

Metabolic Metro Map

Nucleotide & Protein Metabolism

Carbo Metabolism

Information Systems Laboratory, Electrical Engineering Department,
Stanford University



INSTITUTE FOR RESEARCH IN FUNDAMENTAL SCIENCES

APPLICATIONS OF CONVEX OPTIMIZATION IN METABOLIC NETWORK ANALYSIS

Mojtaba Tefagh

September 19, 2019

Amino Acid Metabolism

Vitamin & Cofactor Metabolism



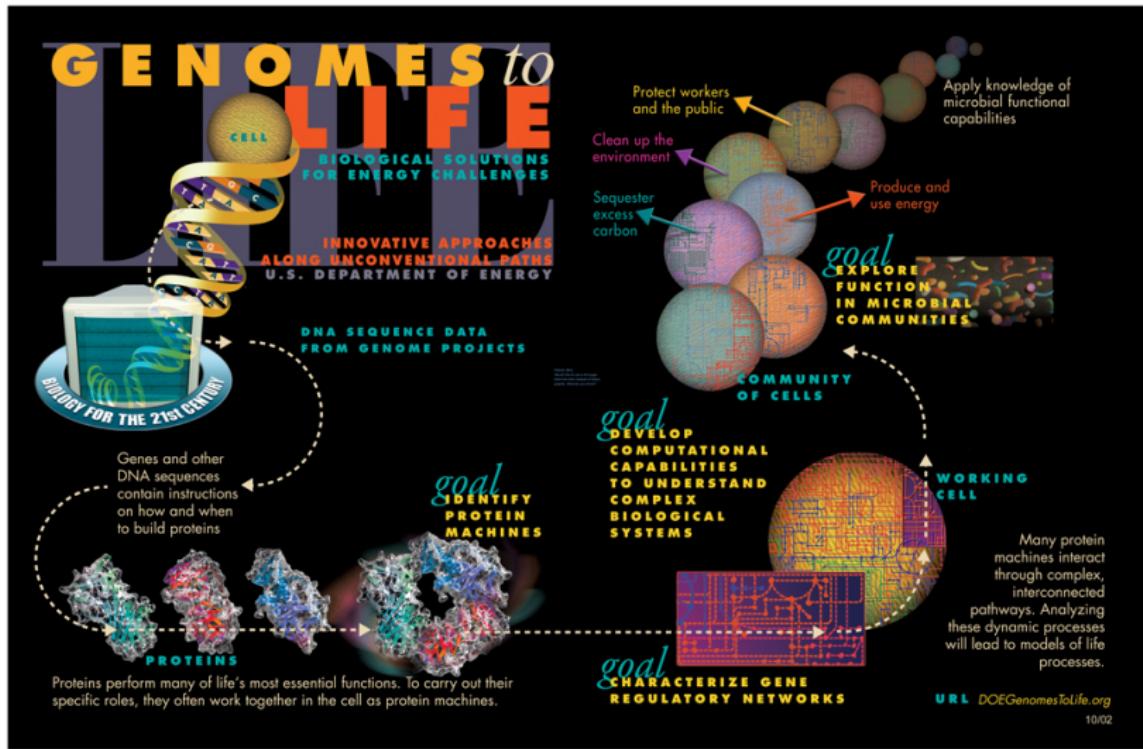
Outline

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- Introduction
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 - COBRA
- Consistency Checking
- QFCA
 - Background
 - Flux Coupling Equations
 - Fictitious Metabolites
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- Metabolic Network Reductions
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Motivation

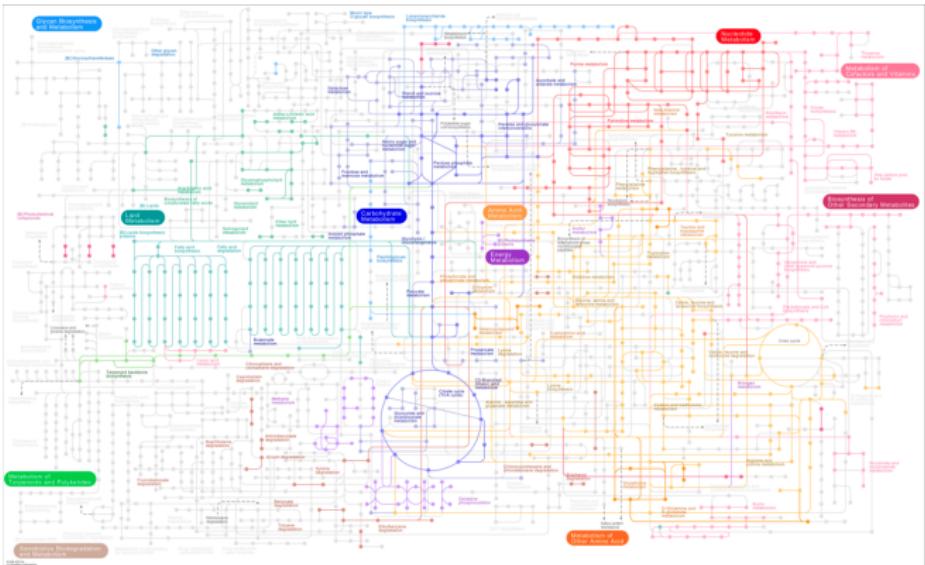


Introduction

Systems Biology

“However, many things have a plurality of parts and are not merely a complete aggregate but instead some kind of a whole beyond its parts.”

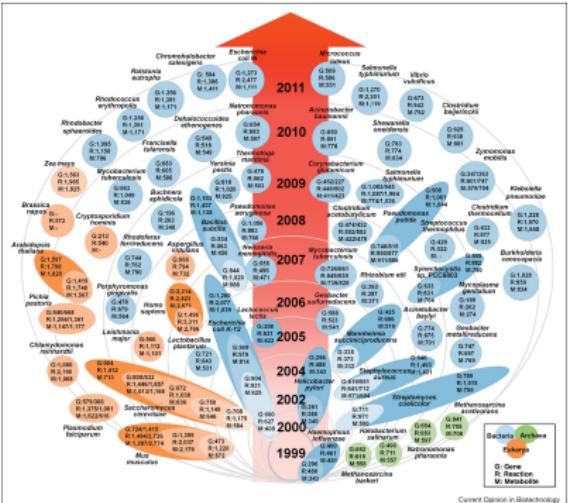
Aristotle, *Metaphysics 8.6*



A metabolic network from KEGG pathway database

Introduction

Constraint-Based Reconstruction and Analysis

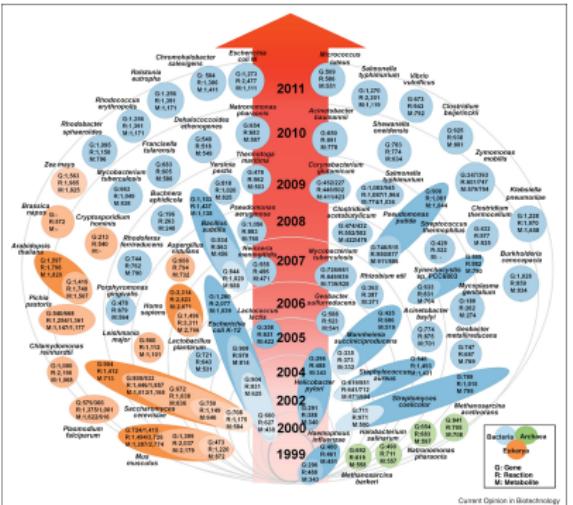


Source: [Kim et al., 2012]

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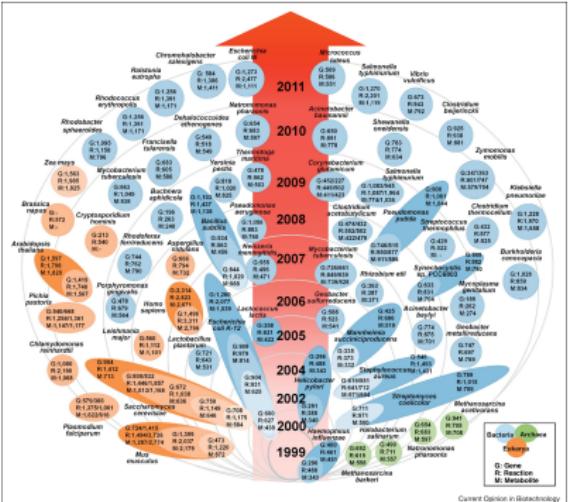


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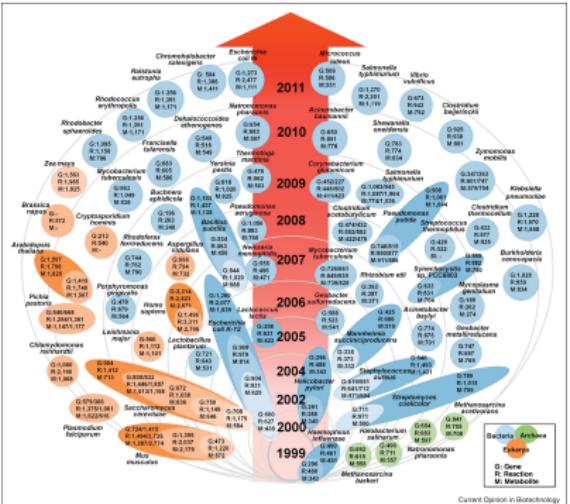


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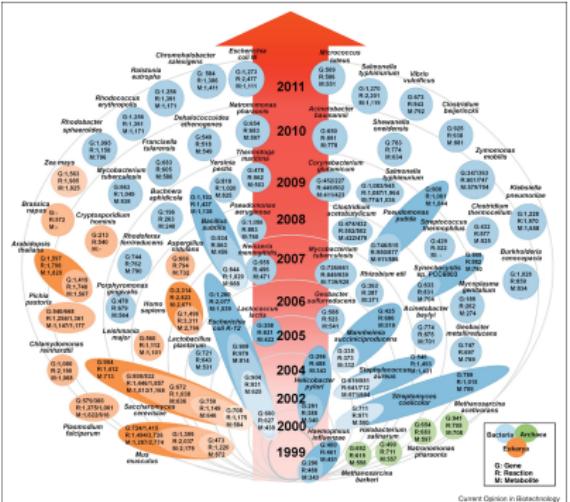


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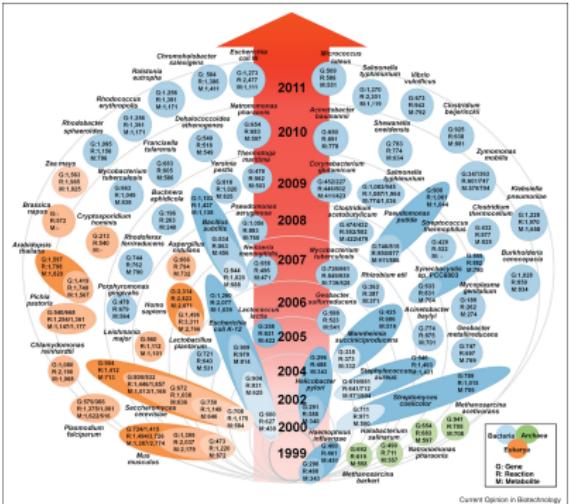


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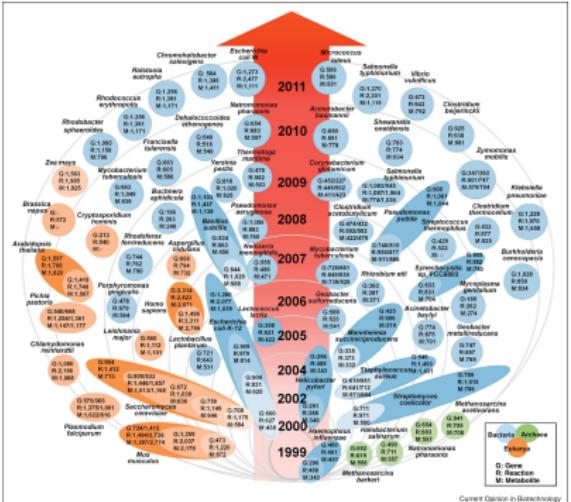
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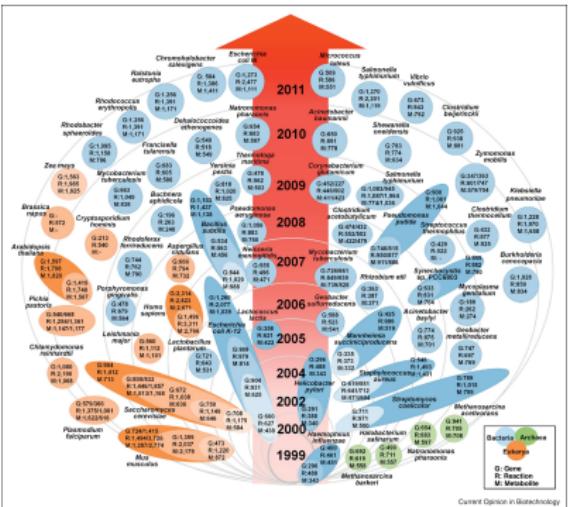


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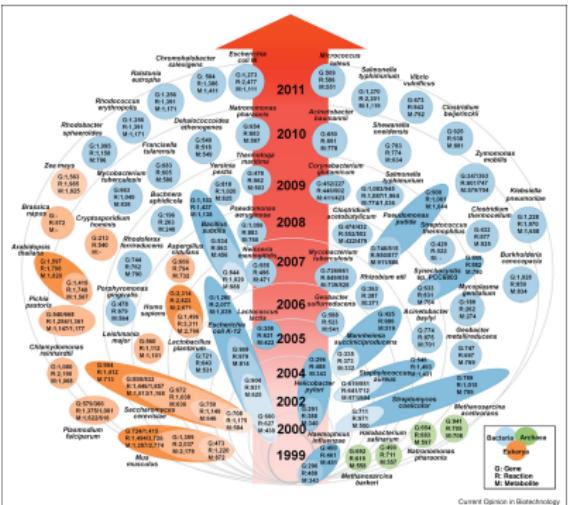


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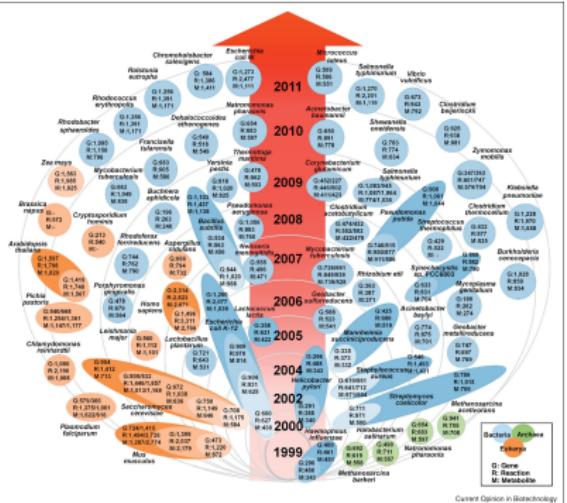
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- ▶ Steady-state flux cone:

$$\mathcal{C} = \{v \in \mathbf{R}^n \mid Sv = 0, v_{\mathcal{I}} \geq 0\}$$



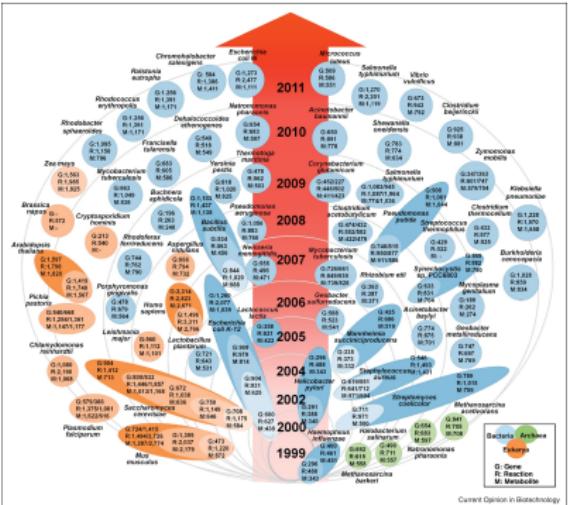
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- ▶ We call $R_i \in \mathcal{R}$ a blocked reaction if $v_i = 0, \forall v \in \mathcal{C}$.



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Consistency Checking

The Naive Approach

Definition ([Schuster and Hilgetag, 1994])

A metabolic network with no blocked reactions is called a flux consistent metabolic network.



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- *The forward direction:*

$$\begin{aligned} & \text{maximize} && v_i \\ & \text{subject to} && v \in \mathcal{C} \\ & && v_i \leq 1 \end{aligned}$$



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Consistency Checking

SWIFTCC



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- ▶ Identifying irreversible blocked reactions by,

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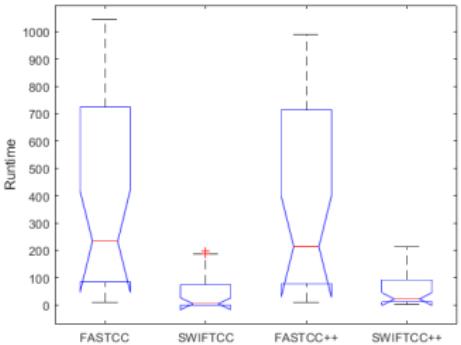
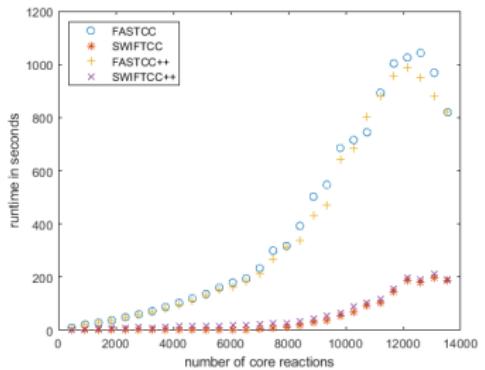
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- ▶ Requires one QR decomposition.

- ▶ Requires one LP.

Consistency Checking

Benchmark



SWIFTCC is more than 8× faster than FASTCC on average over 29 iterations of varying sizes for the Recon3D model.



FCA [Burgard et al., 2004]

Let (R_i, R_j) be an arbitrary pair of unblocked reactions.



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Directional Coupling: $R_i \longrightarrow R_j$ if

$$v_i \neq 0 \Rightarrow v_j \neq 0, \quad \forall v \in \mathcal{C}.$$



QFCA

Flux Coupling Analysis

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Partial Coupling: $R_i \longleftrightarrow R_j$ if

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Full Coupling: $R_i \iff R_j$ if there exists a constant $c \neq 0$ such that

$$v_i = cv_j, \quad \forall v \in \mathcal{C}.$$



Problem

Given the stoichiometric matrix S and the subset of irreversible reactions \mathcal{I} , identify all the blocked reactions and the pairs of reactions which are directional, partially, or fully coupled.



QFCA

Feasibility-based Flux Coupling Analysis

Problem

Given the stoichiometric matrix S and the subset of irreversible reactions \mathcal{I} , identify all the blocked reactions and the pairs of reactions which are directional, partially, or fully coupled.

FFCA [David et al., 2011]

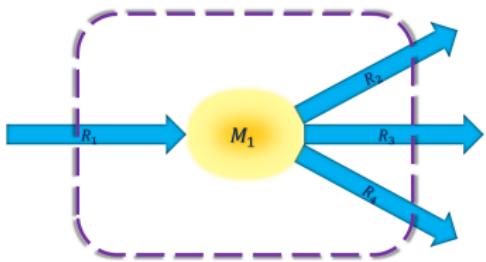
By $n(n_i + 2n_r) + 2n_p$ LP's:

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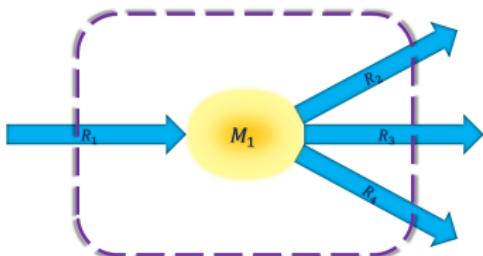
For $t = 2, 3, 4$, $R_t \rightarrow R_1$ can be inferred from the DCE corresponding to M_1 .

QFCA

Directional Coupling Equation

- ▶ For $R_{i_1}, R_{i_2}, \dots, R_{i_l} \in \mathcal{I}$, there exists $c_{i_1}, c_{i_2}, \dots, c_{i_l} > 0$, such that

$$v_j = c_{i_1} v_{i_1} + c_{i_2} v_{i_2} + \dots + c_{i_l} v_{i_l}.$$



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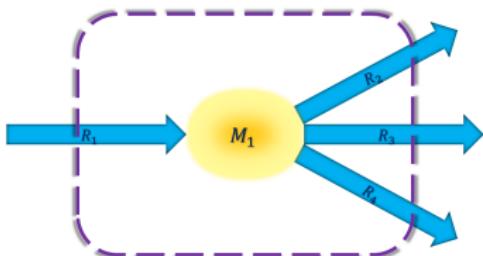
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- ▶ There exists $c'_{i_{l+1}} \neq 0$,

$$v_j = c'_{i_1} v_{i_1} + c'_{i_2} v_{i_2} + \dots + c'_{i_{l+1}} v_{i_{l+1}}. \quad \text{For } t = 2, 3, 4, R_t \rightarrow R_1 \text{ can be inferred from the DCE corresponding to } M_1.$$



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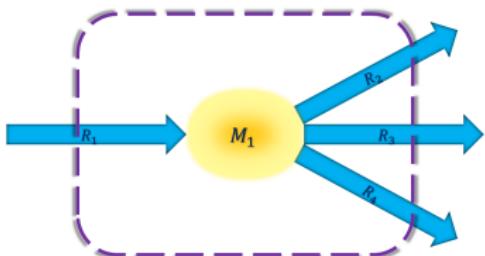
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$v_j = c'_{i_1} v_{i_1} + c'_{i_2} v_{i_2} + \dots + c'_{i_{l+1}} v_{i_{l+1}}$. For $t = 2, 3, 4$, $R_t \rightarrow R_1$ can be inferred from the DCE corresponding to M_1 .

- ▶

$$(1 + \frac{1}{c})v_j = (c_{i_1} + \frac{c'_{i_1}}{c})v_{i_1} + (c_{i_2} + \frac{c'_{i_2}}{c})v_{i_2} + \dots + (c_{i_l} + \frac{c'_{i_l}}{c})v_{i_l} + \frac{c'_{i_{l+1}}}{c}v_{i_{l+1}}$$





Theorem ([Tefagh and Boyd, 2018])

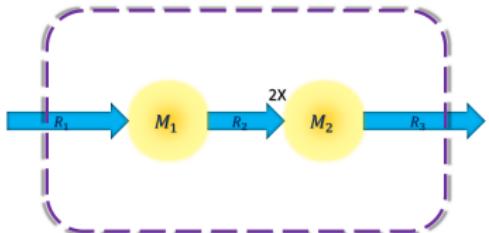
Suppose that $\mathcal{N} = (\mathcal{M}, \mathcal{R}, \mathcal{S}, \mathcal{I})$ has no irreversible blocked reactions. Let R_j be an arbitrary unblocked reaction, and $\mathcal{D}_j \subseteq \mathcal{I}$ denote the set of all the irreversible reactions which are directionally coupled to R_j excluding itself. Then, $\mathcal{D}_j \neq \emptyset$ if and only if there exists $c_d > 0$ for each $R_d \in \mathcal{D}_j$, such that the following directional coupling equation (DCE)

$$v_j = \sum_{d: R_d \in \mathcal{D}_j} c_d v_d,$$

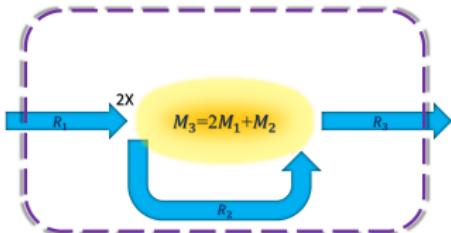
holds for all $v \in \mathcal{C}$. Moreover, for any unblocked $R_i \notin \mathcal{I}$, we have $R_i \rightarrow R_j$ if and only if there exists an extended directional coupling equation (EDCE)

$$v_j = \sum_{d: R_d \in \mathcal{D}_j} c'_d v_d + c'_i v_i \quad c'_i \neq 0,$$

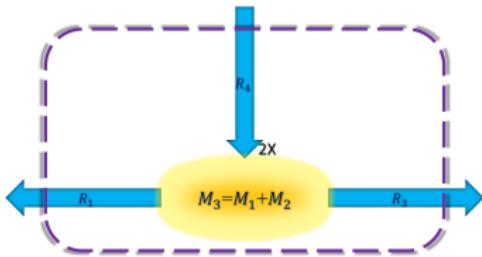
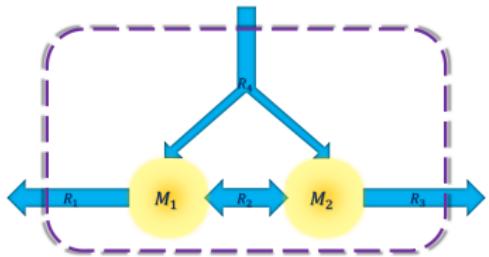
which holds for all $v \in \mathcal{C}$.



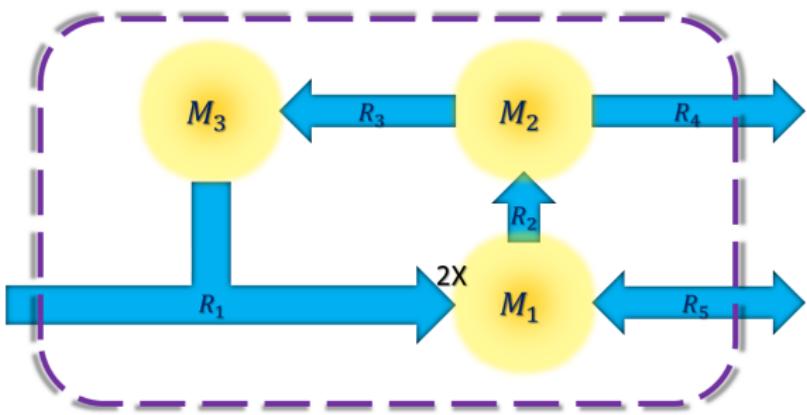
(a) the original metabolic network



(b) the transformed metabolic network



$R_2 \longrightarrow R_4$ can be inferred from the EDCEs corresponding to M_1 and M_2 .



M_1 and $M_1 + M_3$ provide EDCEs, M_2 and $M_2 + M_3$ provide DCEs, and M_3 provides an FCE.



Definition

We call $\lambda \in \mathbf{R}^n$ a fictitious metabolite if there exists $\nu \in \mathbf{R}^m$ such that $\lambda = S^T \nu$.



QFCA

Fictitious Metabolites

14

Definition

We call $\lambda \in \mathbf{R}^n$ a fictitious metabolite if there exists $v \in \mathbf{R}^m$ such that $\lambda = S^T v$.

Theorem

Suppose that in a given metabolic network specified by S and \mathcal{I} , there are no irreversible blocked reactions. Then for any $\lambda \in \mathbf{R}^n$, λ is a fictitious metabolite if and only if

$$\lambda^T v = 0, \quad \forall v \in \mathcal{C}.$$



QFCA

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Lemma

Suppose that in a given metabolic network specified by S and \mathcal{I} , there are no irreversible blocked reactions. Then for any $\lambda \in \mathbf{R}^n$,

$$\lambda^T v = 0, \quad \forall v \in \mathcal{C} \Leftrightarrow \lambda^T u = 0, \quad \forall u \in \ker(S).$$



QFCA

Fictitious Metabolites

$$\begin{aligned}M = & 4 \times 13dp{g[c]} + 2 \times 2pg{[c]} + 2 \times 3pg{[c]} \\& + 4.8756 \times 6pg{c} + 3.8756 \times 6pg{[c]} + 2 \times actp{[c]} \\& - 2 \times adp{[c]} - 4 \times amp{[c]} + 2 \times dhap{[c]} \\& - 1.8756 \times e4p{[c]} + 2 \times f6p{[c]} + 4 \times fdp{[c]} \\& + 2 \times g3p{[c]} + 2 \times g6p{[c]} + 2 \times pep{[c]} \\& + 2 \times pi{[c]} + 1 \times pi{[e]} - 5.7513 \times r5p{[c]} \\& + 5.8756 \times ru5p - D{[c]} - 1.8756 \times s7p{[c]} \\& + 5.8756 \times xu5p - D{[c]}\end{aligned}$$



$$\begin{aligned}
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 & - 2 \times adp{[c]} - 4 \times amp{[c]} + 2 \times dhap{[c]} \\
 & - 1.8756 \times e4p{[c]} + 2 \times f6p{[c]} + 4 \times fdp{[c]} \\
 & + 2 \times g3p{[c]} + 2 \times g6p{[c]} + 2 \times pep{[c]} \\
 & + 2 \times pi{[c]} + 1 \times pi{[e]} - 5.7513 \times r5p{[c]} \\
 & + 5.8756 \times ru5p - D{[c]} - 1.8756 \times s7p{[c]} \\
 & + 5.8756 \times xu5p - D{[c]}
 \end{aligned}$$

- ▶ 3-Phospho-D-glyceroyl-phosphate
- ▶ D-Glycerate-2-phosphate
- ▶ 3-Phospho-D-glycerate
- ▶ 6-Phospho-D-gluconate
- ▶ 6-phospho-D-glucono-1-5-lactone
- ▶ Acetyl-phosphate
- ▶ ADP
- ▶ AMP
- ▶ Dihydroxyacetone-phosphate
- ▶ D-Erythrose-4-phosphate
- ▶ D-Fructose-6-phosphate
- ▶ D-Fructose-1-6-bisphosphate
- ▶ Glyceraldehyde-3-phosphate
- ▶ D-Glucose-6-phosphate
- ▶ Phosphoenolpyruvate
- ▶ Phosphate (pi{[c]})
- ▶ Phosphate (pi{[e]})
- ▶ alpha-D-Ribose-5-phosphate
- ▶ D-Ribulose-5-phosphate
- ▶ Sedoheptulose-7-phosphate
- ▶ D-Xylulose-5-phosphate



QFCA

Positive and Negative Certificates

Table: a bird's eye view of QFCA

	positive certificates	negative certificates	A
\mathcal{B}_R			\emptyset
EDCE	$(S^{(A)})^T x = e_i^{(A)}$	$S^{(A)} u = 0$	$\mathcal{D}_j \cup \{R_j\}$
FCE		$e_i^{(A)^T} u = 1$	$\{j\}$
\mathcal{B}_I	maximize subject to	$\mathbf{1}^T \min(\lambda^{(A)}, \mathbf{1})$ $S^T v = \lambda$ $\lambda_i = 0, \quad i \notin \mathcal{I}$ $\lambda_i \geq 0, \quad i \in \mathcal{I} \setminus A$	
DCE		maximize subject to	$\mathbf{1}^T \min(v_{\mathcal{I}}, \mathbf{1})$ $v \in \mathcal{C}$ $v_A = 0$
			\emptyset
			$\{j\}$



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- ▶ Certificates as potential differences
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- ▶ Certificates as potential differences
- ▶ Certificates as fictitious metabolites
- ▶ Certificates as generalizations of fully coupling constants

$$v_1 = -\frac{\lambda_2}{\lambda_1} v_2 - \frac{\lambda_3}{\lambda_1} v_3 - \cdots - \frac{\lambda_I}{\lambda_1} v_I$$



QFCA

Input: $\mathcal{M}, \mathcal{R}, S, \mathcal{I}$

Output: A, b



QFCA

Final Algorithm

QFCA

Input: $\mathcal{M}, \mathcal{R}, S, \mathcal{I}$

Output: A, b

identifying and removing the blocked reactions from the metabolic network



QFCA

Final Algorithm

QFCA

Input: $\mathcal{M}, \mathcal{R}, S, \mathcal{I}$

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identifying and removing the blocked reactions from the metabolic network
aggregating all the isozymes and removing the newly blocked reactions



QFCA

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QFCA

Input: $\mathcal{M}, \mathcal{R}, S, \mathcal{I}$

Output: A, b

identifying and removing the blocked reactions from the metabolic network

aggregating all the isozymes and removing the newly blocked reactions

identifying the fully coupled pairs of reactions and merging each pair



QFCA

Final Algorithm

QFCA

Input: $\mathcal{M}, \mathcal{R}, S, \mathcal{I}$

Output: A, b

identifying and removing the blocked reactions from the metabolic network
aggregating all the isozymes and removing the newly blocked reactions

identifying the fully coupled pairs of reactions and merging each pair

computing the set of fully reversible reactions and reversibility type pruning



QFCA

Final Algorithm

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Input: $\mathcal{M}, \mathcal{R}, S, \mathcal{I}$

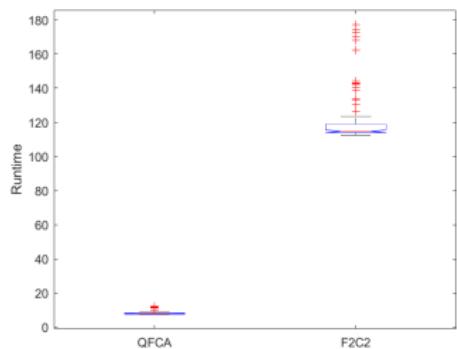
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identifying and removing the blocked reactions from the metabolic network
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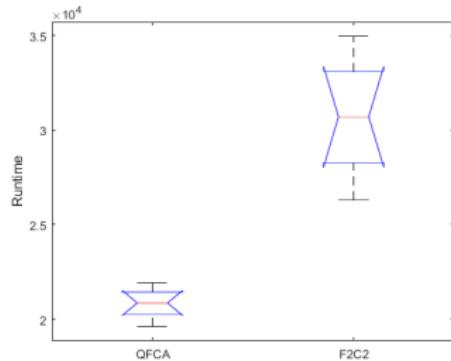
identifying the fully coupled pairs of reactions and merging each pair

computing the set of fully reversible reactions and reversibility type pruning

finding the directional and partial coupling relations by positive certificates



(a) YEASTNET v3.0 with 2292 reversible and 49 irreversible reactions



(b) Recon3D with 5238 reversible and 5362 irreversible reactions

QFCA average runtime is 7% and 68% of F2C2 average runtime, respectively.



► A quantitative approach to FCA

$$v_j \geq cv_i$$



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Equivalently the optimal value of the following LP is zero.

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As a result,

$$(1 - \lambda_j^*)v_j = (c + \lambda_i^*)v_i + \sum_{d \neq i, j} \lambda_d^* v_d,$$



QFCA

Applications

- ▶ A quantitative approach to FCA

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- ▶ Sensitivity analysis



- A quantitative approach to FCA

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- Sensitivity analysis
- The metabolic gap-filling problem

Metabolic Network Reductions

A Toy example

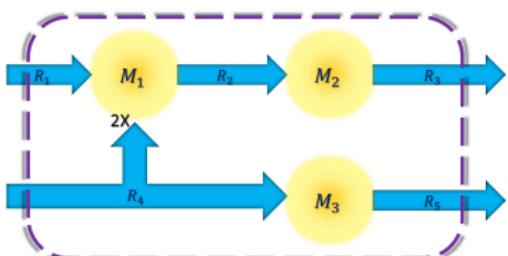
$$\mathcal{N} = (\mathcal{M}, \mathcal{R}, \mathcal{S}, \mathcal{I})$$

$$\mathcal{M} = \{M_1, M_2, M_3\}$$

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$$\mathcal{I} = \mathcal{R}$$

$$\mathcal{S} = \begin{bmatrix} +1 & -1 & 0 & +2 & 0 \\ 0 & +1 & -1 & 0 & 0 \\ 0 & 0 & 0 & +1 & -1 \end{bmatrix}$$



the original metabolic network



Metabolic Network Reductions

A Toy example

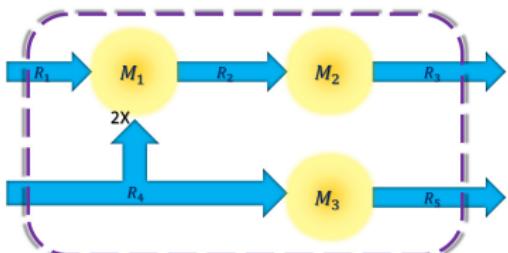
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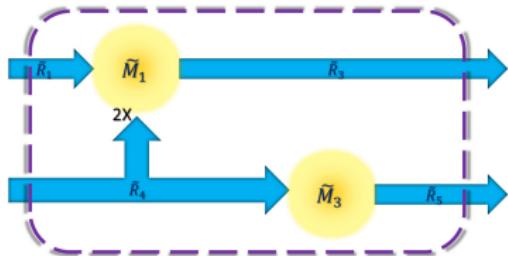
$$v = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} v_1 \\ v_3 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} +1 & 0 & 0 & 0 \\ 0 & +1 & 0 & 0 \\ 0 & +1 & 0 & 0 \\ 0 & 0 & +1 & 0 \\ 0 & 0 & 0 & +1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}.$$

Metabolic Network Reductions

A Toy example

$$\tilde{S} = \begin{bmatrix} +1 & -1 & +2 & 0 \\ 0 & 0 & +1 & -1 \end{bmatrix}$$

- $\tilde{R}_1 \xrightarrow{r_1} \{R_1\}$
- $\tilde{R}_3 \xrightarrow{r_1} \{R_2, R_3\}$
- $\tilde{R}_4 \xrightarrow{r_1} \{R_4\}$
- $\tilde{R}_5 \xrightarrow{r_1} \{R_5\}$



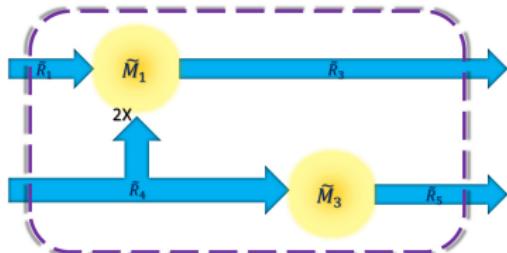
the reduced metabolic network

Metabolic Network Reductions

A Toy example

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the reduced metabolic network

$$Sv = S \begin{bmatrix} +1 & 0 & 0 & 0 \\ 0 & +1 & 0 & 0 \\ 0 & +1 & 0 & 0 \\ 0 & 0 & +1 & 0 \\ 0 & 0 & 0 & +1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} +1 & -1 & +2 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & +1 & -1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}$$

Metabolic Network Reductions

A Toy example

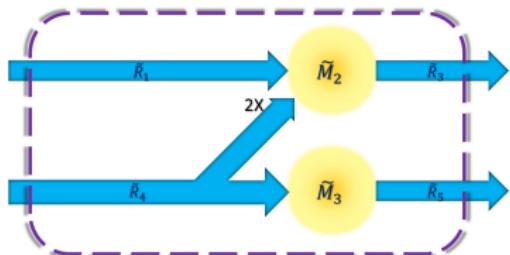
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a DCE-induced reduction

Metabolic Network Reductions

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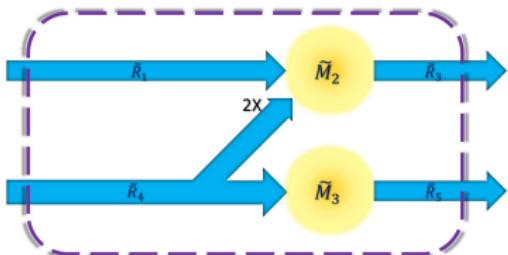
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a DCE-induced reduction

$$v = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} v_1 \\ v_1 + 2v_4 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix} = \begin{bmatrix} +1 & 0 & 0 & 0 \\ +1 & 0 & +2 & 0 \\ 0 & +1 & 0 & 0 \\ 0 & 0 & +1 & 0 \\ 0 & 0 & 0 & +1 \end{bmatrix} \begin{bmatrix} v_1 \\ v_3 \\ v_4 \\ v_5 \end{bmatrix}$$

Metabolic Network Reductions

QFCA Reductions



- ▶ First, we eliminate all the blocked reactions.

Metabolic Network Reductions

QFCA Reductions



- ▶ First, we eliminate all the blocked reactions.
- ▶ Second, we merge all the fully coupled reactions.



Metabolic Network Reductions

QFCA Reductions

- ▶ First, we eliminate all the blocked reactions.
- ▶ Second, we merge all the fully coupled reactions.
- ▶ Third, we remove the eligible reactions by the DCE-induced reductions.



Metabolic Network Reductions

QFCA Reductions

- ▶ First, we eliminate all the blocked reactions.
- ▶ Second, we merge all the fully coupled reactions.
- ▶ Third, we remove the eligible reactions by the DCE-induced reductions.

$$\mathcal{N} \xleftarrow{\phi_1, r_1} \tilde{\mathcal{N}}_1 \xleftarrow{\phi_2, r_2} \dots \xleftarrow{\phi_{n-\tilde{n}}, r_{n-\tilde{n}}} \tilde{\mathcal{N}}_{n-\tilde{n}}$$
$$\tilde{S} = SPA$$
$$\phi^{n-\tilde{n}}(\tilde{v}) = PA\tilde{v}$$

$$A = \begin{pmatrix} & & & \\ & \begin{matrix} 0 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & 0 \end{matrix} & & \\ & & I_{\tilde{n} \times \tilde{n}} & \\ & & & \\ & \begin{matrix} \lambda_{11} & & 0 \\ \vdots & & \\ \lambda_{a_1 1} & \lambda_{12} & \\ & \vdots & \\ & \lambda_{a_2 2} & \\ & & \ddots & \\ & & & \lambda_{1f} \\ & 0 & & \lambda_{a_f f} \end{matrix} & 0 \\ & & & \\ & & C & \end{pmatrix}$$



Metabolic Network Reductions

Canonical Reductions

We say that the metabolic network $\tilde{\mathcal{N}} = (\tilde{\mathcal{M}}, \tilde{\mathcal{R}}, \tilde{\mathcal{S}}, \tilde{\mathcal{I}})$ is a reduction of $\mathcal{N} = (\mathcal{M}, \mathcal{R}, \mathcal{S}, \mathcal{I})$ if



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1. there exists a surjection $\phi : \tilde{\mathcal{C}} \rightarrow \mathcal{C}$,
2. there exists a reduction map $r : \tilde{\mathcal{R}} \rightarrow \mathcal{P}(\mathcal{R})$ such that

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3. and the following diagram commutes

$$\begin{array}{ccc} \tilde{\mathcal{C}} & \xrightarrow{\text{supp}} & \mathcal{P}(\tilde{\mathcal{R}}) \\ \phi \downarrow & & \downarrow \tilde{r} \\ \mathcal{C} & \xrightarrow{\text{supp}} & \mathcal{P}(\mathcal{R}) \end{array}$$

where $\tilde{r} : \mathcal{P}(\tilde{\mathcal{R}}) \rightarrow \mathcal{P}(\mathcal{R})$ is defined by

$$\tilde{r}(\{\tilde{R}_i\}_{i \in I}) = \bigcup_{i \in I} r(\tilde{R}_i).$$



Metabolic Network Reductions

Canonical Reductions

$\phi_1 \circ \phi_2 : \tilde{\mathcal{C}}_2 \rightarrow \mathcal{C}$ is a surjection because the composition of surjective functions is surjective,



Metabolic Network Reductions

Canonical Reductions

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$$\exists \tilde{R}_j \in r_2(\tilde{R}_i) \setminus \bigcup_{k \neq i} r_2(\tilde{R}_k) \Rightarrow \exists R_t \in r_1(\tilde{R}_j) \setminus \bigcup_{k \neq j} r_1(\tilde{R}_k) \Rightarrow R_t \in \tilde{r}_1 \circ r_2(\tilde{R}_i) \setminus \bigcup_{k \neq i} \tilde{r}_1 \circ r_2(\tilde{R}_k),$$



Metabolic Network Reductions

Canonical Reductions

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and the following diagram commutes

$$\begin{array}{ccc} \tilde{\mathcal{C}}_2 & \xrightarrow{\text{supp}} & \mathcal{P}(\tilde{\mathcal{R}}_2) \\ \phi_2 \downarrow & & \downarrow \tilde{r}_2 \\ \tilde{\mathcal{C}}_1 & \xrightarrow{\text{supp}} & \mathcal{P}(\tilde{\mathcal{R}}_1) \\ \phi_1 \downarrow & & \downarrow \tilde{r}_1 \\ \mathcal{C} & \xrightarrow{\text{supp}} & \mathcal{P}(\mathcal{R}) \end{array}$$

because for any $\tilde{v} \in \tilde{\mathcal{C}}_2$

$$\text{supp}(\phi_1 \circ \phi_2(\tilde{v})) = \tilde{r}_1(\text{supp}(\phi_2(\tilde{v}))) = \tilde{r}_1 \circ \tilde{r}_2(\text{supp}(\tilde{v})).$$

Metabolic Network Reductions

Canonical reductions preserve EM's



Definition ([Schuster and Hilgetag, 1994])

We call a nonzero feasible flux distribution $0 \neq v \in \mathcal{C}$ an *elementary mode* (EM), if its support is minimal, or equivalently, if there does not exist any other nonzero feasible flux distribution $0 \neq u \in \mathcal{C}$ such that $\text{supp}(u) \subset \text{supp}(v)$.



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Minimal conserved pool identification (MCPI)

Replace FCA by *Metabolite concentration coupling analysis* (MCCA) and everything works!



Metabolic Network Reductions

Canonical reductions are minimal

Theorem (The reduction theorem)

Suppose that $\tilde{\mathcal{N}} = (\tilde{\mathcal{M}}, \tilde{\mathcal{R}}, \tilde{\mathcal{S}}, \tilde{\mathcal{I}})$ is a metabolic network reduction of $\mathcal{N} = (\mathcal{M}, \mathcal{R}, \mathcal{S}, \mathcal{I})$ by the surjection $\phi : \tilde{\mathcal{C}} \rightarrow \mathcal{C}$ and the reduction map $r : \tilde{\mathcal{R}} \rightarrow \mathcal{P}(\mathcal{R})$. For each $\tilde{R}_i, \tilde{R}_j \in \tilde{\mathcal{R}}$ such that $\tilde{R}_i \longrightarrow \tilde{R}_j$, any reaction in $r(\tilde{R}_i) \setminus \bigcup_{k \neq i} r(\tilde{R}_k)$ is directionally coupled to any reaction in $r(\tilde{R}_j)$.

Conversely, if there exists a reaction in $r(\tilde{R}_i)$ which is directionally coupled to some reaction in $r(\tilde{R}_j) \setminus \bigcup_{k \neq j} r(\tilde{R}_k)$, then $\tilde{R}_i \longrightarrow \tilde{R}_j$.



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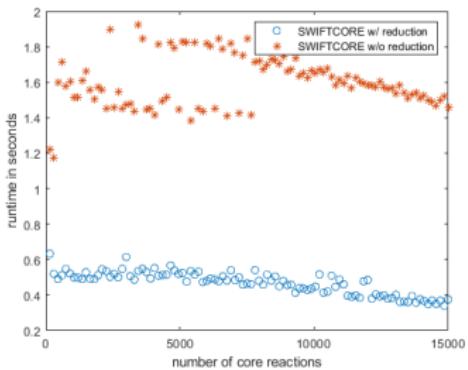
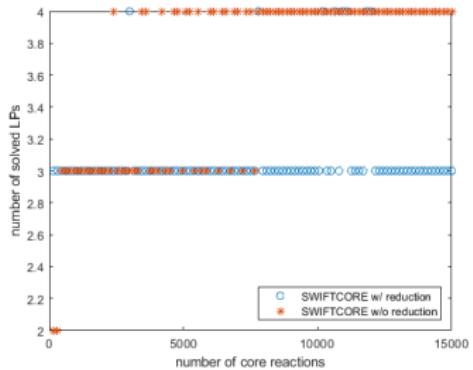
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Remark

By setting $i = j$ in the reduction theorem, any reaction in $r(\tilde{R}_i) \setminus \bigcup_{k \neq i} r(\tilde{R}_k)$ is directionally coupled to any reaction in $r(\tilde{R}_i)$.

Metabolic Network Reductions

Benchmark



SWIFTCORE runs more than 3× faster on the reduced BiGG universal model

$$m = 13249, n = 24311, nnz(S) = 95774$$

$$\tilde{m} = 1278, \tilde{n} = 10255, nnz(\tilde{S}) = 56457$$

Metabolic Network Reductions

Biological Intuition



The DCE reduced reactions are...

Metabolic Network Reductions

Biological Intuition



29

The DCE reduced reactions are...

- essential reactions

Essential reactions are the symmetric counterpart of the blocked reactions.

Metabolic Network Reductions

Biological Intuition



29

The DCE reduced reactions are...

- ▶ essential reactions
- ▶ exchange reactions

Essential reactions are the symmetric counterpart of the blocked reactions.



Metabolic Network Reductions

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The DCE reduced reactions are...

- ▶ essential reactions
- ▶ exchange reactions
- ▶ of older evolutionary age

Essential reactions are the symmetric counterpart of the blocked reactions.

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The DCE reduced reactions are...

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- ▶ of older evolutionary age
- ▶ evolutionary more conserved

Essential reactions are the symmetric counterpart of the blocked reactions.



Metabolic Network Reductions

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The DCE reduced reactions are...

- ▶ essential reactions
- ▶ exchange reactions
- ▶ of older evolutionary age
- ▶ evolutionary more conserved
- ▶ essential in a wide range of conditions

Essential reactions are the symmetric counterpart of the blocked reactions.



Metabolic Network Reductions

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The DCE reduced reactions are...

- ▶ essential reactions
- ▶ exchange reactions
- ▶ of older evolutionary age
- ▶ evolutionary more conserved
- ▶ essential in a wide range of conditions
- ▶ their associated genes are more expressed

Essential reactions are the symmetric counterpart of the blocked reactions.



Metabolic Network Reductions

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- ▶ the reactions that produce biomass metabolites uniquely

Essential reactions are the symmetric counterpart of the blocked reactions.



Metabolic Network Reductions

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- ▶ of older evolutionary age
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- ▶ essential in a wide range of conditions
- ▶ their associated genes are more expressed
- ▶ the reactions that produce biomass metabolites uniquely
- ▶ the reactions enriching the vital metabolic processes of the cell

Essential reactions are the symmetric counterpart of the blocked reactions.

Conclusions



- ▶ QFCA



Conclusions

- ▶ QFCA
 - ▶ Flux coupling equations



Conclusions

- ▶ QFCA
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 - ▶ Fictitious metabolites



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 - ▶ Providing lower bounds
 - ▶ Robust to missing reactions



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 - ▶ Metabolic gap-filling problem



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- ▶ Metabolic Network Reduction
 - ▶ Decreasing the size



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- ▶ Decreasing the size
- ▶ Preserving sparsity



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- ▶ Context-free reductions



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 - ▶ Preserving EM's
 - ▶ The first axiomatic framework



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Further Topics



- ▶ Closure of a metabolic network



Further Topics

- ▶ Closure of a metabolic network
- ▶ SWIFTCC++



Further Topics

- ▶ Closure of a metabolic network
- ▶ SWIFTCC++
- ▶ SWIFTCORE



Further Topics

- ▶ Closure of a metabolic network
- ▶ SWIFTCC++
- ▶ SWIFTCORE
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- ▶ SPARSEQFCA
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- ▶ SWIFTGAPFILL
- ▶ SPARSEQFCA
- ▶ Inhibition analysis
- ▶ Biological fidelity

Metabolic Metro Map

Nucleotide & Protein Metabolism

Carbohydrate Metabolism



Thank You!

Photosynthesis

Cellular Respiration

Amino Acid Metabolism

Vitamin & Cofactor Metabolism

Lipid Metabolism
Messengers



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