Constraint-based Modeling of Metabolic Networks

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Mathematical representation

Stoichiometric matrix
- Rows $\sim$ internal metabolites $i = 1, \ldots, m$
- Columns $\sim$ internal and external reactions $j = 1, \ldots, n$
- $S_{ij}$: stoichiometric coefficient of reactant $i$ in reaction $j$

Set of irreversible reactions
- $\mathcal{Irr} \subseteq \{1, \ldots, n\}$

Metabolic model
- $\mathcal{M} = (S, \mathcal{Irr})$
1. Kinetic modeling

- Metabolites $i$ and reactions $j$
- $C_i(t)$: metabolite concentrations at time $t$
- $v_j = v_j(C, k)$: 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

\[
\begin{pmatrix}
\frac{dC_1}{dt} \\
\frac{dC_2}{dt}
\end{pmatrix} =
\begin{pmatrix}
1 & -1 & 0 \\
0 & 1 & -1
\end{pmatrix}
\begin{pmatrix}
v_1(C, k) \\
v_2(C, k) \\
v_3(C, k)
\end{pmatrix}
\]

$v_1(C, k) = \frac{v_m1}{(1+(C_2/k_1)^p)}$

$v_2(C, k) = \frac{v_m2 \cdot C_1}{(k_1 + C_1)}$

$v_3(C, k) = \frac{v_m3 \cdot C_2}{(k_2 + C_2)}$

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 $\Rightarrow$ flux vector $v \in \mathbb{R}^n$
- Stoichiometric constraints (mass balance):

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

- Thermodynamics constraints (reaction directionality):
  $v_j \geq 0$, if $j$ is irreversible

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

Steady-state flux cone

Set of all possible steady-state flux distributions
\[
C = \{ v \in \mathbb{R}^n \mid Sv = 0, \; v_i \geq 0, \; i \in \text{Irr} \}
\]

$\Rightarrow$ 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)

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

Example

- E. coli metabolism
- Genome-scale reconstruction (iJO1366)
- 1336 metabolites, 2251 reactions
- Objective function: biomass
- Glucose and oxygen uptake reactions
- Aerobic and anaerobic growth

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 \( j = 1, \ldots, n \):

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