Metabolic network analysis

Optimization-based methods

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29 October, 2010

Linear Programming

What is linear programming?

Linear programming is a technique for the optimization of a linear objective function, subject to linear equality and linear inequality constraints.

A linear program in standard form

$$\begin{aligned} min \quad & c^t x \\ s.t. \quad & Ax = b \\ & x \geq 0 \end{aligned}$$

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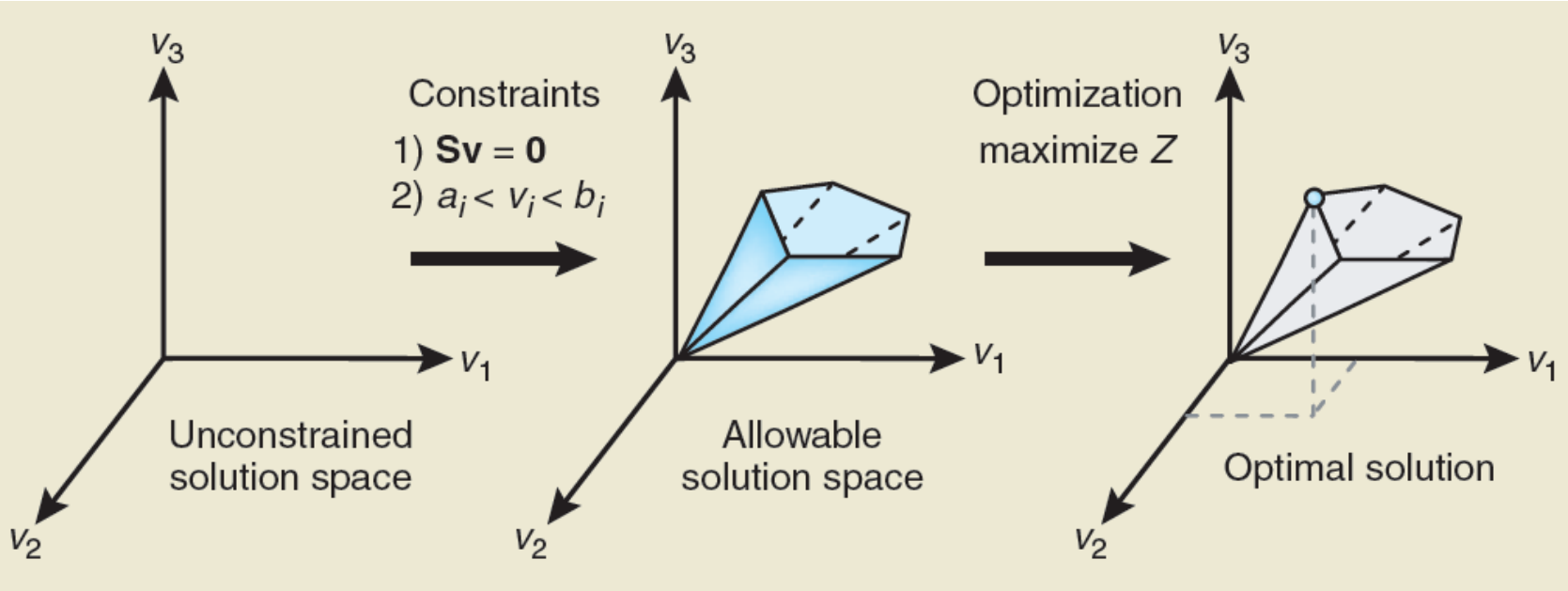

Flux Balance Analysis

Motivation

Given a metabolic network find the most suitable flux distribution for a certain task.

Example tasks

- Optimal flux distribution for biomass production (growth).
- Minimize ATP production to guarantee optimal metabolic energy efficiency.
- Maximize the production of a chosen metabolite to determine production capabilities of a given network.

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Method

Step 1.

Identify an objective function Z.

Step 2.

Set bounds on the flux variables ($v_i^{min} \leq v_i \leq v_i^{max}$ for all $i \in \{1, ..., n\}$)

Step 3.

Solve the linear program:

$$\begin{aligned} min \quad & Z^t v \\ s.t. \quad & Sv = 0 \\ & v^{min} \leq v \leq v^{max} \end{aligned}$$

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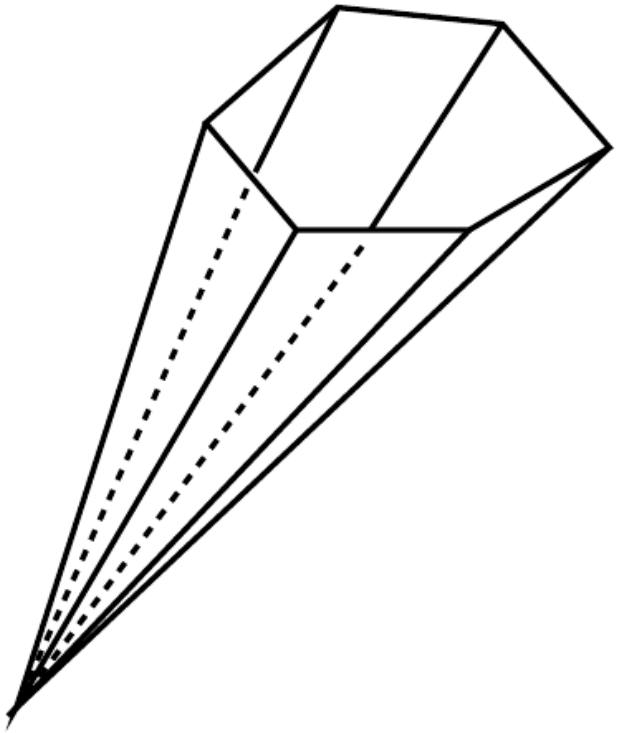
FBA's method in pictures



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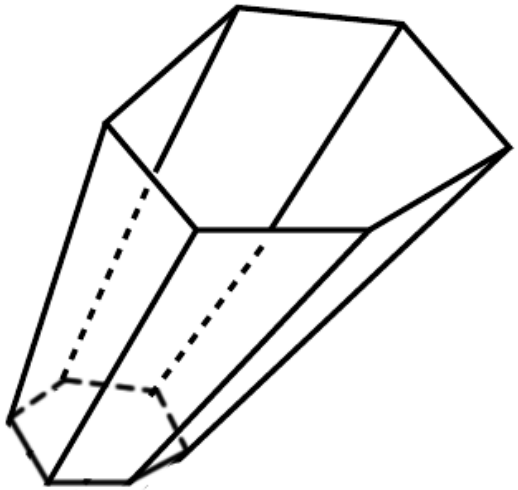

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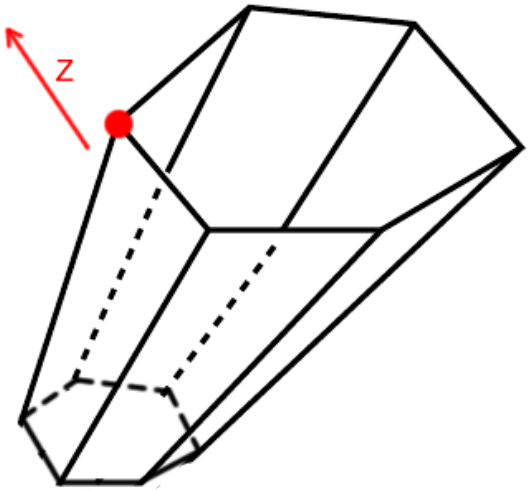

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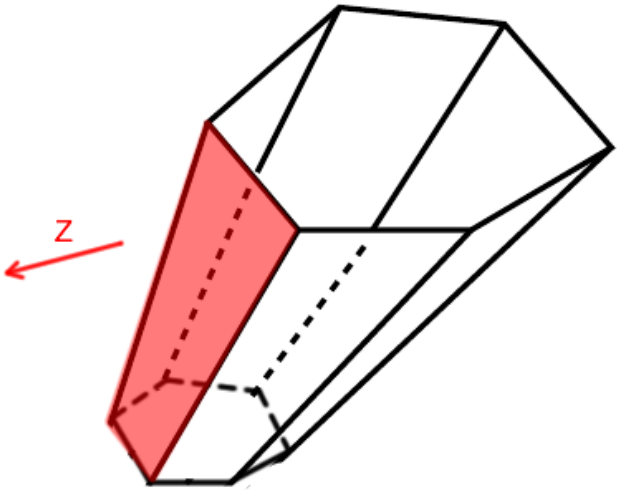
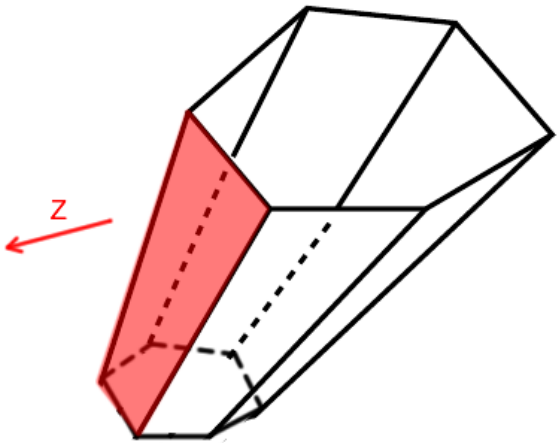


Flux Variability analysis

Question

What happens when there are multiple flux distributions with the same 'best' objective value? (i.e. the set of solution is a face of the polyhedron)



Importance

The biological conclusions drawn from different optima can be different.

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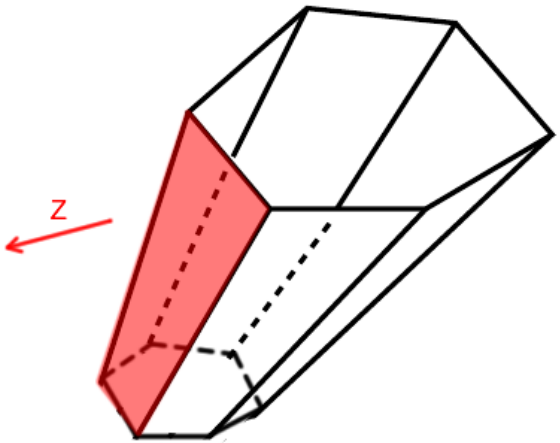

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Flux Variability analysis

Idea 1

Find all flux distributions that have the same 'best' objective value. (Computationally expensive)

Idea 2

Instead of finding all flux distributions, find the range in which the fluxes vary. (Flux variability analysis)

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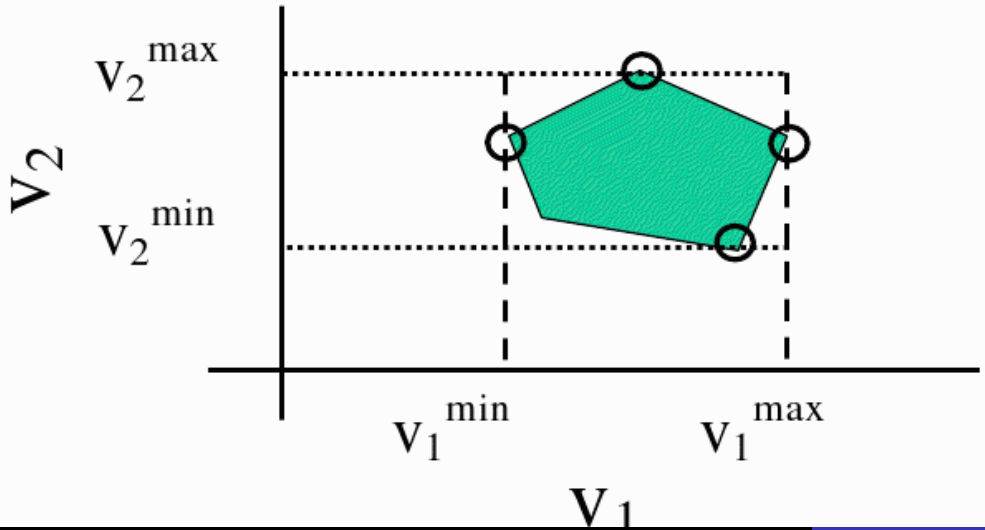
Example

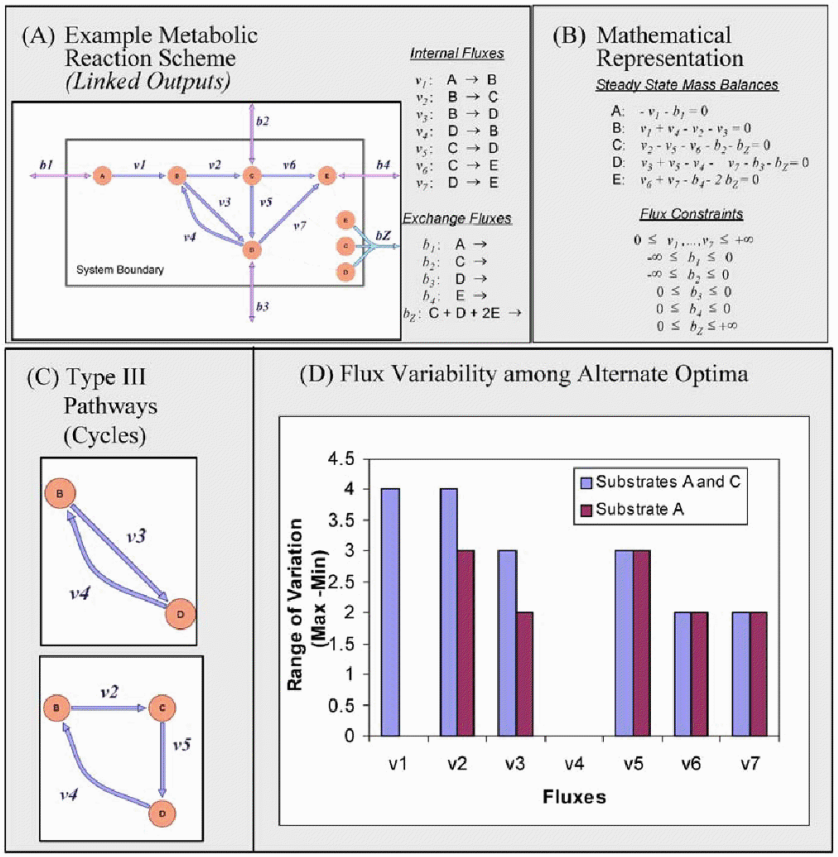
Flux variability analysis

Solve the linear program for all $j \in \{1, ..., n\}$:

$$\begin{aligned} min/max \quad & v_j \\ s.t. \quad & Sv = 0 \\ & v^{min} \leq v \leq v^{max} \\ & Z^t v = Z_{obj} \end{aligned}$$



Example


(A) Example Metabolic Reaction Scheme (Linked Outputs)
Internal Fluxes
v1: A → B
v2: B → C
v3: B → D
v4: D → B
v5: C → D
v6: C → E
v7: D → E
Exchange Fluxes
b1: A →
b2: C →
b3: D →
b4: E →
bZ: C + D + 2E →
System Boundary
(B) Mathematical Representation
Steady State Mass Balances
A: - v1 - b1 = 0
B: v1 + v4 - v2 - v3 = 0
C: v2 - v5 - v6 - b2 - bZ = 0
D: v3 + v5 - v4 - v7 - b3 - bZ = 0
E: v6 + v7 - b4 - 2 bZ = 0
Flux Constraints
0 ≤ v1,...,v7 ≤ +∞
-∞ ≤ b1 ≤ 0
-∞ ≤ b2 ≤ 0
0 ≤ b3 ≤ 0
0 ≤ b4 ≤ 0
0 ≤ bZ ≤ +∞
(C) Type III Pathways (Cycles)
(D) Flux Variability among Alternate Optima
Substrates A and C
Substrate A
Range of Variation (Max -Min)
Fluxes
v1
v2
v3
v4
v5
v6
v7

Summary: Optimization based methods

Advantages

- For an objective function we get a 'fast' answer what the optimal flux distribution is.
- Successfully employed for several microorganisms.

Drawbacks

- Sensitivity to the definition of objective function.
- Optimal flux distribution might not be unique.
- Microorganisms could use different optimization criteria depending on their environment.
- The exploration of all suitable objective function is a difficult task.

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