is product in second conversion and enzyme in third.

Some More Elaborate Enzymatic Networks

Examples from

ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
Mathematical Biosciences 210 (2007) 598–618
Mathematical Biosciences

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

David Angeli , Patrick De Leenheer , Eduardo D. Sontag

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

A futile cycle of two two-step pathways

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

Two futile cycles in a cascade

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

One futile cycle with two alternate pathways in each direction

Persistence in Enzymatic Networks

ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
Mathematical Biosciences
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

The three example enzymatic networks are persistent, i.e. if all species are initially present, then none tend to extinction.

Proof: The networks are conservative and their minimal siphons coincide with the supports of the canonical conservation laws.

Persistence in Enzymatic Networks

ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
Mathematical Biosciences
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

The three example enzymatic networks are persistent, i.e. if all species are initially present, then none tend to extinction.

Proof: The networks are conservative and their minimal siphons coincide with the supports of the canonical conservation laws.

Enzymatic Networks: Persistence and Beyond

- Computing minimal siphons can be complex.
- Intuition: The three example networks are different, yet *they look the same* and *I can see* that they (and other enzymatic networks) are persistent. *All sensible enzymatic networks should be persistent; enzymatic feedback mechanisms keep things going.*
- Goal: Formalize this intuition.

  Define enzymatic networks and pertinent attributes to:
  - Express biochemical reality; and
  - Facilitate mathematical reasoning and results, e.g.: ***If a binary enzymatic network is futile and cascaded, then it is persistent.***

Enzymatic Networks: Persistence and Beyond

- Computing minimal siphons can be complex.
- Intuition: The three example networks are different, yet *they look the same* and *I can see* that they (and other enzymatic networks) are persistent.
  All sensible enzymatic networks should be persistent; enzymatic feedback mechanisms keep things going.
- Goal: Formalize this intuition.

  Define enzymatic networks and pertinent attributes to:
  - Express biochemical reality; and
  - Facilitate mathematical reasoning and results, e.g.:
    If a binary enzymatic network is futile and cascaded, then it is persistent.

Enzymatic Networks: Persistence and Beyond

- Computing minimal siphons can be complex.
- Intuition: The three example networks are different, yet *they look the same* and *I can see* that they (and other enzymatic networks) are persistent.
  All sensible enzymatic networks should be persistent; enzymatic feedback mechanisms keep things going.
- Goal: Formalize this intuition.

  Define enzymatic networks and pertinent attributes to:
  - Express biochemical reality; and
  - Facilitate mathematical reasoning and results, e.g.:
    If a binary enzymatic network is futile and cascaded, then it is persistent.

Enzymatic Networks: Persistence and Beyond

- Computing minimal siphons can be complex.
- Intuition: The three example networks are different, yet *they look the same* and *I can see* that they (and other enzymatic networks) are persistent.
  All sensible enzymatic networks should be persistent; enzymatic feedback mechanisms keep things going.
- Goal: Formalize this intuition.

  Define enzymatic networks and pertinent attributes to:
  - Express biochemical reality; and
  - Facilitate mathematical reasoning and results, e.g.:
    If a binary enzymatic network is futile and cascaded, then it is persistent.

Axiomatics ahead

Half the battle in understanding is having the right representation.
Attributed to Pierre-Simon Laplace

An Algebra for Binary Enzymatic Networks

Defining Binary Enzymatic Networks

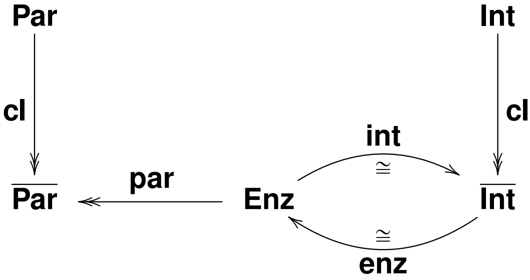
Binary Enzymatic Network

A reaction network $\mathscr{N} = (\mathscr{S}, \mathscr{C}, \mathscr{R})$ is a binary enzymatic network provided the five conditions (Enz1)-(Enz5) are satisfied.

$$E + A \rightleftharpoons EA \rightarrow E + B$$

$\mathscr{S}$: Set of species	$\{E, A, B, EA\}$
$\mathscr{C}$: Set of complexes	$\{E + A, E + B, EA\}$
$\mathscr{R}$: Set of reactions	$\{(E + A, EA), (EA, E + A), (EA, E + B)\}$

Preview: The Maps in Conditions (Enz1)-(Enz5)



Binary Enzymatic Networks – Condition (Enz1)

Condition (Enz1) : species roles

There are four sets **Enz**, **Sub**, **Pro**, **Int** satisfying

- $\emptyset \neq \mathbf{Enz}, \mathbf{Sub}, \mathbf{Pro}, \mathbf{Int} \subsetneq \mathscr{S}$ and
- $\mathscr{S} = \left(\mathbf{Enz} \cup \mathbf{Sub} \cup \mathbf{Pro}\right) \sqcup \mathbf{Int}$.

Enz : Enzymes
Sub : Substrates
Pro : Products
Int : Intermediates

$\mathbf{Par} := \mathbf{Sub} \cup \mathbf{Pro}$ Enzyme partners

$\mathbf{Enz_0} := \mathbf{Enz} \backslash \mathbf{Par}$ Enzymes that are not enzyme partners

$$\mathscr{S} = \left(\mathbf{Enz} \cup \mathbf{Par}\right) \sqcup \mathbf{Int} = \mathbf{Enz_0} \sqcup \mathbf{Par} \sqcup \mathbf{Int}$$

Binary Enzymatic Networks – Condition (Enz2)

Condition (Enz2) : starting and ending info on conversions

There is the set **Cat** $\subseteq$ **Enz** $\times$ **Sub** $\times$ **Pro** of *catalysis triples*.
The three canonical projections restricted to **Cat** are surjective.

$(E, A, B) \in \mathbf{Cat} \quad \Leftrightarrow$ Enzyme E catalyzes (somehow) the conversion of substrate A into product B

Equivalence relation on $\mathbf{Par} = \mathbf{Sub} \cup \mathbf{Pro}$:

$$A \sim B \quad \Leftrightarrow \quad (E, A, B) \in \mathbf{Cat} \text{ for some enzyme } E.$$

Quotient map: $\mathbf{cl} : \mathbf{Par} \to \overline{\mathbf{Par}}$.

Binary Enzymatic Networks – Condition (Enz3)

Condition (Enz3) : conversions each enzyme catalyzes

There is a surjective map $\mathbf{par} : \mathbf{Enz} \to \overline{\mathbf{Par}}$ satisfying

- $\forall\, E \in \mathbf{Enz}, E \notin \mathbf{par}(E)$, and
- $\forall\, (E, A, B) \in \mathbf{Cat}, \{A, B\} \subseteq \mathbf{par}(E)$.

$\mathbf{par}(E)$: Equivalence class of partners of enzyme E
$E \notin \mathbf{par}(E)$: No self-catalyzed enzyme conversion

$\mathbf{sub}(E) := \mathbf{par}(E) \cap \mathbf{Sub}$ Substrates of E
$\mathbf{pro}(E) := \mathbf{par}(E) \cap \mathbf{Pro}$ Products of E

Binary Enzymatic Networks – Condition (Enz4)

Condition (Enz4) : the intermediates for each enzyme

There are

- an equivalence relation on **Int** with quotient map $\mathbf{cl} : \mathbf{Int} \to \overline{\mathbf{Int}}$, and
- two mutually inverse bijections $\mathbf{int} : \mathbf{Enz} \to \overline{\mathbf{Int}}$ and $\mathbf{enz} : \overline{\mathbf{Int}} \to \mathbf{Enz}$.

$\mathbf{int}(E)$: Intermediates in conversion catalyzed by enzyme E

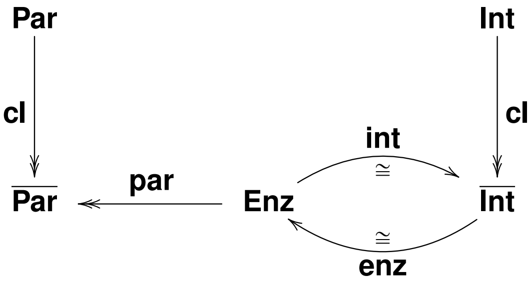
$\mathbf{enz}(\mathscr{Y})$: Enzyme that catalyzes conversions where intermediates in class $\mathscr{Y}$ occur

Binary Enzymatic Networks – Condition (Enz5)

Condition (Enz5) : the reactions

All intermediate pathways are specified for each catalysis triples (E, A, B).

The Maps in Conditions (Enz1)-(Enz5)



Initial Substrates and Terminal Products

$\mathscr{C}(E)$: Complexes of enzyme E

$$\mathscr{C}(E) = \{E + A : A \in \mathbf{par}(E)\} \sqcup \mathbf{int}(E)$$

$\mathbf{isub}(E)$: Initial substrates of E

$$A \in \mathbf{isub}(E) \Leftrightarrow \begin{cases} A \in \mathbf{sub}(E) \\ E + A \text{ ultimately reacts to} \\ \quad \text{every complex in } \mathscr{C}(E) \end{cases}$$

$\mathbf{tpro}(E)$: Terminal products of E

$$B \in \mathbf{tpro}(E) \Leftrightarrow \begin{cases} B \in \mathbf{pro}(E) \\ \text{Every complex in } \mathscr{C}(E) \\ \quad \text{ultimately reacts to } E + B \end{cases}$$

Reversing Enzyme, Futile Network

Reversing Enzyme

An enzyme F is a *reversing enzyme* for an enzyme E provided $\emptyset \neq \mathbf{tpro}(E) = \mathbf{isub}(F)$.

Futile Network

A binary enzymatic network is *futile* provided every enzyme is a reversing enzyme.

- "Every enzyme has a reversing enzyme" did not work.
- In examples, there is a *futility involution* $\varphi : \mathbf{Enz} \to \mathbf{Enz}$.
  - $\varphi \circ \varphi = \mathrm{Id}_{\mathbf{Enz}}$.
  - For every enzyme E, E and $\varphi(E)$ are mutually reversing enzymes.

Reversing Enzyme, Futile Network

Reversing Enzyme

An enzyme F is a *reversing enzyme* for an enzyme E provided $\emptyset \neq \mathbf{tpro}(E) = \mathbf{isub}(F)$.

Futile Network

A binary enzymatic network is *futile* provided every enzyme is a reversing enzyme.

- "Every enzyme has a reversing enzyme" did not work.
- In examples, there is a *futility involution* $\varphi : \mathbf{Enz} \to \mathbf{Enz}$.
  - $\varphi \circ \varphi = \mathrm{Id}_{\mathbf{Enz}}$.
  - For every enzyme E, E and $\varphi(E)$ are mutually reversing enzymes.

Reversing Enzyme, Futile Network

Reversing Enzyme

An enzyme F is a *reversing enzyme* for an enzyme E provided $\emptyset \neq \mathbf{tpro}(E) = \mathbf{isub}(F)$.

Futile Network

A binary enzymatic network is *futile* provided every enzyme is a reversing enzyme.

- "Every enzyme has a reversing enzyme" did not work.
- In examples, there is a *futility involution* $\varphi : \mathbf{Enz} \to \mathbf{Enz}$.
  - $\varphi \circ \varphi = \mathrm{Id}_{\mathbf{Enz}}$.
  - For every enzyme E, E and $\varphi(E)$ are mutually reversing enzymes.

Reversing Enzyme, Futile Network

Reversing Enzyme

An enzyme F is a *reversing enzyme* for an enzyme E provided $\varnothing \neq \mathbf{tpro}(E) = \mathbf{isub}(F)$.

Futile Network

A binary enzymatic network is *futile* provided every enzyme is a reversing enzyme.

- "Every enzyme has a reversing enzyme" did not work.
- In examples, there is a *futility involution* $\varphi : \mathbf{Enz} \to \mathbf{Enz}$.
  - $\varphi \circ \varphi = \mathrm{Id}_{\mathbf{Enz}}$.
  - For every enzyme E, E and $\varphi(E)$ are mutually reversing enzymes.

Cascaded Network

Cascade Index of Enzymes

$$\mathbf{Enz}_0 = \mathbf{Enz} \setminus \mathbf{Par}$$
$$\mathbf{Enz}_m = \Big(\mathbf{Enz} \setminus \big(\mathbf{Enz}_0 \sqcup \cdots \sqcup \mathbf{Enz}_{m-1}\big)\Big) \cap \bigcup_{E \in \mathbf{Enz}_{m-1}} \mathbf{tpro}(E)$$

Cascaded Network

A binary enzymatic network is *cascaded* provided

$$\mathbf{Enz} = \bigsqcup_{m=0}^{\infty} \mathbf{Enz}_m.$$

Illustrative (Simple, Anticlimactic ☹) Example

$$
\begin{array}{ccccc}
E + A & \rightleftharpoons & EA & \rightarrow & E + B \\
F + A & \leftarrow & FB & \leftrightharpoons & F + B
\end{array}
$$

$$
\begin{array}{lll}
\textbf{Enz} = \{E, F\} & \textbf{Sub} = \{A, B\} & \textbf{Par} = \{A, B\} \\
\textbf{Enz}_0 = \{E, F\} & \textbf{Pro} = \{A, B\} & \textbf{Int} = \{EA, FB\}
\end{array}
$$

$$\textbf{Cat} = \{(E, A, A), (E, A, B), (F, B, B), (F, B, A)\}$$

$$\textbf{ParGraph} : \quad A \rightleftarrows B$$

$$\overline{\textbf{Par}} = \{\{A, B\}\} \qquad \overline{\textbf{Int}} = \{\{EA\}, \{FB\}\}$$

$$
\begin{array}{ll}
\textbf{cl}(A) = \{A, B\} & \textbf{cl}(EA) = \{EA\} \\
\textbf{cl}(B) = \{A, B\} & \textbf{cl}(FB) = \{FB\}
\end{array}
$$

Illustrative (Simple, Anticlimactic ☹) Example

$$\begin{array}{lllll} E + A & \rightleftharpoons & EA & \rightarrow & E + B \\ F + A & \leftarrow & FB & \leftrightharpoons & F + B \end{array}$$

$$\mathbf{Enz} = \{E, F\} \qquad \mathbf{Sub} = \{A, B\} \qquad \mathbf{Par} = \{A, B\}$$

$$\mathbf{Enz}_0 = \{E, F\} \qquad \mathbf{Pro} = \{A, B\} \qquad \mathbf{Int} = \{EA, FB\}$$

$$\mathbf{Cat} = \{(E, A, A), (E, A, B), (F, B, B), (F, B, A)\}$$

$$\mathbf{ParGraph} : \quad A \rightleftarrows B$$

$$\overline{\mathbf{Par}} = \{\{A, B\}\} \qquad \overline{\mathbf{Int}} = \{\{EA\}, \{FB\}\}$$

$$\mathbf{cl}(A) = \{A, B\} \qquad \mathbf{cl}(EA) = \{EA\}$$

$$\mathbf{cl}(B) = \{A, B\} \qquad \mathbf{cl}(FB) = \{FB\}$$

Illustrative (Simple, Anticlimactic ☹) Example

$$\begin{array}{ccccc} E + A & \rightleftharpoons & EA & \rightarrow & E + B \\ F + A & \leftarrow & FB & \leftrightharpoons & F + B \end{array}$$

$$\begin{array}{lll} \textbf{Enz} = \{E, F\} & \textbf{Sub} = \{A, B\} & \textbf{Par} = \{A, B\} \\ \textbf{Enz}_0 = \{E, F\} & \textbf{Pro} = \{A, B\} & \textbf{Int} = \{EA, FB\} \end{array}$$

$$\textbf{Cat} = \{(E, A, A), (E, A, B), (F, B, B), (F, B, A)\}$$

$$\textbf{ParGraph} : \quad A \rightleftarrows B$$

$$\overline{\textbf{Par}} = \{\{A, B\}\} \qquad \overline{\textbf{Int}} = \{\{EA\}, \{FB\}\}$$

$$\begin{array}{ll} \textbf{cl}(A) = \{A, B\} & \textbf{cl}(EA) = \{EA\} \\ \textbf{cl}(B) = \{A, B\} & \textbf{cl}(FB) = \{FB\} \end{array}$$

Illustrative (Simple, Anticlimactic ☹) Example

$$\begin{array}{ccccc} E + A & \rightleftharpoons & EA & \rightarrow & E + B \\ F + A & \leftarrow & FB & \leftrightharpoons & F + B \end{array}$$

$$\begin{array}{lll} \mathbf{Enz} = \{E, F\} & \mathbf{Sub} = \{A, B\} & \mathbf{Par} = \{A, B\} \\ \mathbf{Enz}_0 = \{E, F\} & \mathbf{Pro} = \{A, B\} & \mathbf{Int} = \{EA, FB\} \end{array}$$

$$\mathbf{Cat} = \{(E, A, A), (E, A, B), (F, B, B), (F, B, A)\}$$

$$\mathbf{ParGraph} : \quad A \rightleftarrows B$$

$$\overline{\mathbf{Par}} = \{\{A, B\}\} \qquad \overline{\mathbf{Int}} = \{\{EA\}, \{FB\}\}$$

$$\begin{array}{ll} \mathbf{cl}(A) = \{A, B\} & \mathbf{cl}(EA) = \{EA\} \\ \mathbf{cl}(B) = \{A, B\} & \mathbf{cl}(FB) = \{FB\} \end{array}$$

Illustrative (Simple, Anticlimactic ☹) Example

$$
\begin{array}{ccccc}
E+A & \rightleftharpoons & EA & \rightarrow & E+B \\
F+A & \leftarrow & FB & \leftrightharpoons & F+B
\end{array}
$$

$$
\begin{array}{lll}
\textbf{Enz} = \{E, F\} & \textbf{Sub} = \{A, B\} & \textbf{Par} = \{A, B\} \\
\textbf{Enz}_0 = \{E, F\} & \textbf{Pro} = \{A, B\} & \textbf{Int} = \{EA, FB\}
\end{array}
$$

$$\textbf{Cat} = \{(E, A, A), (E, A, B), (F, B, B), (F, B, A)\}$$

$$\textbf{ParGraph} : \quad A \rightleftarrows B$$

$$\overline{\textbf{Par}} = \{\{A, B\}\} \qquad \overline{\textbf{Int}} = \{\{EA\}, \{FB\}\}$$

$$
\begin{array}{ll}
\textbf{cl}(A) = \{A, B\} & \textbf{cl}(EA) = \{EA\} \\
\textbf{cl}(B) = \{A, B\} & \textbf{cl}(FB) = \{FB\}
\end{array}
$$

Illustrative (Simple, Anticlimactic ☹) Example

$$\begin{array}{ccccc} E + A & \rightleftharpoons & EA & \rightarrow & E + B \\ F + A & \leftarrow & FB & \leftrightharpoons & F + B \end{array}$$

$$\textbf{Enz} = \{E, F\} \qquad \textbf{Sub} = \{A, B\} \qquad \textbf{Par} = \{A, B\}$$

$$\textbf{Enz}_0 = \{E, F\} \qquad \textbf{Pro} = \{A, B\} \qquad \textbf{Int} = \{EA, FB\}$$

$$\textbf{Cat} = \{(E, A, A), (E, A, B), (F, B, B), (F, B, A)\}$$

$$\textbf{ParGraph} : \quad A \rightleftarrows B$$

$$\overline{\textbf{Par}} = \{\{A, B\}\} \qquad \overline{\textbf{Int}} = \{\{EA\}, \{FB\}\}$$

$$\textbf{cl}(A) = \{A, B\} \qquad \textbf{cl}(EA) = \{EA\}$$

$$\textbf{cl}(B) = \{A, B\} \qquad \textbf{cl}(FB) = \{FB\}$$

Illustrative (Simple, Anticlimactic ☹) Example – continued

$$\begin{array}{ccccc} E+A & \rightleftharpoons & EA & \rightarrow & E+B \\ F+A & \leftarrow & FB & \leftrightharpoons & F+B \end{array}$$

$$\mathbf{par}(E) = \{A, B\} \quad \mathbf{int}(E) = \{EA\} \quad \mathbf{enz}(\{EA\}) = E$$
$$\mathbf{par}(F) = \{A, B\} \quad \mathbf{int}(F) = \{FB\} \quad \mathbf{enz}(\{FB\}) = F$$

$$\mathbf{sub}(E) = \{A\} \quad \mathbf{pro}(E) = \{A, B\}$$
$$\mathbf{sub}(F) = \{B\} \quad \mathbf{pro}(F) = \{A, B\}$$

$$\mathbf{isub}(E) = \mathbf{tpro}(F) = \{A\}$$
$$\mathbf{isub}(F) = \mathbf{tpro}(E) = \{B\}$$

$$\varphi(E) = F$$
$$\varphi(F) = E$$

Illustrative (Simple, Anticlimactic ☹) Example – continued

$$\begin{array}{ccccc} E + A & \rightleftharpoons & EA & \rightarrow & E + B \\ F + A & \leftarrow & FB & \leftrightharpoons & F + B \end{array}$$

$$\begin{array}{lll} \mathbf{par}(E) = \{A, B\} & \mathbf{int}(E) = \{EA\} & \mathbf{enz}(\{EA\}) = E \\ \mathbf{par}(F) = \{A, B\} & \mathbf{int}(F) = \{FB\} & \mathbf{enz}(\{FB\}) = F \end{array}$$

$$\begin{array}{ll} \mathbf{sub}(E) = \{A\} & \mathbf{pro}(E) = \{A, B\} \\ \mathbf{sub}(F) = \{B\} & \mathbf{pro}(F) = \{A, B\} \end{array}$$

$$\begin{array}{l} \mathbf{isub}(E) = \mathbf{tpro}(F) = \{A\} \\ \mathbf{isub}(F) = \mathbf{tpro}(E) = \{B\} \end{array}$$

$$\begin{array}{l} \varphi(E) = F \\ \varphi(F) = E \end{array}$$

Illustrative (Simple, Anticlimactic ☹) Example – continued

$$\begin{array}{ccccc} E + A & \rightleftharpoons & EA & \rightarrow & E + B \\ F + A & \leftarrow & FB & \leftrightharpoons & F + B \end{array}$$

$$\begin{array}{lll} \mathbf{par}(E) = \{A, B\} & \mathbf{int}(E) = \{EA\} & \mathbf{enz}\big(\{EA\}\big) = E \\ \mathbf{par}(F) = \{A, B\} & \mathbf{int}(F) = \{FB\} & \mathbf{enz}\big(\{FB\}\big) = F \end{array}$$

$$\begin{array}{ll} \mathbf{sub}(E) = \{A\} & \mathbf{pro}(E) = \{A, B\} \\ \mathbf{sub}(F) = \{B\} & \mathbf{pro}(F) = \{A, B\} \end{array}$$

$$\begin{array}{l} \mathbf{isub}(E) = \mathbf{tpro}(F) = \{A\} \\ \mathbf{isub}(F) = \mathbf{tpro}(E) = \{B\} \end{array}$$

$$\begin{array}{l} \varphi(E) = F \\ \varphi(F) = E \end{array}$$

Illustrative (Simple, Anticlimactic ☹) Example – continued

$$E + A \rightleftharpoons EA \rightarrow E + B$$
$$F + A \leftarrow FB \leftrightharpoons F + B$$

$$\mathbf{par}(E) = \{A, B\} \quad \mathbf{int}(E) = \{EA\} \quad \mathbf{enz}(\{EA\}) = E$$
$$\mathbf{par}(F) = \{A, B\} \quad \mathbf{int}(F) = \{FB\} \quad \mathbf{enz}(\{FB\}) = F$$

$$\mathbf{sub}(E) = \{A\} \quad \mathbf{pro}(E) = \{A, B\}$$
$$\mathbf{sub}(F) = \{B\} \quad \mathbf{pro}(F) = \{A, B\}$$

$$\mathbf{isub}(E) = \mathbf{tpro}(F) = \{A\}$$
$$\mathbf{isub}(F) = \mathbf{tpro}(E) = \{B\}$$

$$\varphi(E) = F$$
$$\varphi(F) = E$$

Illustrative (Simple, Anticlimactic ☹) Example – continued

$$\begin{array}{ccccc} E+A & \rightleftharpoons & EA & \rightarrow & E+B \\ F+A & \leftarrow & FB & \leftrightharpoons & F+B \end{array}$$

$$\begin{array}{lll} \mathbf{par}(E) = \{A, B\} & \mathbf{int}(E) = \{EA\} & \mathbf{enz}(\{EA\}) = E \\ \mathbf{par}(F) = \{A, B\} & \mathbf{int}(F) = \{FB\} & \mathbf{enz}(\{FB\}) = F \end{array}$$

$$\begin{array}{ll} \mathbf{sub}(E) = \{A\} & \mathbf{pro}(E) = \{A, B\} \\ \mathbf{sub}(F) = \{B\} & \mathbf{pro}(F) = \{A, B\} \end{array}$$

$$\begin{array}{l} \mathbf{isub}(E) = \mathbf{tpro}(F) = \{A\} \\ \mathbf{isub}(F) = \mathbf{tpro}(E) = \{B\} \end{array}$$

$$\begin{array}{l} \varphi(E) = F \\ \varphi(F) = E \end{array}$$

The paper

J Math Chem (2011) 49:2158–2176
DOI 10.1007/s10910-011-9895-3

ORIGINAL PAPER

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

Gilles Gnacadja