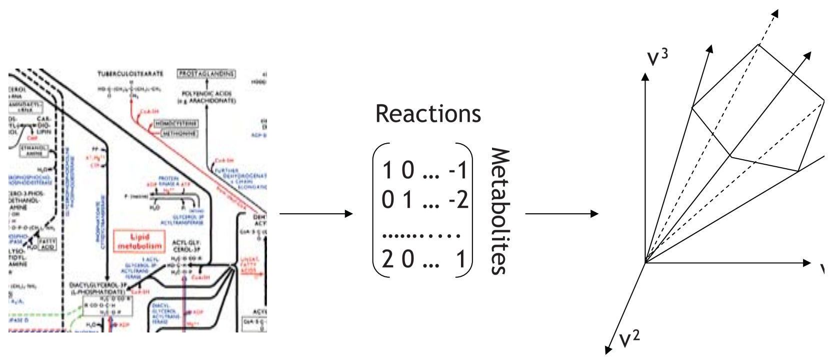
Steady-state flux cone

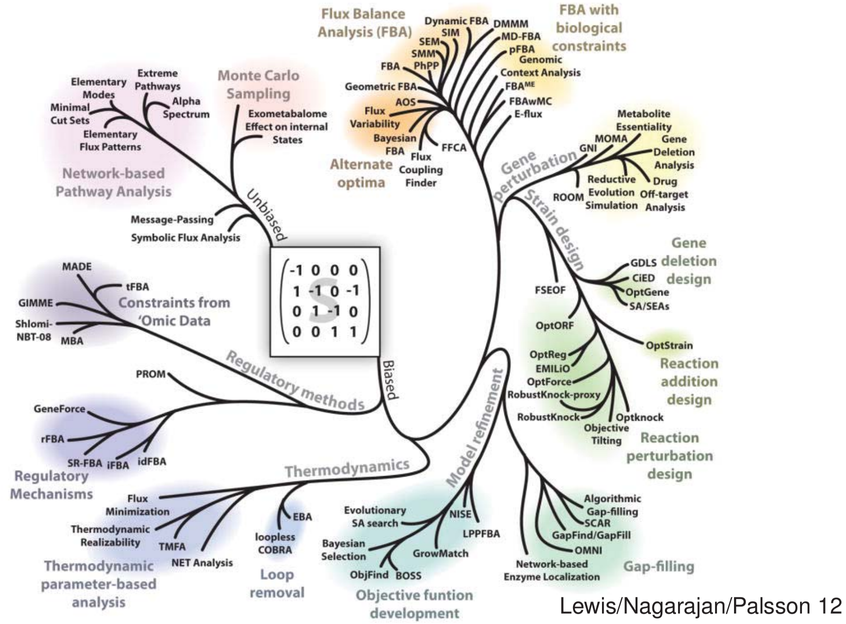
Set of all possible steady-state flux distributions

$$C = \{v \in \mathbb{R}^n \mid Sv = 0,\ v_i \geq 0,\ i \in Irr\}$$

$\rightsquigarrow$ polyhedral cone



Constraint-based analysis methods



Lewis/Nagarajan/Palsson 12

3. Flux balance analysis (FBA)

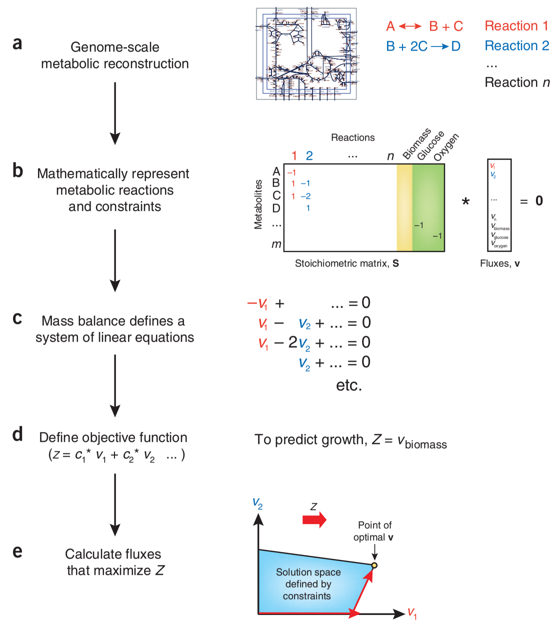
- ▷ Assume cellular behavior is determined by a certain biological objective.
- ▷ Determine a corresponding "best" flux distribution.
- ▷ Use mathematical optimization to predict phenotype.
- ▷ Simplest case: Linear programming (LP)

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

- ▷ 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)

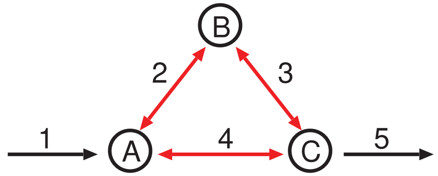
- Optimal solutions to FBA problems need not be unique.
- Enumerating all optimal solutions is computationally expensive.
- Alternative: Flux variability analysis (FVA)

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

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

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

Thermodynamic constraints



$$\begin{array}{rcl} 1 = v_1 = v_2 + v_4 & & v_2 \text{ free} \\ v_2 = v_3 & \Leftrightarrow & v_4 = 1 - v_2 \\ v_3 + v_4 = v_5 & & v_5 = 1 \end{array}$$

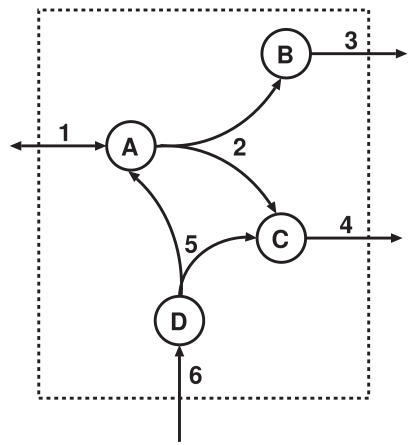
- Flux through internal cycles is unbounded $\leadsto$ thermodynamically infeasible
- Include additional (non-linear) thermodynamic constraints (Beard/Qian 02)
- Fast thermodynamic FVA (tFVA) (Müller/Bockmayr 12)
- Application: Modules in the optimal flux space (Müller/Bockmayr 13)

5. Flux coupling analysis (FCA)

Burgard et al. 04

- $C = \{v \mid Sv = 0,\ v_k \ge 0, k \in Irr\}$ 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, $i \overset{\lambda}{\backsim} j$, if there exists $\lambda \in \mathbb{R} \setminus \{0\}$ such that for all $v \in C, v_j = \lambda v_i$.
- $i \overset{\lambda}{\backsim} j$ implies $i \overset{=0}{\leftrightarrow} j$, which is equivalent to $i \overset{=0}{\rightarrow} j$ and $j \overset{=0}{\rightarrow} i$.

Example



$$\begin{array}{ccl} 2 & \overset{=0}{\rightarrow} & 3 \\ 3 & \overset{=0}{\rightarrow} & 2 \\ 4 & \overset{=0}{\rightarrow} & 1,2,3,5,6 \\ 5 & \overset{=0}{\rightarrow} & 6 \\ 6 & \overset{=0}{\rightarrow} & 5 \end{array}$$