Reconstruction and Validation of *Saccharomyces cerevisiae* iND750, A Fully Compartmentalized Genome-Scale Metabolic Model

Natalie C. Duarte, Markus J. Herrgård, and Bernhard Ø. Palsson
University of California, San Diego, 9500 Gilman Drive, La Jolla, California, 92093-0412, USA

Abstract

Successful integration of diverse biological data sets can only be achieved through a modeling framework. The first genome-scale metabolic reconstruction of a eukaryotic organism, *Saccharomyces cerevisiae* iFF708, was recently completed by Förster and Famili [1].

As part of the iterative model building process (Fig. 1), the contents the *S. cerevisiae* iFF708 were used to develop an expanded network named *S. cerevisiae* iND750 [2]. Three primary features distinguish *S. cerevisiae* iND750 from iFF708: iND750 is fully compartmentalized (Fig. 2); iND750 directly incorporates genomic, transcriptomic, and proteomic data as associations between genes, transcripts, proteins, and reactions (Fig. 3); and iND750's reactions are both elementally and charge- balanced, enabling a cell-wide proton balance.

To comprehensively evaluate iND750's performance, phenotypic predictions for 682 gene deletion strains on seven media compositions were compared to *in vivo* results from two large-scale experiments [3,4]. An 83% agreement was found between iND750's predictions and the experimental observations.

Analysis of the failure modes led to the identification of gaps and inconsistencies in the body of information used for the reconstruction. In many cases, the false predictions led to direct suggestions of how to potentially improve the model or of specific experiments that could be performed to further improve our understanding of yeast metabolism.

Genome-Scale Modeling

What are genome-scale models?

Genome-scale models account for all of an organism's genes that are related to a particular cellular process.

**Which cellular processes have been modeled at the genome scale?**

- Metabolism
- Transcriptional regulation
- Intracellular signaling
- Transcription and translation

Which organisms have been modeled at the genome scale?

Genome-scale metabolic models have been reconstructed for several bacterial species. The yeast reconstruction is the first metabolic model of a eukaryotic cell.

Reconstruction of *S. cerevisiae* Metabolic Models

Figure 1: A schematic detailing the reconstruction of *S. cerevisiae* iFF708, the first yeast metabolic model, and *S. cerevisiae* iND750, the expanded model.
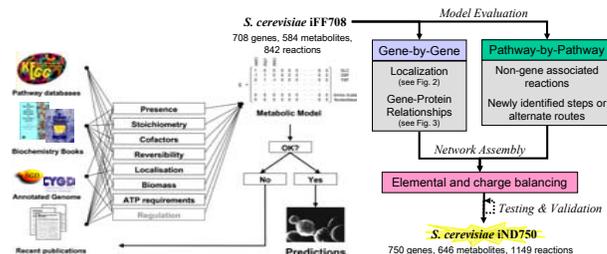
The *S. cerevisiae* iFF708 and *S. cerevisiae* iND750 networks can be found at: http://systemsbiology.ucsd.edu

S. cerevisiae iND750 is Fully Compartmentalized

- *S. cerevisiae* iND750 includes **8 cellular localizations** (Fig. 2). Reactions were assigned to the cytosol by default.

- Many **transport reactions** had to be inferred. Metabolites were assumed to be exchanged by similar mechanisms across various intracellular membranes.
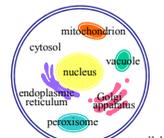

Figure 2: Compartmentalization of *S. cerevisiae* iND750

Gene-Protein-Reaction Associations Represent the Logical Relationships between ORFs, transcripts, Proteins, and Reactions
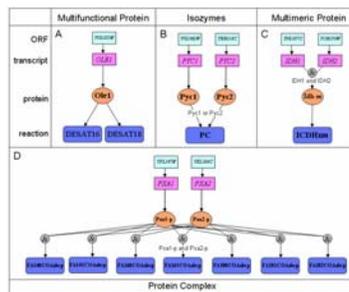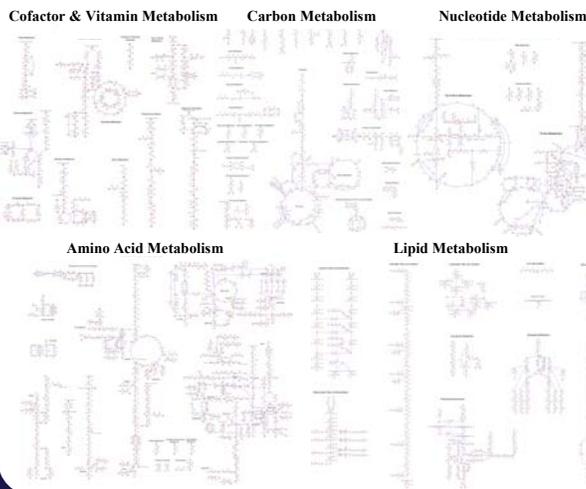

Figure 3: A **multifunctional protein** catalyzes more than one reaction; **isozymes** catalyze the same reaction independently; a **multimeric protein** is composed of more than one transcript; a **protein complex** requires more than protein to catalyze a reaction.

All of the gene-protein-reaction associations for *S. cerevisiae* iND750 can be found at: http://systemsbiology.ucsd.edu

S. cerevisiae iND750 Metabolic Network Maps

The metabolic network maps for *S. cerevisiae* iND750 can be found at: http://systemsbiology.ucsd.edu

Cofactor & Vitamin Metabolism   Carbon Metabolism   Nucleotide Metabolism

Amino Acid Metabolism   Lipid Metabolism

Cellular Behaviors are Simulated Using the Constraint-Based Approach
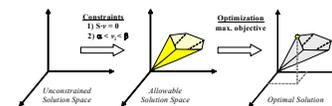

Figure 4: Physico-chemical constraints are used to eliminate infeasible cellular behaviors from the solution space. A particular optimal solution is then selected from the allowable solution space using linear optimization.

S. cerevisiae iND750 Correctly Predicts 3,430/4,154 Growth Phenotypes Under Seven Media Conditions

- *In vivo* growth rates of 682 gene deletion strains [3,4] were qualitatively compared to predictions made by *S. cerevisiae* iND750.
- iND750 correctly predicted **83%** growth phenotypes (viable/non-viable)
- Analysis of **failure modes** revealed that false positive predictions were primarily caused by the model's limited inclusion of cellular processes outside of metabolism.

Conclusions

- We can successfully build multi-compartmental metabolic models of eukaryotic cells with elementally and charge-balanced reactions.
- Genome-scale models can be used to compute growth phenotypes of organisms with altered genotypes in various media conditions.
- Analysis of the failure modes can be used to improve the model, identify inconsistencies in our knowledge base, and highlight areas where require further experimental investigation is required.

References

1. Förster, J., et al., *Genome-scale reconstruction of the Saccharomyces cerevisiae metabolic network.* Genome Res, 2003. **13**(2): p. 244-53.
2. Duarte, N.C., M.J. Herrgård, and B.Ø. Palsson, *Reconstruction and validation of Saccharomyces cerevisiae iND750, a fully compartmentalized genome-scale metabolic model.* Genome Res, 2004. **14**(7): p. 1298-1309.
3. Giaever, G., et al., *Functional profiling of the Saccharomyces cerevisiae genome.* Nature, 2002. **418**(6896): p. 387-91.
4. Steinmetz, L.M., et al., *Systematic screen for human disease genes in yeast.* Nat Genet, 2002. **31**(4): p. 400-4.

Acknowledgments