5. Flux coupling analysis (FCA)

Burgard et al. 04

- $C = \{v \mid Sv = 0,\ v_k \geq 0, k \in Irr\}$ flux cone
- A reaction i is blocked if $v_i = 0$, for all $v \in C$.
- Let i and j be two unblocked reactions.
  - i is directionally coupled to j, $i \overset{=0}{\rightarrow} j$, if for all $v \in C$, $v_i = 0$ implies $v_j = 0$.
  - i and j are partially coupled, $i \overset{=0}{\leftrightarrow} j$, if for all $v \in C$, $v_i = 0$ is equivalent to $v_j = 0$.
  - i and j are fully coupled, $i \backsim^{\lambda} j$, if there exists $\lambda \in \mathbb{R} \setminus \{0\}$ such that for all $v \in C, v_j = \lambda v_i$.
- $i \backsim^{\lambda} j$ implies $i \overset{=0}{\leftrightarrow} j$, which is equivalent to $i \overset{=0}{\rightarrow} j$ and $j \overset{=0}{\rightarrow} i$.

LP-based flux coupling analysis

- Reaction i is blocked iff

$$\max\{\pm v_i \mid Sv = 0, v_k \geq 0, k \in Irr\} = 0$$

- Two unblocked reactions i and j are directionally coupled, i.e., $i \overset{=0}{\rightarrow} j$ iff

$$\max\{\pm v_j \mid Sv = 0, v_k \geq 0, k \in Irr, v_i = 0\} = 0$$

- $O(n^2)$ linear programming problems

Fast Flux Coupling Calculation F2C2

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Network	FFCA		F2C2	
	♯LPs	Time	♯LPs	Time
M. barkeri, *iAF*692	301975	59m40s	774	7s
S. cerevisiae, *iND*750	472629	1h50m17s	1280	21s
M. tuberculosis, *iNJ*661	556504	3h5m36s	1506	22s
E. coli, *iJR*904	655437	2h40m33s	1580	26s
E. coli, *iAF*1260	4256786	4d31m26s	3309	2m47s
E. coli, *iJO*1366	4877262	4d5h30m46s	3955	3m55s
H. sapiens, *Recon*1	4566304	4d18h3m37s	3903	5m20s

Reversibility types

- A reversible reaction i is called fully reversible if there exists a flux vector $v \in C$ such that $v_i \neq 0$ and $v_j = 0$ for all $j \in Irr$.
- Otherwise, reaction i is called pseudo-irreversible.

Reaction classification

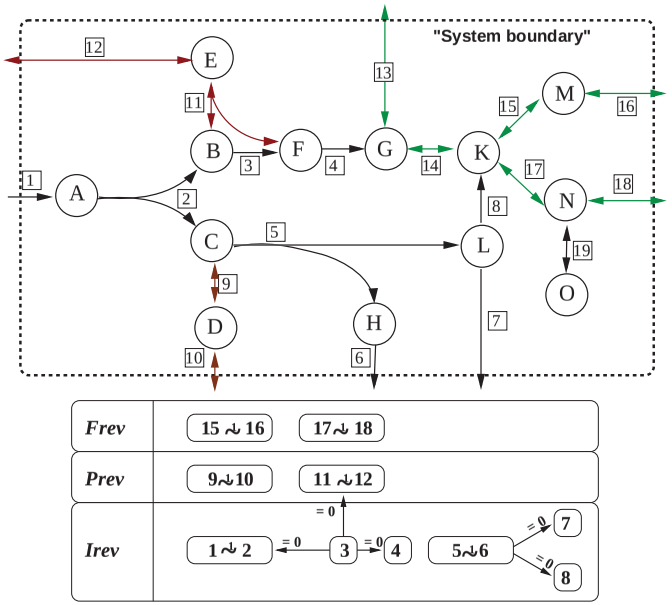
- $Blk = \{i \mid i \text{ is blocked}\}$.
- $Frev = \{i \mid i \text{ is fully reversible}\}$,
- $Prev = \{i \mid i \text{ is pseudo-irreversible and there exist } v^+, v^- \in C \text{ such that } v_i^+ > 0, v_i^- < 0\}$,
- $Irev = \{i \mid i \notin Frev \cup Prev \text{ and } v_i \neq 0 \text{ for some } v \in C\}$,

Possible coupling relations

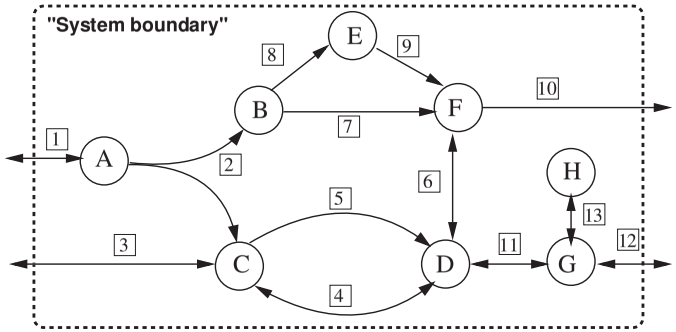
- If $i,j \in Irev$, all couplings are possible, i.e., $i \overset{=0}{\rightarrow} j$, $i \overset{=0}{\leftrightarrow} j$, $i \backsim^{\lambda} j$.
- If $i \in Irev$ and $j \in Prev$, the only possible coupling is $j \longrightarrow i$.
- If $i,j \in Prev$, the only possible coupling is $i \backsim^{\lambda} j$.
- If $i,j \in Frev$, the only possible coupling is $i \backsim^{\lambda} j$.

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

Example



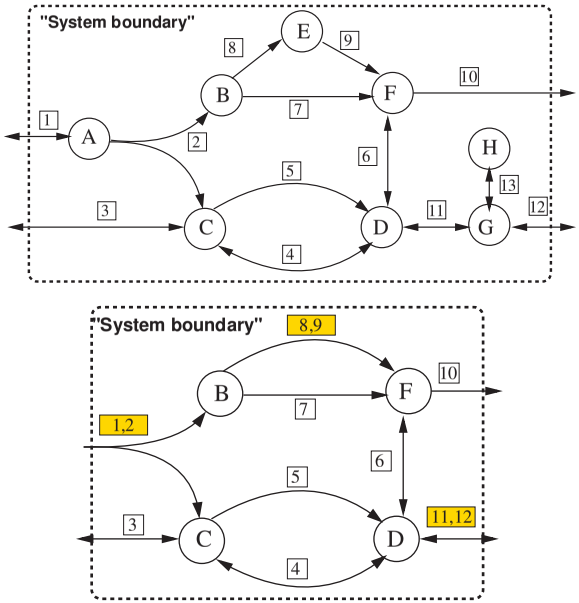
Network simplication



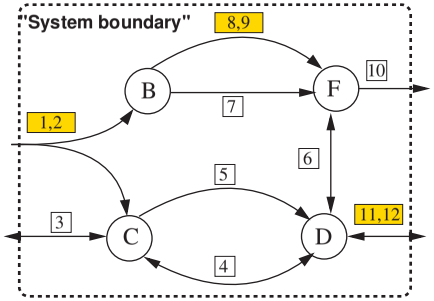
- Dead-end metabolites
- Blocked reactions
- Fully coupled reactions

$\rightsquigarrow$ iterative reduction

Example



Reducing the number of LP problems

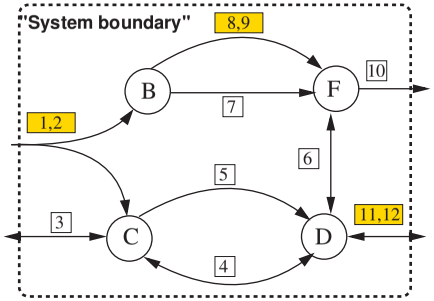


- Trivial uncoupling for “parallel” reactions (Lemma 2, F2C2)
- Trivial directional coupling (Obs. 5, F2C2)
- Reusing LP solutions
  If $v \in C$, $I_v = \{i \mid v_i = 0\}$, $J_v = \{j \mid v_j \neq 0\}$, then $i \not\to j$, for all $(i,j) \in I_v \times J_v$.

Transitivity rules

Known flux coupling	$i \rightharpoonup j$	$i \overset{=0}{\leftrightarrow} j$	$i \overset{=0}{\to} j$	$j \overset{=0}{\to} i$
$k \rightharpoonup i$	$k \rightharpoonup j$	$i \overset{=0}{\leftrightarrow} j$	$k \overset{=0}{\to} j$	$j \overset{=0}{\to} k$
$k \overset{=0}{\leftrightarrow} i$	$k \overset{=0}{\leftrightarrow} j$	$k \overset{=0}{\leftrightarrow} j$	$k \overset{=0}{\to} j$	$j \overset{=0}{\to} k$
$k \overset{=0}{\to} i$	$k \overset{=0}{\to} j$	$k \overset{=0}{\to} j$	$k \overset{=0}{\to} j$	
$k \not\to i$	$k \not\to j$	$k \not\to j$		$k \not\to j$
$i \not\to k$	$j \not\to k$	$j \not\to k$	$j \not\to k$	

Example



- Trivial directional coupling: $(1,2) \overset{=0}{\to} (8,9)$
- Solving LP: $10 \not\to (8,9)$
- Transitivity: $10 \not\to (1,2)$

Fast Flux Coupling Calculation F2C2

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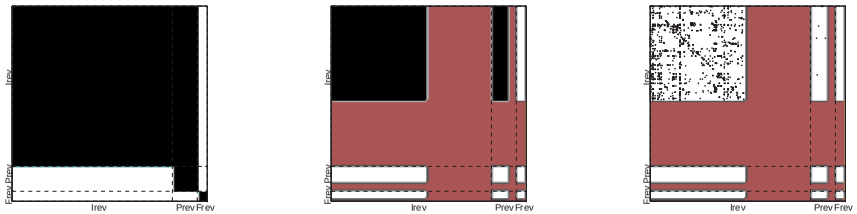

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