Flux Coupling Analysis, Part II

A. Bockmayr
(joint work with A. Larhlimi, CompLife'06)

FB Mathematik und Informatik, Freie Universität Berlin

Molekulare Netzwerke, WS 2010

Flux coupling algorithms

- Flux Coupling Finder (FCF) [Burgard et al. 2004]:
  - Based on linear fractional optimization
  - Shortcomings:
    - ⋆ FCF needs bounds on the fluxes through exchange reactions.
    - ⋆ FCF requires a reconfiguration of the metabolic network.
    - ⋆ A post-processing step is needed to deduce reaction couplings.
    - ⋆ A large number of linear optimization problems has to be solved.
- Alternative approach ?

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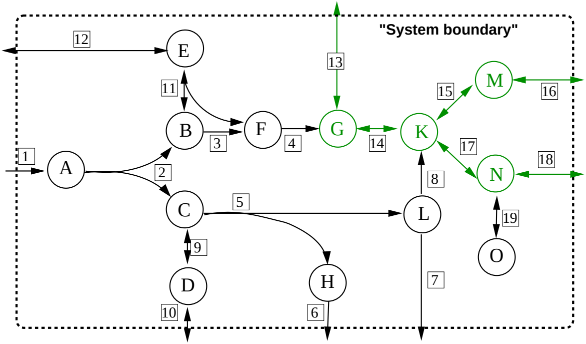
Reaction classification

- The steady state flux cone

$$C = \{v \in \mathbb{R}^{m \times n} \mid Sv = 0, v_i \geq 0 \text{ for all } i \in Irr\}$$

- **Lineality space**

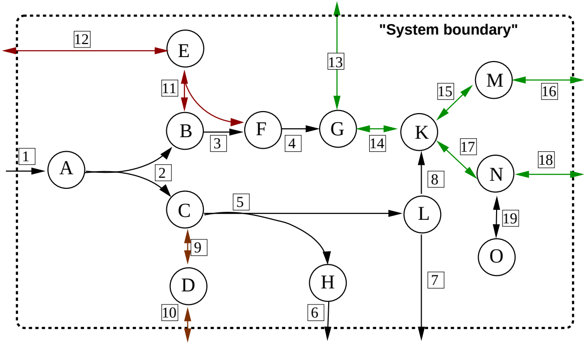
$$\text{lin.space}(C) = \{v \in \mathbb{R}^{m \times n} \mid Sv = 0, v_i = 0 \text{ for all } i \in Irr\}$$



Classification of reversible reactions

A reversible reaction $j \in Rev$ is called **pseudo-irreversible** *if $v_j = 0$ for all $v \in \mathrm{lin.space}(C)$.*

A reversible reaction that is not pseudo-irreversible is called **fully reversible**.



Decomposition of the reaction set

- *Frev* $= \{i \mid i \text{ is fully reversible}\}$.
- *Prev* $= \{i \mid i \text{ is pseudo-irreversible and there exist } v^+, v^- \in C \text{ such that } v_i^+ > 0, v_i^- < 0\}$,
- *Irev* $= Irr \cup \{i \mid i \text{ is pseudo-irreversible and } v_i \geq 0, \text{ for all } v \in C \text{ or } v_i \leq 0, \text{ for all } v \in C\}$.

Question

How do flux coupling relations depend on the reversibility type of reactions?

Reversibility type and flux coupling

Definition

Let i, j be two unblocked reactions. The coupling relations $\stackrel{=0}{\rightarrow}, \stackrel{=0}{\leftrightarrow}, \backsim^{\lambda}$ are defined in the following way:

1. $i \stackrel{=0}{\rightarrow} j$ if for all $v \in C$, $v_i = 0$ implies $v_j = 0$.
2. $i \stackrel{=0}{\leftrightarrow} j$ if for all $v \in C$, $v_i = 0$ is equivalent to $v_j = 0$.
3. $i \backsim^{\lambda} j$ if there exists $\lambda \in \mathbb{R}$ such that for all $v \in C, v_j = \lambda v_i$.

Theorem

Let i, j be two unblocked reactions such that at least one of the relations $i \stackrel{=0}{\rightarrow} j$, $i \stackrel{=0}{\leftrightarrow} j$ or $i \backsim^{\lambda} j$ is satisfied. Then either (a) or (b) holds:

(a) *i and j are both (pseudo-)irreversible: $i, j \in Irev \cup Prev$.*

(b) *i and j are both fully reversible: $i, j \in Frev$.*

Pseudo-irreversible reactions

Proposition

Suppose i, j are unblocked, $i \in Prev$ and $j \in Irev \cup Prev$. Then the following are equivalent

1. $i \stackrel{=0}{\rightarrow} j$
2. $i \stackrel{=0}{\leftrightarrow} j$
3. $i \backsim^{\lambda} j$

Reversibility type and flux coupling

i/j	*Irev*			*Prev*			*Frev*		
	$\overset{=0}{\rightarrow}$	$\overset{=0}{\leftrightarrow}$	$\backsim^{\lambda}$	$\overset{=0}{\rightarrow}$	$\overset{=0}{\leftrightarrow}$	$\backsim^{\lambda}$	$\overset{=0}{\rightarrow}$	$\overset{=0}{\leftrightarrow}$	$\backsim^{\lambda}$
Irev	$\surd$	$\surd$	$\surd$	$\surd$					
Prev				$\surd$	$\surd$	$\surd$			
Frev							$\surd$	$\surd$	$\surd$

- Coupling relations do not occur for arbitrary pairs of reactions
- Many cases are not possible (only 10/27 possible cases of reaction couplings)

Reversibility type and flux coupling

i/j	*Irev*			*Prev*			*Frev*		
	$\stackrel{=0}{\longrightarrow}$	$\stackrel{=0}{\longleftrightarrow}$	$\backsim^{\lambda}$	$\stackrel{=0}{\longrightarrow}$	$\stackrel{=0}{\longleftrightarrow}$	$\backsim^{\lambda}$	$\stackrel{=0}{\longrightarrow}$	$\stackrel{=0}{\longleftrightarrow}$	$\backsim^{\lambda}$
Irev	$\surd$	$\surd$	$\surd$	$\surd$					
Prev				$\surd$	$\surd$	$\surd$			
Frev							$\surd$	$\surd$	$\surd$

- Fluxes through pseudo-irreversible (or fully reversible) reactions that are coupled are proportional to each other (enzyme subset)

Reversibility type and flux coupling

i/j	*Irev* $\stackrel{=0}{\longrightarrow}$	*Irev* $\stackrel{=0}{\longleftrightarrow}$	*Irev* $\backsim^{\lambda}$	*Prev* $\stackrel{=0}{\longrightarrow}$	*Prev* $\stackrel{=0}{\longleftrightarrow}$	*Prev* $\backsim^{\lambda}$	*Frev* $\stackrel{=0}{\longrightarrow}$	*Frev* $\stackrel{=0}{\longleftrightarrow}$	*Frev* $\backsim^{\lambda}$
Irev	$\surd$	$\surd$	$\surd$	$\surd$					
Prev				$\surd$	$\surd$	$\surd$			
Frev							$\surd$	$\surd$	$\surd$

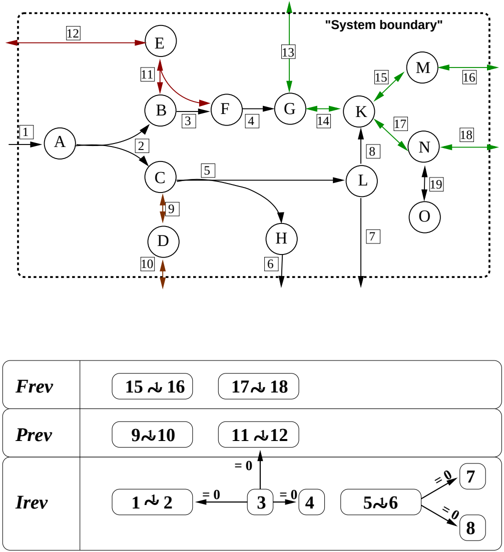
- Symmetric couplings can occur only between reactions with the same reversibility type
- Reactions in an enzyme subset must have the same reversibility type

Reversibility type and flux coupling

i/j	*Irev*			*Prev*			*Frev*		
	$\overset{=0}{\rightarrow}$	$\overset{=0}{\leftrightarrow}$	$\backsim^{\lambda}$	$\overset{=0}{\rightarrow}$	$\overset{=0}{\leftrightarrow}$	$\backsim^{\lambda}$	$\overset{=0}{\rightarrow}$	$\overset{=0}{\leftrightarrow}$	$\backsim^{\lambda}$
Irev	$\surd$	$\surd$	$\surd$	$\surd$					
Prev				$\surd$	$\surd$	$\surd$			
Frev							$\surd$	$\surd$	$\surd$

- Only a zero flux through an irreversible reaction may imply a zero flux through another irreversible reaction

Reversibility type and flux coupling



A new algorithm for flux coupling analysis

- Compute a set of generators of the flux cone C using existing tools for polyhedral computations
- Classify the reactions according to their reversiblity type
- Apply the mathematical results to identify blocked and coupled reactions

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Computational results

Metabolic network	Blk	Irev	Prev	Frev	MMB	FCMMB	TOTAL	FCF
Red Blood Cell	0	31	14	6	2.32	0.26	2,58	110.65
Central metabolism of *E. coli*	0	92	18	0	214.49	2.55	217,04	477.14
Human cardiac mitochondria	121	83	3	9	1262.65	0.34	1262,99	13426.91
Helicobacter pylori	346	128	15	39	13551.44	0.43	13551,87	318374.15
E. coli K-12	435	480	49	110	261306.15	5.32	261311,47	$\geq$ 1 week