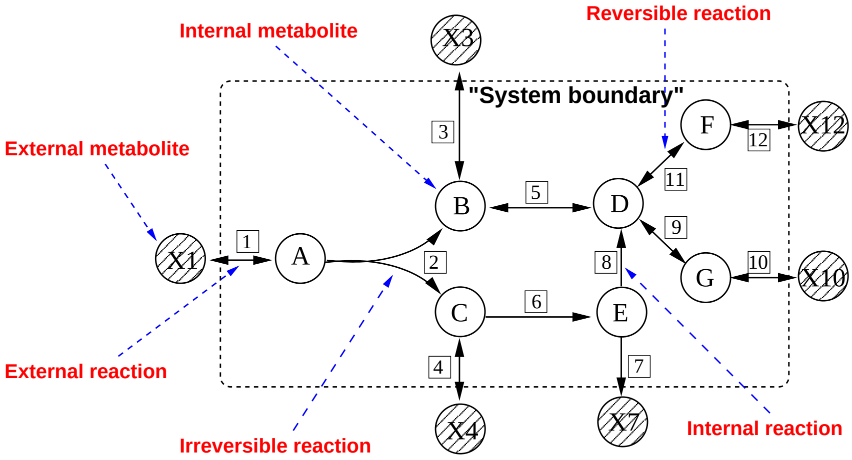
Application: Metabolic networks



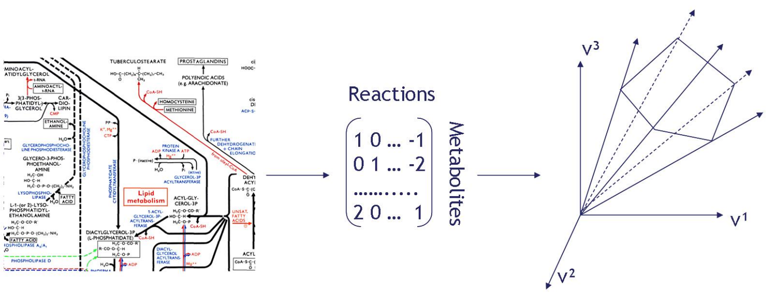
Stoichiometric matrix

- Metabolites (internal) $\rightsquigarrow$ rows
- Biochemical reactions $\rightsquigarrow$ columns

Reaction $kA + lC \xrightarrow{j} mE + nH$ gives
$$\begin{array}{c} A \\ B \\ C \\ D \\ E \\ F \\ G \\ H \end{array} \begin{pmatrix} \ldots & -k & \ldots \\ & 0 & \\ & -l & \\ & 0 & \\ & m & \\ & 0 & \\ & 0 & \\ \ldots & n & \ldots \end{pmatrix}$$

Flux cone

- Flux balance: $Sv = 0$
- Irreversibiliy of some reactions: $v_i \geq 0, i \in Irr$.
- *Steady-state flux cone* $C = \{v \in \mathbb{R}^n \mid Sv = 0, v_i \geq 0, \text{ for } i \in Irr\}$



Flux balance analysis

- Use linear programming to study flux distribution in a cell
$$\max\{c^T v \mid Sv = 0, \ \ v_{\min} \leq v \leq v_{\max}\}$$
- Objective function
  - Maximize biomass production
  - Maximize metabolite production (e.g. biofuel)
- *Metabolic engineering*

Farkas Lemma

Theorem. Suppose $A \in \mathbb{Q}^{m\times n}$ and $b \in \mathbb{Q}^m$.

1. The system $Ax \leq b$ has no solution $x \in \mathbb{Q}^n$ if and only if there exists $u \in \mathbb{Q}^m, u \geq 0$ such that $u^T A = 0$ and $u^T b = -1$.
2. If $Ax \leq b$ is solvable, then an inequality $c^T x \leq \delta$ with $c \in \mathbb{Q}^n$ and $\delta \in \mathbb{Q}$ is satisfied by all rational solutions of $Ax \leq b$ if and only if there exists $u \in \mathbb{Q}^m, u \geq 0$ such that $u^T A = c^T$ and $u^T b \leq \delta$.

Rules for reasoning with linear inequalities:

$$\text{nonneg\_lin\_com:}\quad \frac{Ax \leq b}{(u^T A)x \leq u^T b} \quad \text{if} \quad \begin{cases} u \in \mathbb{Q}^m, \\ u \geq 0 \end{cases}$$

$$\text{weak\_rhs:}\quad \frac{a^T x \leq \beta}{a^T x \leq \beta'} \quad \text{if} \quad \beta \leq \beta'$$

Duality

$$\begin{array}{llllll} \textit{Primal problem:} & z_P & = & \max\{\mathbf{c}^\mathbf{T} x \mid & Ax \leq b, \quad x \in \mathbb{R}^n\} & \text{(P)} \\ \textit{Dual problem:} & w_D & = & \min\{b^T u \mid & A^T u = \mathbf{c}, \quad u \geq 0\} & \text{(D)} \\ & & = & \min\{u^T b \mid & u^T A = c^T, \quad u \geq 0\} & \end{array}$$

Note: The dual computes a smallest upper bound for the objective function of the primal, which is of the form $c^T x = u^T Ax \leq u^T b = \delta$ (cf. Farkas Lemma).

Note: The dual of the dual is the primal.

Duality: General form (2)

(P)			(D)		
max	$c^T x$		min	$b^T u$	
w.r.t.	$A_{i*} x \leq b_i$,	$i \in M_1$	w.r.t	$u_i \geq 0$,	$i \in M_1$
	$A_{i*} x \geq b_i$,	$i \in M_2$		$u_i \leq 0$,	$i \in M_2$
	$A_{i*} x = b_i$,	$i \in M_3$		u_i free,	$i \in M_3$
	$x_j \geq 0$,	$j \in N_1$		$(A_{*j})^T u \geq c_j$,	$j \in N_1$
	$x_j \leq 0$,	$j \in N_2$		$(A_{*j})^T u \leq c_j$,	$j \in N_2$
	x_j free,	$j \in N_3$		$(A_{*j})^T u = c_j$,	$j \in N_3$

primal	max	min	dual
constraints	$\leq b_i$	≥ 0	variables
	$\geq b_i$	≤ 0	
	$= b_i$	free	
variables	≥ 0	$\geq c_j$	constraints
	≤ 0	$\leq c_j$	
	free	$= c_j$	

Duality theorems

- *Weak duality:* If x^* is primal feasible and u^* is dual feasible, then

$$c^T x^* \leq z_P \leq w_D \leq b^T u^*.$$

- *Strong duality*
  - If (P) and (D) both have feasible solutions, then both programs have optimal solutions and the optimum values of the objective functions are equal.
  - If one of the programs (P) or (D) has no feasible solution, then the other is either unbounded or has no feasible solution.
  - If one of the programs (P) or (D) is unbounded, then the other has no feasible solution.
- *Only four possibilities:*
  1. z_P and w_D are both finite and equal.
  2. $z_P = +\infty$ and (D) is infeasible.
  3. $w_D = -\infty$ and (P) is infeasible.
  4. (P) and (D) are both infeasible.

Maximum flow and duality

- Primal problem

$$\begin{array}{lll}
\max & \displaystyle\sum_{e:\text{source}(e)=s} x_e - \sum_{e:\text{target}(e)=s} x_e & \\
\text{s.t.} & \displaystyle\sum_{e:\text{target}(e)=v} x_e - \sum_{e:\text{source}(e)=v} x_e = 0, & \forall v \in V \setminus \{s,t\} \\
 & 0 \leq x_e \leq c_e, & \forall e \in E
\end{array}$$

- Dual problem

$$\begin{array}{lll}
\min & \displaystyle\sum_{e \in E} c_e y_e & \\
\text{s.t.} & z_w - z_v + y_e \geq 0, & \forall e = (v,w) \in E \\
 & z_s = 1, z_t = 0 & \\
 & y_e \geq 0, & \forall e \in E
\end{array}$$

Maximum flow and duality (2)

- Let (y^*, z^*) be an optimal solution of the dual.
- Define $S = \{v \in V \mid z_v^* > 0\}$ and $T = V \setminus S$.
- (S,T) is a minimum cut.
- Max-flow min-cut theorem is a special case of linear programming duality.

Complexity of linear programming

Theorem (Khachyian 79) The following problems are solvable in polynomial time:

- Given a matrix $A \in \mathbb{Q}^{m \times n}$ and a vector $b \in \mathbb{Q}^m$, decide whether $Ax \leq b$ has a solution $x \in \mathbb{Q}^n$, and if so, find one.
- (Linear programming problem) Given a matrix $A \in \mathbb{Q}^{m \times n}$ and vectors $b \in \mathbb{Q}^m, c \in \mathbb{Q}^n$, decide whether $\max\{c^T x \mid Ax \leq b, x \in \mathbb{Q}^n\}$ is infeasible, finite, or unbounded. If it is finite, find an optimal solution. If it is unbounded, find a feasible solution x_0, and find a vector $d \in \mathbb{Q}^n$ with $Ad \leq 0$ and $c^T d > 0$.

Polynomial algorithms for linear programming

- *Ellipsoid method* (Khachyian 79)
- *Interior point methods* (Karmarkar 84)

Complexity of constraint solving: Overview

Satisfiability	over $\mathbb{Q}$	over $\mathbb{Z}$	over $\mathbb{N}$
Linear equations	polynomial	polynomial	NP-complete
Linear inequalities	polynomial	NP-complete	NP-complete

Satisfiability	over $\mathbb{R}$	over $\mathbb{Z}$
Linear constraints	polynomial	NP-complete
Non-linear constraints	decidable	undecidable

References

- J. Matousek, B. Gärtner: Understanding and using linear programming, Springer, 2007.
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