3. Flux balance analysis (FBA)

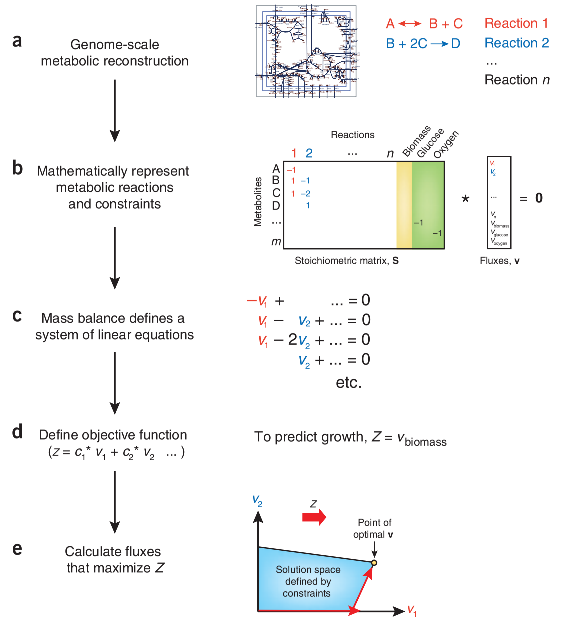
- Assume cellular behavior is determined by a certain biological objective.
- Determine a corresponding "best" flux distribution.
- Use mathematical optimization to predict phenotype.
- Simplest case: Linear programming (LP)

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

- Flux balance problem (FBA)

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

Example



- *E. coli* metabolism
- Genome-scale reconstruction (*i*JO1366)
- 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

4. Flux variability analysis (FVA)

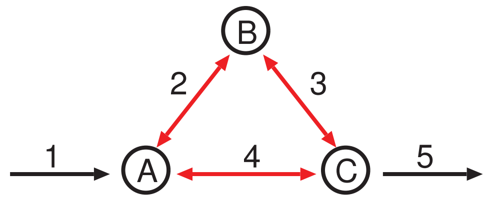
- Optimal solutions to FBA problems need not be unique.
- Enumerating all optimal solutions is computationally expensive.
- Alternative: Flux variability analysis (FVA)

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

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

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

Thermodynamic constraints



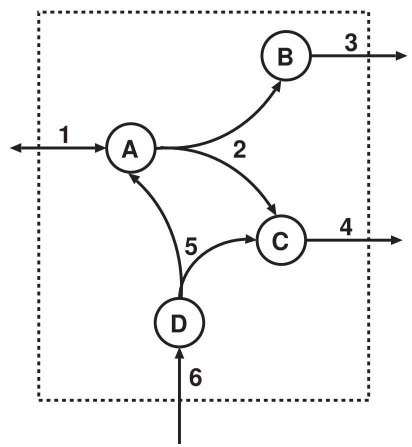
- Flux through internal cycles is unbounded ⇝ thermodynamically infeasible
- Include additional (non-linear) thermodynamic constraints (Beard/Qian 02)
- Fast thermodynamic FVA (tFVA) (Müller/Bockmayr 12)
- Application: Modules in the optimal flux space (Müller/Bockmayr 13)

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



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

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

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

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

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

LP-based flux coupling analysis

- Reaction i is blocked iff

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

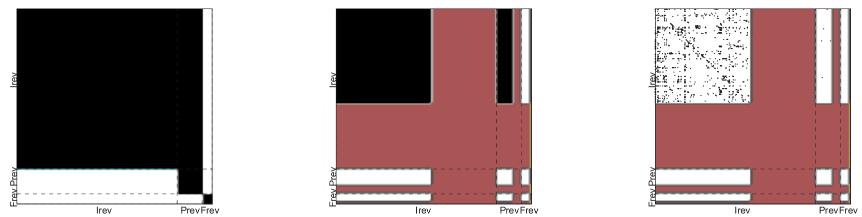
- Two unblocked reactions i and j are directionally coupled, i.e., $i \overset{=0}{\rightarrow} j$ iff

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

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

Fast Flux Coupling Calculation F2C2

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