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Constraint-based Optimisation Tools for Semi-automated Refinement of Genome-scale Yeast Metabolic Models

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Introduction

Motivation

- Genome-scale metabolic network models are useful for analysing the cellular behaviour of organisms
- Semi-automated procedure for model validation and refinement are important for quality assurance in such models
- Computational tools for iterative model validation and optimisation are necessary to assist hypothesis generation and evaluation

Genome scale metabolic models for *S. cerevisiae*

- A consensus reconstruction: Yeast1, community driven, rigorously evidenced, well annotated [1]
- Further development: Yeast4, expanded from Yeast1, with improved representation of metabolic transport, lipid metabolism, etc. [2]
- Yeast4: 1102 unique metabolite reactions, and 924 metabolites located in 15 cellular compartments

Methods

Framework of Flux Balance Analysis (FBA)

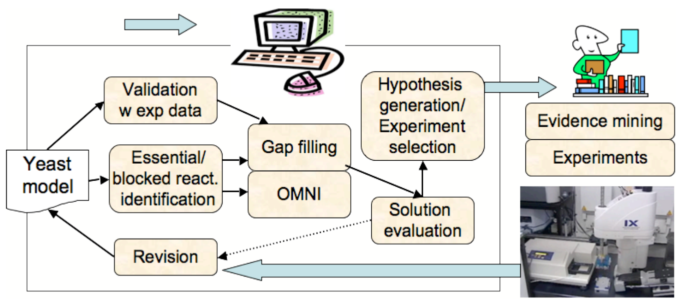
- Identification of flux distribution using stoichiometry model, assuming steady states, with constraints on mass balance and thermodynamics to maximise/minimise an objective function (e.g. to max growth rate)
- Utilisation of constraint-based optimisation, linear/nonlinear programming (LP/NLP), mixed integer linear programming (MILP)

Gap filling

- Structural Gaps in metabolic networks
  - Reaction gaps, missing gene-protein-reaction associations, etc.
- Mechanisms to rescue reaction gaps
  - Reversibility; transport; biomass formation; metabolite exchange
  - Addition of missing reactions from reference model
- Identification of minimal set of reactions to add on, in order to restore biomass formation or blocked reactions [4]

Optimal Metabolic Network Identification (OMNI)

- Models under-constrained:
  - Reactions absent in yeast, irreversible or unfavorable under certain conditions, suppressed due to regulatory, etc.
- Bi-level constrained optimsation:
  - Minimisation of discrepancies between observations and predictions while maximising the growth rate [5]
  - Converting to MILP by exploiting duality for LP



Approach

Applications

Computational tool implementation

- Implemented in Python, using CPLEX, glpk, lpSolve as LP/MILP solvers
- Read/write models in SBML format
  - Model stored in bipartiate graph and/or stoichiometry matrices
  - Suitable for both FBA and logical model simulations
- Converting model network (bi-level) optimisation problem to constraint-based optimisation problem: LP, MILP.
- Algorithms for gap filling, OMNI
- Search algorithms for graph traverse, and identification of minimal models

Model validation with experimental data

- Single deletion data under minimal medium
- Wildtype growing under different conditions: RobotScientist's [3] automated titration experiments on yeast utilising amino acids as sole C/N source
- Awareness of data quality issue

Gap filling procedure

- Constraint-based optimisation and literature searching
- Solutions for 14 of 16 false inviable single deletions under minimal medium
- Further curation needed to fill in the missing reaction esp. for alternative pathways of ergosterol biosynthesis

Single deletant	Non-producible biomass comp.	Revision suggestions	Revision field	Reference
IPT1, CSG2, PXA2, PXA1	MIP2C	Remove MIP2C from biomass, not essential for cell growth.	Biomass formation	PIMD: 9368028
SLC1	phosphatidylcholine triglyceride,…	1-acyl-sn-gylcerol-3-phosphate acyltransferase: SLC1 => SLC1 | SLC4.	GPR	PIMD: 17726007
ILV6	L-valine, L-isoleucine	2-aceto-2-hydroxybutanoate synthase and acetolactate synthase: ILV6: ILV2 => ILV6: ILV2 |ILV2.	GPR	PMID: 10213630
TGL2	triglyceride	Adding 2 putative transport reactions between cytosol and lipid particle.	Transport reaction	Gap filling algorithm
…	…	…	…	…

OMNI procedure

- More than 1 solution for 12 out of 48 false viable cases subject to OMNI
- Solution evaluation: *in-silico* simulation using phenotype data in SGD
- Application of a minimal set of revisions, resulting in:
  True inviables increased by 12, at the cost of 1 extra false inviable
- Suggested revisions:
  - Constraining the reaction directionality
  - Removing reactions:
    e.g. alternative pathway for quinolinate synthesis absent in yeast
  - Adding regulator rules to control reaction activation
    e.g. GALT and GALE activated only after sensing glalatose
  - Testing in vivo by robot: auxotrphy experiments

Conclusions

- Proposed computational tools can effectively search for (multiple) revision suggestions for yeast metabolic models
- Semi-automated model refinement, supported with literature search and robot scientist experiments, helps to improve the model in phenotype prediction
- **Future work**
  - Use of logic programming to integrate models with evidence from experimental data and constraint-based analysis
  - Learning GPR associations and regulatory rules and automated suggestion of experiments, either *in-silico* or *in-vivo*

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