Constraint-based Modeling of Metabolic Networks

Alexander Bockmayr
Freie Universität Berlin

Research Center MATHEON
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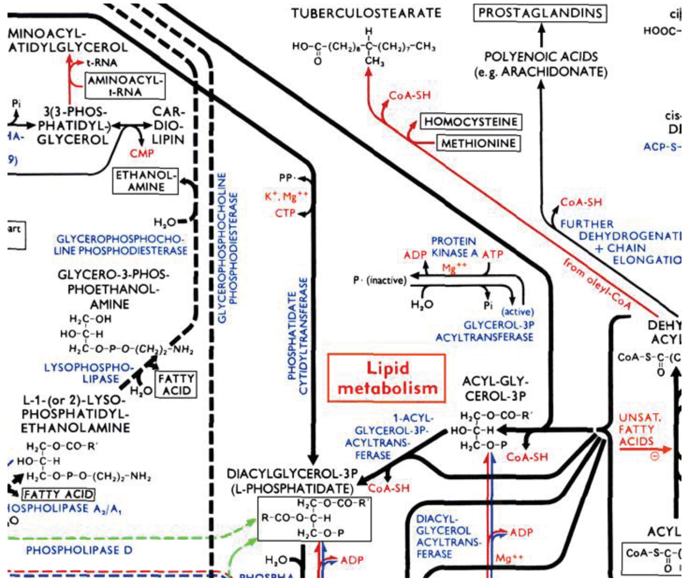
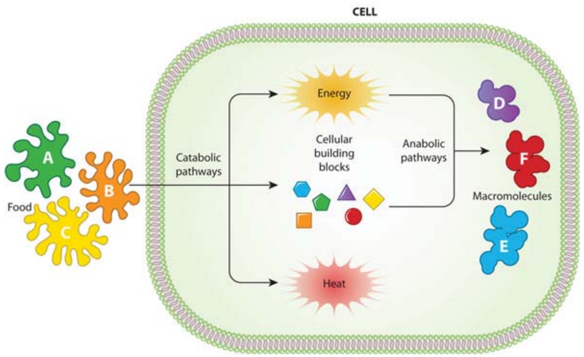
Metabolic networks



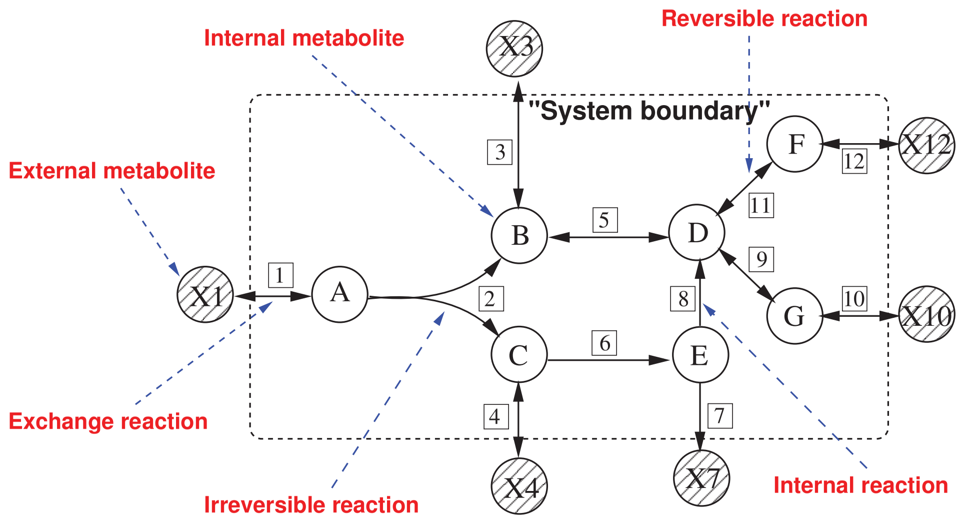
http://web.expasy.org/pathways/

Importance

- ▷ Biology
  - Cell metabolism
  - Catabolism, anabolism
- ▷ Medicine
  - Metabolic disorders
  - Cancer
- ▷ Biotechnology
  - Biofuel
  - Bioleaching



Mathematical representation



Algebraic description

- Stoichiometric matrix $S \in \mathbb{R}^{m \times n}$
  - Rows $\rightsquigarrow$ internal metabolites $i = 1, \ldots, m$
  - Columns $\rightsquigarrow$ internal and exchange reactions $j = 1, \ldots, n$
  - S_{ij}: stoichiometric coefficient of reactant i in reaction j
- Set of irreversible reactions Irr
- Metabolic model $\mathscr{M} = (S, Irr)$

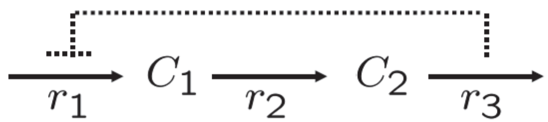
1. Kinetic modeling

- Metabolites i and reactions j
- $C_i(t)$: metabolite concentrations at time t
- $v_j(t) = v_j(C(t), k)$: reaction rates, depending on kinetic law and kinetic parameters k
- S_{ij}: stoichiometric coefficient

$$\frac{dC_i}{dt} = \sum_{j=1}^{n} S_{ij} v_j \quad \text{or} \quad \frac{dC}{dt} = S \cdot v(C, k)$$

- System of ordinary differential equations (ODEs)

Example



$$\begin{pmatrix} dC_1/dt \\ dC_2/dt \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \end{pmatrix} \cdot \begin{pmatrix} v_1(C,k) \\ v_2(C,k) \\ v_3(C,k) \end{pmatrix}$$

$$\begin{aligned} v_1(C,k) &= v_{m1}/(1 + (C_2/k_i)^p) \\ v_2(C,k) &= v_{m2} \cdot C_1/(k_1 + C_1) \\ v_3(C,k) &= v_{m3} \cdot C_2/(k_2 + C_2) \end{aligned}$$

Which kinetic laws?

Which kinetic parameters?

2. Constraint-based modeling

- Steady-state assumption
  Assume metabolite concentrations C_i and reaction rates v_j are constant (over some time interval)
  $\rightsquigarrow$ steady-state flux vector $v \in \mathbb{R}^n$
- Stoichiometric constraints (mass balance):

$$\sum_{j=1}^{n} S_{ij} v_j = 0, \text{ for all } i = 1, \ldots, m$$

- Thermodynamic irreversibility constraints:

$$v_j \geq 0, \text{ if } j \text{ is irreversible}$$

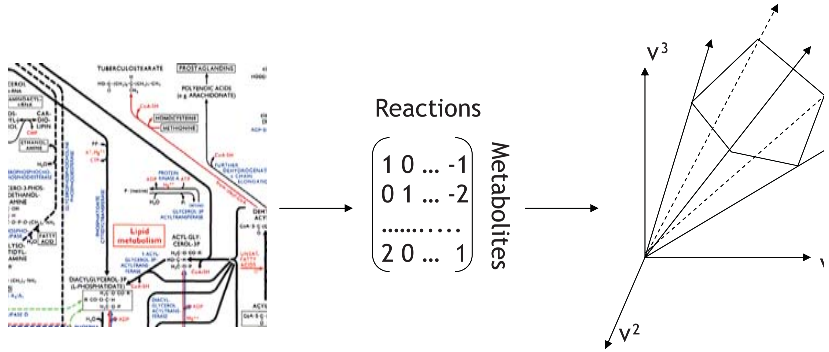
$\rightsquigarrow$ system of linear equations and inequalities in $\mathbb{R}^n$

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



3. Flux balance analysis (FBA)

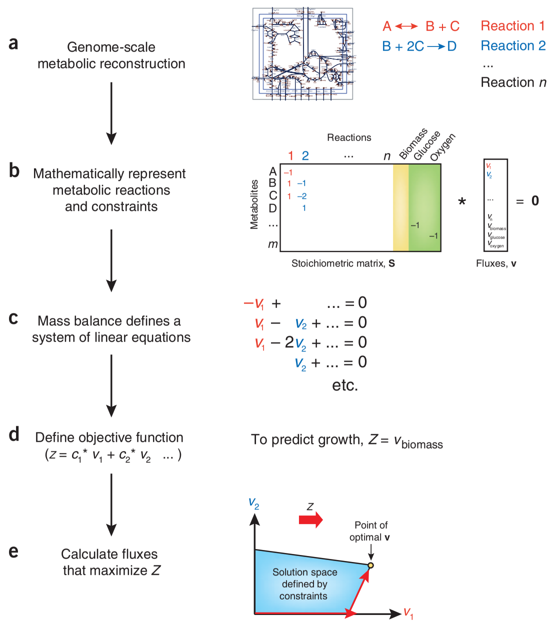
- Assume cellular behavior is determined by a certain biological objective.
- Determine a corresponding “best” flux distribution.
- Use mathematical optimization to predict phenotype.
- Simplest case: Linear programming (LP)

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

- 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 $j = 1, \ldots, n$:

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