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# Automatic identification and restoration of reaction gaps in the consensus reconstruction network for yeast metabolism

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## Introduction

### Motivation

- An **automated** procedure of identifying and filling of **reaction gaps** in genome-scale metabolic networks within the framework of **flux balance analysis**.
- To identify the non-producible metabolites in the network
  - constraint-based optimisation** techniques
  - graph traverse algorithm**
- Search for reactions to add into the model to restore the **reachability** of the metabolites or clusters of metabolites
- This is part of an iterative process of converting a genome-scale reconstruction into an executable computational model:
  - representing** the reactions in mathematical form,
  - validating and refining** the mathematical model.

### Consensus network reconstruction for yeast metabolism

- Yeastnet1.0: community driven, rigorously evidenced and well annotated [1] <http://www.comp-sys-bio.org/yeastnet/>
- Yeastnet2.0: a recent expanded network reconstruction that includes a detailed and evidence description of lipid metabolism.
- Yeastnet2.0: 1834 unique chemical reactions, 886 ORFs and 1418 metabolites located in 15 different compartments.
- Need for automated procedure for network validation.**

## Method

### Background

- Flux Balance Analysis (FBA)
- Structural Gaps in metabolic networks
  - Reaction gaps**, orphan enzymes, ...
- Mechanisms to rescue reaction gaps in the networks
  - => reversibility; transportation; cell consumption
  - => adding missing reactions from reference model
  - => metabolite exchange (uptake or secretion)
- Focus on bridging gaps that block the cell from producing some metabolites: assuming all metabolites are all consumable, all reactions reversible.**

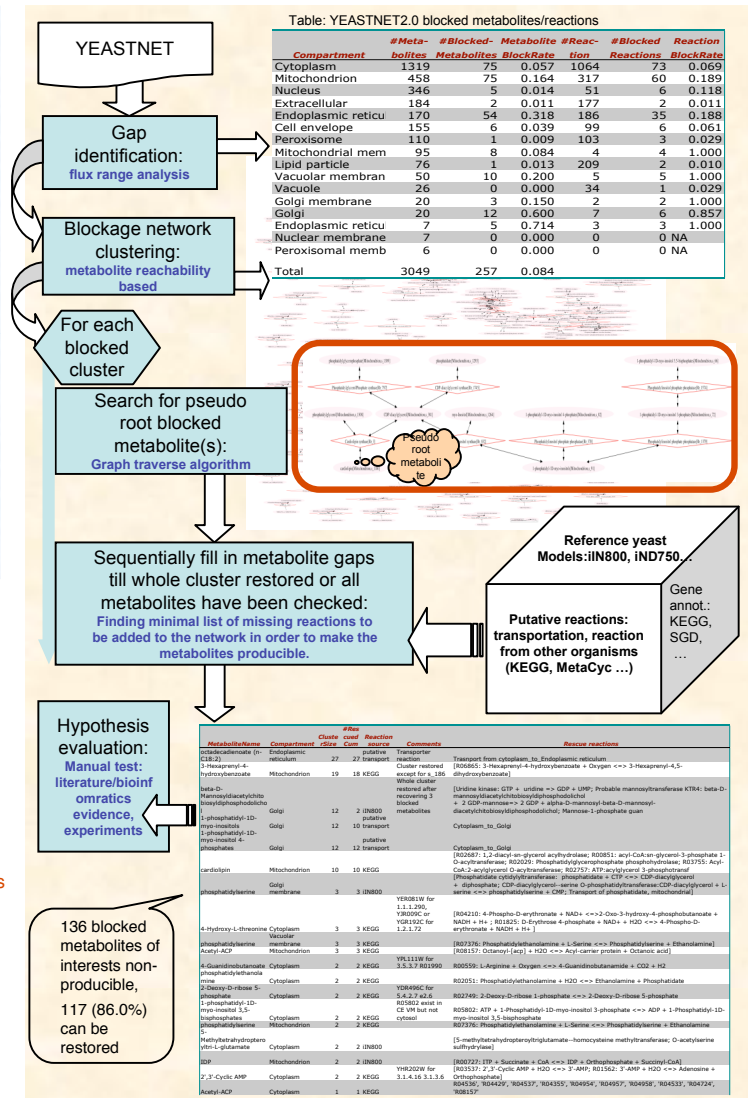
### Procedure

- Gap identification: **flux range analysis**
- Blocked metabolite clustering:
  - Check metabolite reachability with blockage network
  - Blockage network: formed by blocked reactions.
- Finding **pseudo root blocked metabolites**: graph traverse.
- Gap filling: **mixed integer linear programming**, principle of minimum metabolite

$$\begin{aligned} & \text{Minimize } \sum a \\ & \text{s.t. } Sv + Uy = 0, \\ & v_{\min,i} \leq v_i \leq v_{\max,i}, \forall i \in R \text{ in current model} \\ & a_j y_{\min,j} \leq y_j \leq a_j y_{\max,j}, \forall j \in R \text{ in database} \\ & v_i \geq \varepsilon - M(1 - b_i), \forall i \in R \text{ with metabolite } m \text{ as product} \\ & v_i \leq -\varepsilon + M(1 - b_i), \forall i \in R \text{ with metabolite } m \text{ as reactant and reversible} \\ & \sum b > 0, a, b \in \{0,1\} \\ & \text{where } \varepsilon, M > 0, \varepsilon \rightarrow 0, M \rightarrow \infty; \\ & S \text{ and } U \text{ are stoichiometric matrices for model and database, respectively.} \end{aligned}$$

Computational tools implemented in python, LP solver Ipsolve.

## Applications



## Conclusions

- One-step further computational effort over the initial manual curation towards a **gapless network reconstruction model**.
- We can systematically **decrease the inconsistency** of the model and potentially improve the accuracy of the model simulation.
- This approach can **generate hypotheses** (suggesting good candidate reactions) for manual verification or further robot experimental tests.

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