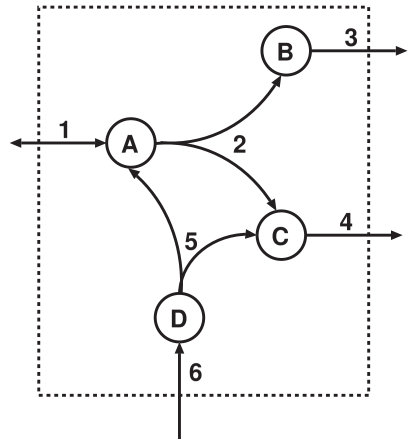
5. Flux coupling analysis (FCA)

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, $i \overset{=0}{\to} j$, 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 $i \overset{=0}{\to} j$ and $j \overset{=0}{\to} i$.

Example



$2 \overset{=0}{\to} 3$

$3 \overset{=0}{\to} 2$

$4 \overset{=0}{\to} 1,2,3,5,6$

$5 \overset{=0}{\to} 6$

$6 \overset{=0}{\to} 5$

LP-based flux coupling analysis

- Reaction i is blocked iff

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

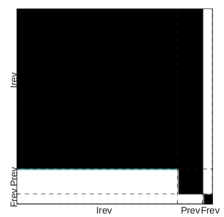
- Two unblocked reactions i and j are directionally coupled, i.e., $i \overset{=0}{\to} j$ iff

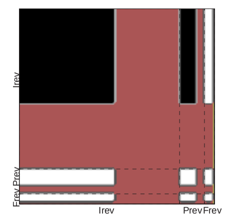
$$\max\{\pm v_j \mid Sv = 0, v_k \geq 0, k \in Irr, v_i = 0\} = 0$$

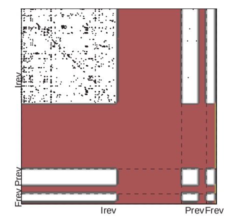
- $O(n^2)$ linear programming problems

Fast Flux Coupling Calculation F2C2

Larhlimi/David/Selbig/Bockmayr 12







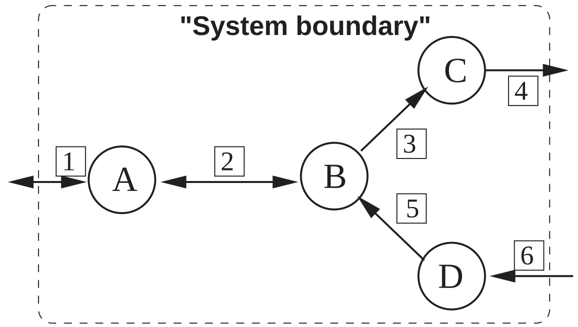
Network	FFCA		F2C2	
	♯LPs	Time	♯LPs	Time
M. barkeri, iAF692	301975	59m40s	774	7s
S. cerevisiae, iND750	472629	1h50m17s	1280	21s
M. tuberculosis, iNJ661	556504	3h5m36s	1506	22s
E. coli, iJR904	655437	2h40m33s	1580	26s
E. coli, iAF1260	4256786	4d31m26s	3309	2m47s
E. coli, iJO1366	4877262	4d5h30m46s	3955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

6. Elementary flux modes

Schuster/Hilgetag'94

- $C = \{v \in \mathbb{R}^n \mid Sv = 0,\ v_i \geq 0, i \in Irr\}$ steady-state flux cone
- Support of $v \in \mathbb{R}^n$: $supp(v) = \{i \in \{1,\ldots,n\} \mid v_i \neq 0\}$.
- Elementary flux mode (EFM):
  Flux vector $v \in C \setminus \{0\}$ with minimal support, i.e., there is no $v' \in C \setminus \{0\}$ with $supp(v') \subsetneq supp(v)$.

Example



$$e^1 = (1,1,1,1,0,0), \quad e^2 = (-1,-1,0,0,1,1), \quad e^3 = (0,0,1,1,1,1)$$

Basic properties

- Proposition Let $e \in C$ be an EFM. If $v \in C$ with $supp(v) = supp(e)$. Then $v = \lambda e$, for some $\lambda \in \mathbb{R} \setminus \{0\}$.

  $\rightsquigarrow$ EFMs are uniquely determined by their support.
- Proposition A flux vector $v \in C$ is an EFM iff there exist no $v^1, v^2 \in C \setminus \{0\}$ s.t. $supp(v^1), supp(v^2) \subsetneq supp(v)$, $v = v^1 + v^2$.

  $\rightsquigarrow$ EFMs correspond to irreducible elements of the flux cone.
- Proposition Any $v \in C$ can be written as a non-negative linear combination of EFMs:

$$v = \sum_{e \in EFM} \lambda_e e, \quad \lambda_e \geq 0$$

$\rightsquigarrow$ EFMs define a finite conic basis of the flux cone.

Computing EFMs

- If all reactions are irreversible, EFMs correspond to extreme rays of the flux cone (Gagneur/Klamt 04).
- EFMs can be computed by algorithms that enumerate the extreme rays of a pointed cone $\rightsquigarrow$ double description method
- Software
  - Metatool (Pfeiffer et al. 99, Univ. Jena)
  - efmtool (Terzer 09, ETH Zurich)
- Enumerating EFMs is computionally hard (Acuña et al. 09 and 10).

MILP to enumerate shortest EFMs

de Figueiredo et al. 09

Assume all reactions are irreversible.

$$\min \sum_{j=1}^{n} a_j$$

$$\begin{aligned} & Sv = 0, v \geq 0, \\ & a_j \leq v_j \leq M\, a_j, \quad \text{for } j = 1, \ldots, n, \qquad \text{“BigM”} \\ & \textstyle\sum_{j=1}^{n} a_j \geq 1, \\ & v \in \mathbb{R}^n, a \in \{0,1\}^n \end{aligned}$$

Forbidding the i-th solution (v^i, a^i):

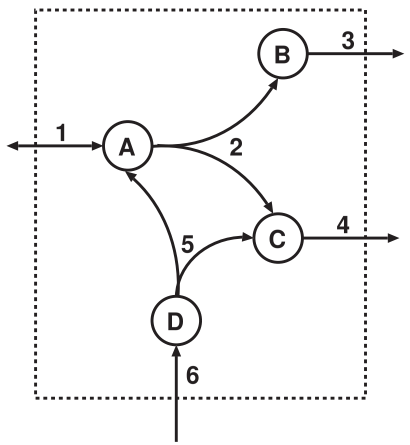
$$\sum_{j \in supp(v^i)} a_j \leq |supp(v^i)| - 1, \quad \text{for } i = 1, 2, \ldots, k \quad \text{“no-good cut”}$$

Minimal cut sets

Klamt/Gilles'03

- $C = \{v \in \mathbb{R}^n \mid Sv = 0,\ v_i \geq 0, i \in Irr\}$ steady-state flux cone
- A cut set for a reaction $r \in \{1, \ldots, n\}$ is a reaction set $M \subseteq \{1, \ldots, n\}$ such that for all $v \in C$, $v_i = 0$ for all $i \in M$ implies $v_r = 0$.
- A cut set M for r is minimal, if there is no cut set $M' \subsetneq M$ for r strictly contained in M.

Example



Elementary flux modes:

$$\begin{aligned} e^1 &= (1,1,1,1,0,0) \\ e^2 &= (-1,0,0,1,1,1) \\ e^3 &= (0,1,1,2,1,1) \end{aligned}$$

Minimal cut sets for reaction 3:

$\{3\}, \{2\}, \{4\}, \{1,6\}, \{1,5\}$