Constraint-based Modeling of Metabolic Networks

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Mathematical representation

Algebraic description

- Stoichiometric matrix
  - Rows \( \rightarrow \) internal metabolites \( i = 1, \ldots, m \)
  - Columns \( \rightarrow \) internal and external reactions \( j = 1, \ldots, n \)
  - \( S_{ij} \): stoichiometric coefficient of reactant \( i \) in reaction \( j \)
- Set of irreversible reactions
- Metabolic model

\[ M = (S, \text{Irr}) \]
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

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

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

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):
  $$v_j \geq 0, \text{ if } j \text{ is irreversible}$$
  $\Rightarrow$ system of linear equations and inequalities in $\mathbb{R}^n$

Steady-state flux cone

Set of all possible steady-state flux distributions

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

$\Rightarrow$ 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)
  \[
  \text{max} \{c^T x \mid Ax \leq b, x \in \mathbb{R}^n\}
  \]
- Flux balance problem (FBA)
  \[
  \text{max} \{c^T v \mid Sv = 0, l \leq v \leq u\} \quad \text{(FBA)}
  \]

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
  \[
  z_{\text{opt}} = \max \{z = c^T v \mid Sv = 0, l \leq v \leq u\} \quad \text{(FBA)}
  \]
  For all \(j = 1, \ldots, n\):
  \[
  \max \{\pm v_j \mid Sv = 0, l \leq v \leq u, c^T v = z_{\text{opt}}\} \quad \text{(FVA)}
  \]

5. Flux coupling analysis (FCA)

- C = \{v \mid Sv = 0, v_k \geq 0, k \in \mathbb{N}\} 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 \(j\), \(i \supseteq 0 j\), if for all \(v \in C\), \(v_i = 0\) implies \(v_j = 0\).
  - \(i\) and \(j\) are partially coupled, \(i \leftrightarrow 0 j\), if for all \(v \in C\), \(v_i = 0\) is equivalent to \(v_j = 0\).
  - \(i\) and \(j\) are fully coupled, \(i \sim^\lambda j\), if there exists \(\lambda \in \mathbb{R} \setminus \{0\}\) such that for all \(v \in C\), \(v_j = \lambda v_i\).
  - \(i \sim^\lambda j\) implies \(i \leftrightarrow^0 j\), which is equivalent to \(i \equiv 0 j\) and \(j \equiv 0 i\).
Example

LP-based flux coupling analysis

- Reaction $i$ is blocked iff
  \[ \max \{ \pm v_i | Sv = 0, v_k \geq 0, k \in lrr \} = 0 \]

- Two unblocked reactions $i$ and $j$ are directionally coupled, i.e., $i \rightarrow j$ iff
  \[ \max \{ \pm v_j | Sv = 0, v_k \geq 0, k \in lrr, v_i = 0 \} = 0 \]

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

Fast Flux Coupling Calculation F2C2

Larhlimi/David/Selbig/Bockmayr 12

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<th>Network</th>
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