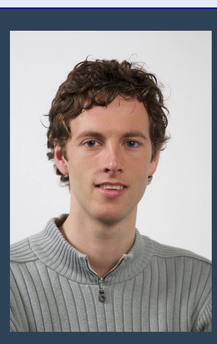
From Millions to One

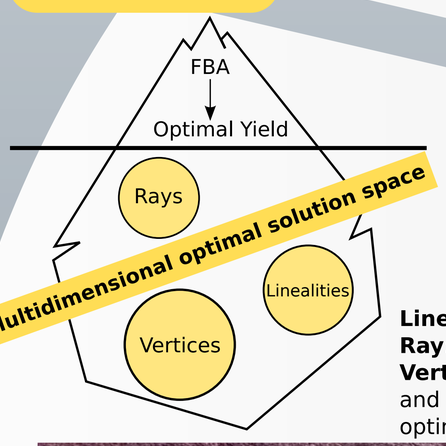
The topological logic of optimal solution spaces of genome-scale stoichiometric models of metabolism

Timo R. Maarleveld[1,2], M. Wortel[2], R. Khandelwal[2], F.J. Bruggeman[2]

1. Centrum Wiskunde & Informatica, 2. VU University Amsterdam **t.r.maarleveld@cwi.nl**

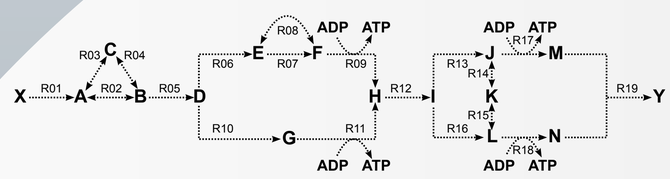


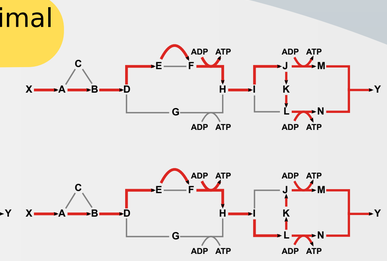
Introduction



Lineality: reversible cycle
Ray: irreversible cycle
Vertex: optimal flux vector and a *corner point* of the optimal solution space

Decomposition of the optimal solution space:
1) 1 lineality (green)
2) 1 ray (blue)
3) 4 vertices (red)





$$\text{Maximize } Z_{obj} = J19$$

$$\text{subject to,}$$

$$\vec{N}\vec{J} = \vec{0}$$

$$-\infty \leq J_r \leq \infty \quad J_r \in \text{reversible reactions}$$

$$0 \leq J_i \leq \infty \quad J_i \in \text{irreversible reactions}$$

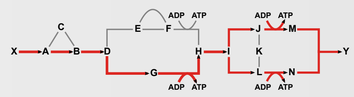
$$0 \leq J_1 \leq 1$$

FBA outcome $Z = 0.5$

Results

Secondary optimization:

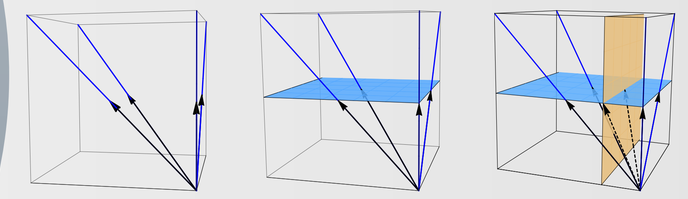
$$\min \sum |J_i|$$



Optimal solution is not a vertex;
its a convex combation of 2 vertices

What if we make each reaction irreversible?

1) Unique set of vertices
2) Vertices are
   1: Elementary flux modes (EFMs)
   2: convex combinations of original EFMs
3) No linealities (but more rays!)

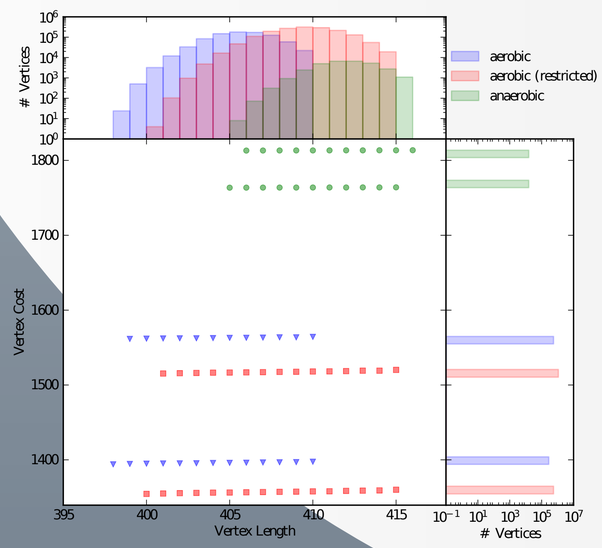


Flux cone | 1 constraint: Vertices are EFMs | 2: constraints Vertices are EFMs and convex combinations of EFMS

Conclusions

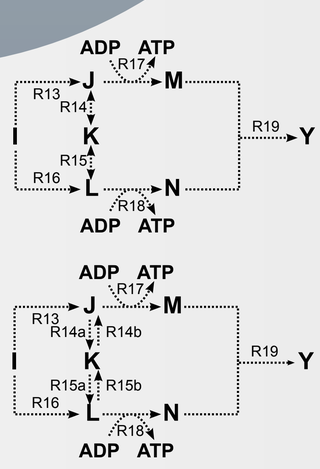
The solution spaces of FBA optimizations are surprisingly structured

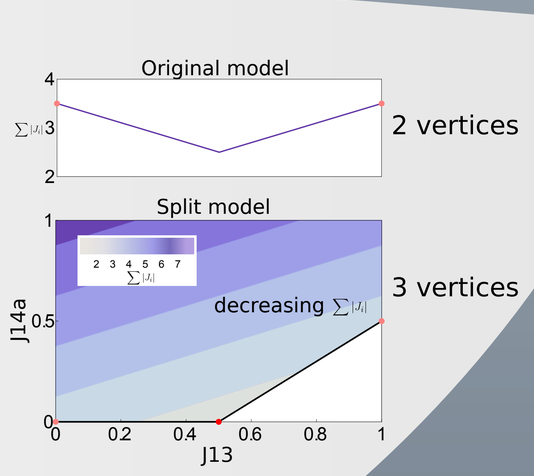
FBA is a very predictive method although its predictions result in vast solution spaces



Vertex Length: Gaussian-shaped distributed

Vertex cost: bimodal distributed





2 vertices | 3 vertices

Splitting the reactions :
1) Changes the solution space
2) Increases the number of vertices,
3) Makes sure that the secondary optimization is linear (since all J_i are positive)
4) The optimum is **always** on a vertex