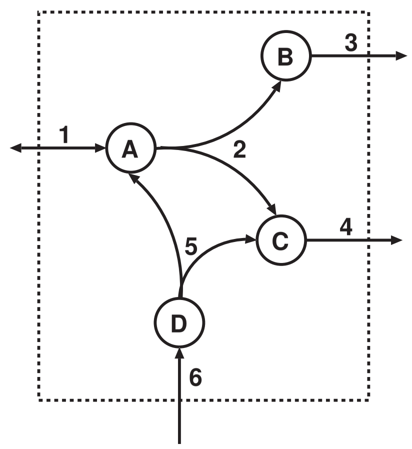
5. Flux coupling analysis (FCA)

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 $j \overset{=0}{\rightarrow} i$.

Example



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

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, the reversible reaction i is called pseudo-irreversible.

Reaction classification

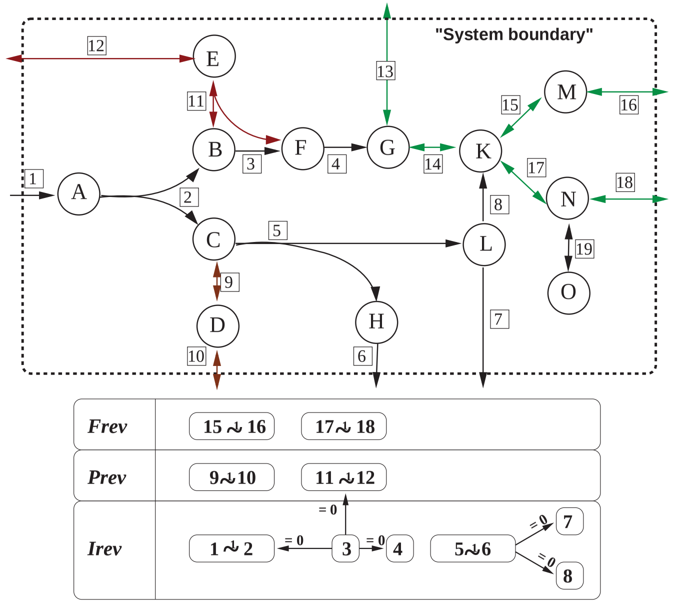
- $Blk = \{i \mid i \text{ is blocked}\}$
- $Frev = \{i \mid i \text{ is fully reversible}\}$
- $Prev = \{i \mid i \text{ is pseudo-irreversible and there exist } v^+, v^- \in C \text{ such that } v_i^+ > 0, v_i^- < 0\}$
- $Irev = \{i \mid i \notin Blk \cup Frev \cup Prev\}$

Possible coupling relations

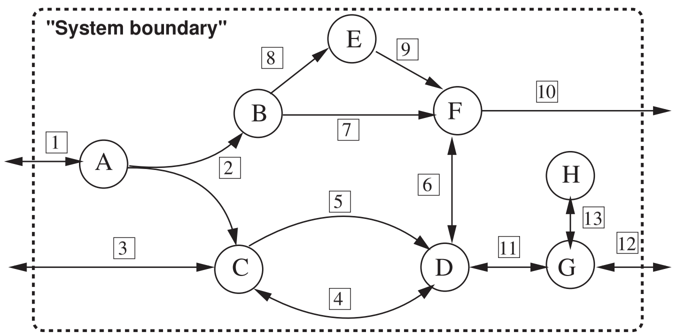
- If $i, j \in Irev$, all couplings are possible, i.e., $i \overset{=0}{\to} j$, $i \overset{=0}{\leftrightarrow} j$, $i \backsim^{\lambda} j$.
- If $i \in Irev$ and $j \in Prev$, the only possible coupling is $i \overset{=0}{\to} j$.
- If $i, j \in Prev$, the only possible coupling is $i \backsim^{\lambda}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

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

Example



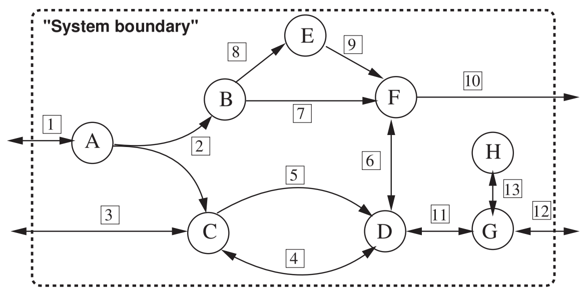
Network simplication

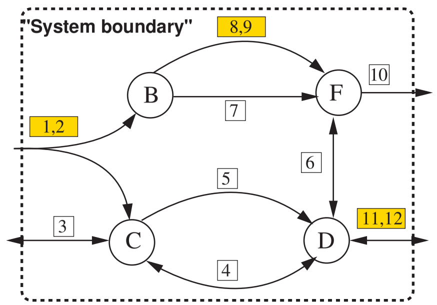


- Dead-end metabolites
- Blocked reactions
- Fully coupled reactions

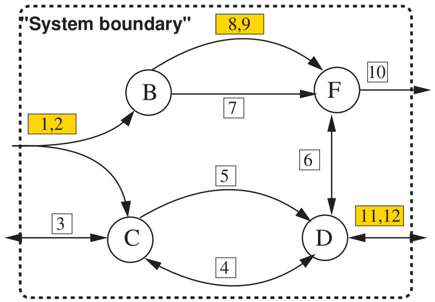
⇝ iterative reduction

Example





Reducing the number of LP problems

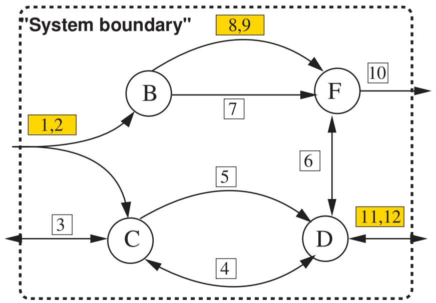


- Trivial uncoupling for "parallel" reactions (Lemma 2, F2C2)
- Trivial directional coupling (Obs. 5, F2C2)
- Reusing LP solutions
  If $v \in C$, $I_v = \{i \mid v_i = 0\}$, $J_v = \{j \mid v_j \neq 0\}$, then $i \not\rightarrow j$, for all $(i,j) \in I_v \times J_v$.

Transitivity rules

Known flux coupling	$i \backsim j$	$i \overset{=0}{\leftrightarrow} j$	$i \overset{=0}{\rightarrow} j$	$j \overset{=0}{\rightarrow} i$
$k \backsim i$	$k \backsim j$	$i \overset{=0}{\leftrightarrow} j$	$k \overset{=0}{\rightarrow} j$	$j \overset{=0}{\rightarrow} k$
$k \overset{=0}{\leftrightarrow} i$	$k \overset{=0}{\leftrightarrow} j$	$k \overset{=0}{\leftrightarrow} j$	$k \overset{=0}{\rightarrow} j$	$j \overset{=0}{\rightarrow} k$
$k \overset{=0}{\rightarrow} i$	$k \overset{=0}{\rightarrow} j$	$k \overset{=0}{\rightarrow} j$	$k \overset{=0}{\rightarrow} j$	
$k \not\rightarrow i$	$k \not\rightarrow j$	$k \not\rightarrow j$		$k \not\rightarrow j$
$i \not\rightarrow k$	$j \not\rightarrow k$	$j \not\rightarrow k$	$j \not\rightarrow k$	

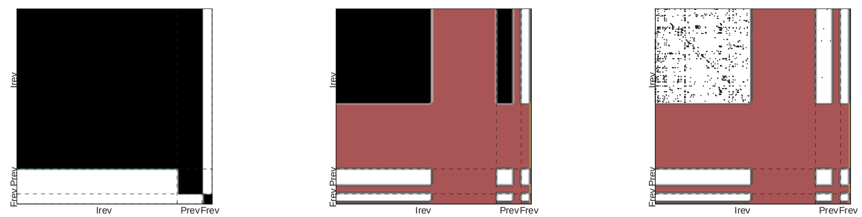
Example



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

Fast Flux Coupling Calculation F2C2

Larhlimi/David/Selbig/Bockmayr 12



Network	FFCA		F2C2	
	♯LPs	Time	♯LPs	Time
M. barkeri, iAF692	301975	59m40s	774	7s
S. cerevisiae, iND750	472629	1h50m17s	1280	21s
M. tuberculosis, iNJ661	556504	3h5m36s	1506	22s
E. coli, iJR904	655437	2h40m33s	1580	26s
E. coli, iAF1260	4256786	4d31m26s	3309	2m47s
E. coli, iJO1366	4877262	4d5h30m46s	3955	3m55s
H. sapiens, Recon1	4566304	4d18h3m37s	3903	5m20s