

3. Flux balance analysis (FBA)

- Assume cellular behavior is determined by a certain biological objective.
- Determine a corresponding “best” flux distribution.
- Use mathematical optimization to predict phenotype.

- Simplest case: Linear programming (LP)

$$\max\{c^T x \mid Ax \leq b, x \in \mathbb{R}^n\}$$

- Flux balance problem (FBA)

$$\max\{c^T v \mid Sv = 0, l \leq v \leq u\} \quad (\text{FBA})$$

4. Flux variability analysis (FVA)

- Optimal solutions to FBA problems need not be unique.
- Enumerating all optimal solutions is computationally expensive.

- Alternative: Analyse flux variability

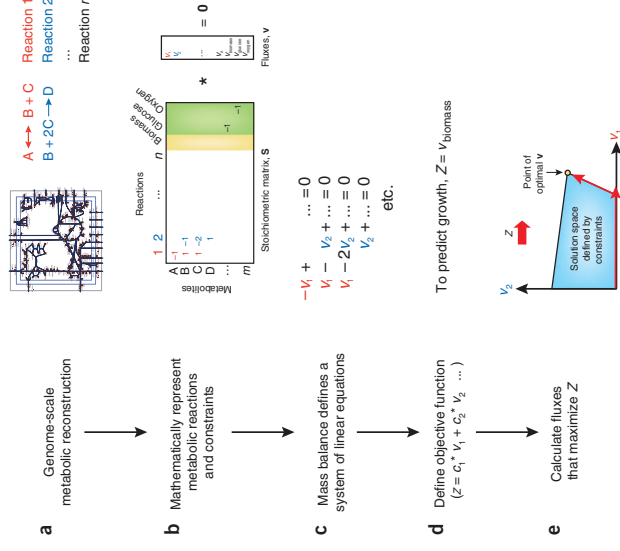
$$Z_{opt} = \max\{z = c^T v \mid Sv = 0, l \leq v \leq u\} \quad (\text{FBA})$$

For all $j = 1, \dots, n$:

$$\max\{\pm v_j \mid Sv = 0, l \leq v \leq u, c^T v = Z_{opt}\} \quad (\text{FVA})$$



Example



- E. coli* metabolism
- Genome-scale reconstruction (J01366)
- 1336 metabolites, 2251 reactions
- Objective function: biomass
- Glucose and oxygen uptake reactions
- Aerobic and anaerobic growth
- Software: e.g. COBRA Toolbox 2.0

Orth/Thiele/Palsson 10

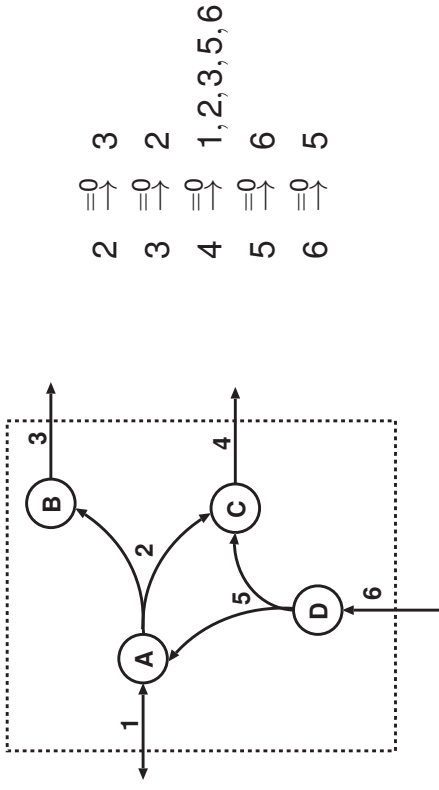
5. Flux coupling analysis (FCA)

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 , $i \xrightarrow{0} j$, if for all $v \in C$, $v_i = 0$ implies $v_j = 0$.
 - i and j are partially coupled, $i \xleftrightarrow{0} j$, if for all $v \in C$, $v_j = 0$ is equivalent to $v_i = 0$.
 - i and j are fully coupled, $i \overset{\lambda}{\leftrightarrow} j$, if there exists $\lambda \in \mathbb{R} \setminus \{0\}$ such that for all $v \in C$, $v_j = \lambda v_i$.
- $i \overset{\lambda}{\leftrightarrow} j$ implies $i \xleftrightarrow{0} j$, which is equivalent to $i \xrightarrow{0} j$ and $j \xrightarrow{0} i$.



Example



- 2 \Rightarrow 3
- 3 \Rightarrow 2
- 4 \Rightarrow 1, 2, 3, 5, 6
- 5 \Rightarrow 6
- 6 \Rightarrow 5



LP-based flux coupling analysis

- ▷ Reaction i is **blocked** iff

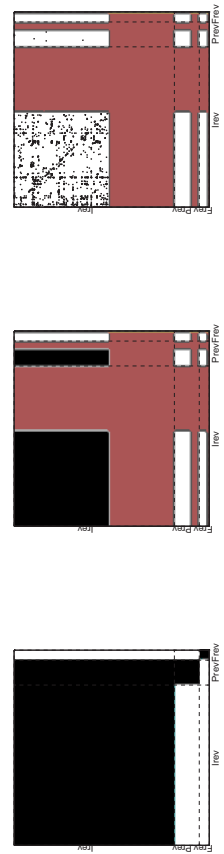
$$\max\{\pm v_j \mid Sv = 0, v_k \geq 0, k \in Irr\} = 0$$
- ▷ Two unblocked reactions i and j are **directionally coupled**, i.e., $i \Rightarrow j$ iff

$$\max\{\pm v_j \mid Sv = 0, v_k \geq 0, k \in Irr, v_i = 0\} = 0$$
- ▷ $O(n^2)$ linear programming problems



Fast Flux Coupling Calculation F2C2

Larhimi/David/Selbig/Bockmayr 12



Network	FFCA		F2C2	
	#LPs	Time	#LPs	Time
<i>M. barkeri</i> , iAF692	301975	59m40s	774	7s
<i>S. cerevisiae</i> , iND750	472629	1h50m17s	1280	21s
<i>M. tuberculosis</i> , iNJ661	566504	3h5m36s	1506	22s
<i>E. coli</i> , iJF904	655437	2h40m33s	1580	26s
<i>E. coli</i> , iAF1260	4256786	4d31m26s	3309	2m47s
<i>E. coli</i> , iJO1366	4877262	4d5h30m46s	3955	3m55s
<i>H. sapiens</i> , iRecon1	4566304	4d18h3m37s	3903	5m20s