

Genome-Scale Reconstruction of *Saccharomyces cerevisiae*

Natalie Duarte, Markus Herrgard, Bernhard Palsson
Systems Biology Research Group, University of California, San Diego

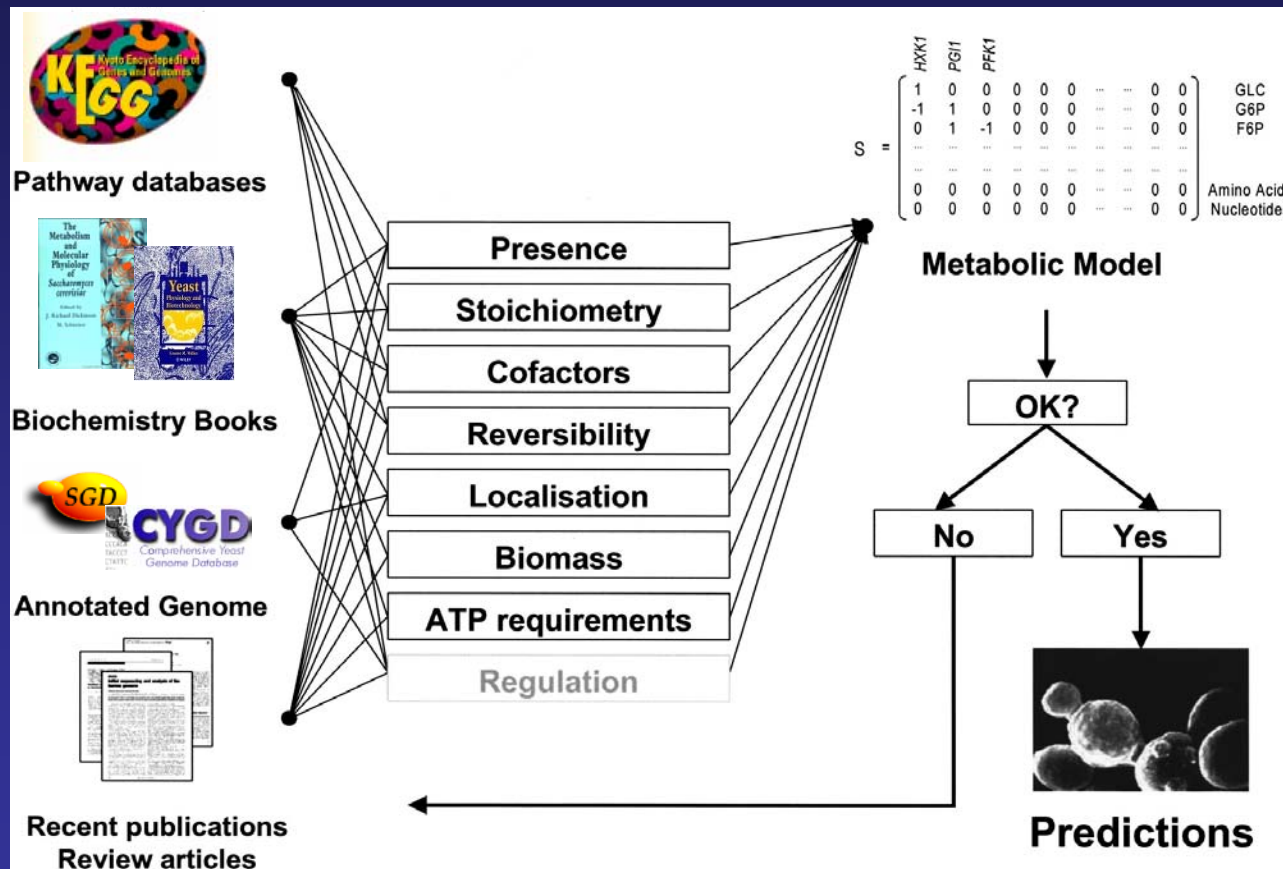
2004 Yeast Genetics and Molecular Biology Meeting
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Genome-scale Reconstruction

- Need a systematic method to interpret the current flood of “omics” data
- Models can be used to integrate data and place them in the context of cellular physiology
 - Requires genome-scale integration of genes, transcripts, proteins
- Genome-scale reconstruction projects for *S. cerevisiae*:
 - Metabolism
 - Transcriptional regulation
 - Intracellular signaling

Reconstruction of *S. cerevisiae* iFF708

The first genome-scale metabolic model of a eukaryotic cell

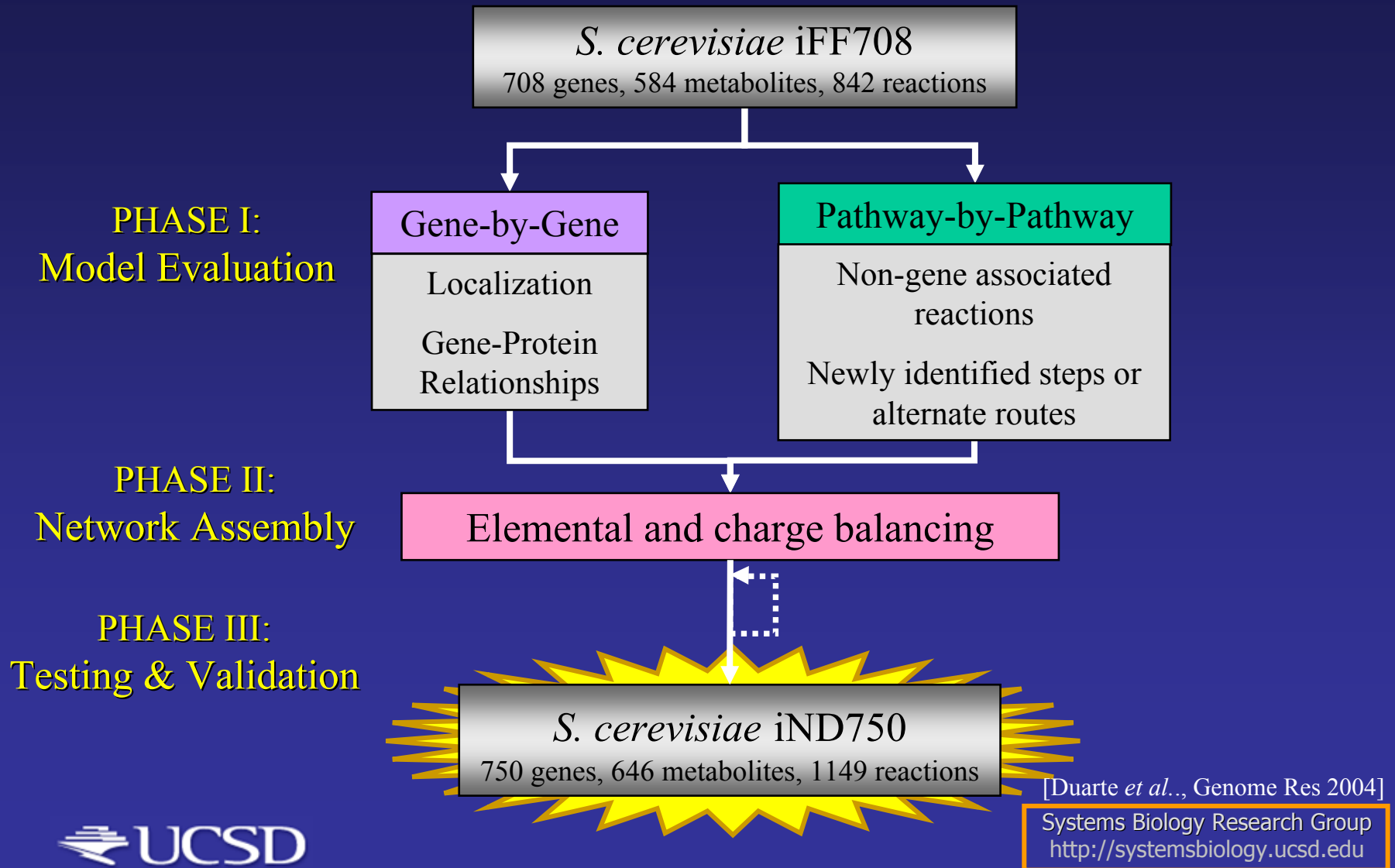


[Förster *et al.*, Genome Res 2003]

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Reconstruction of *S. cerevisiae* iND750

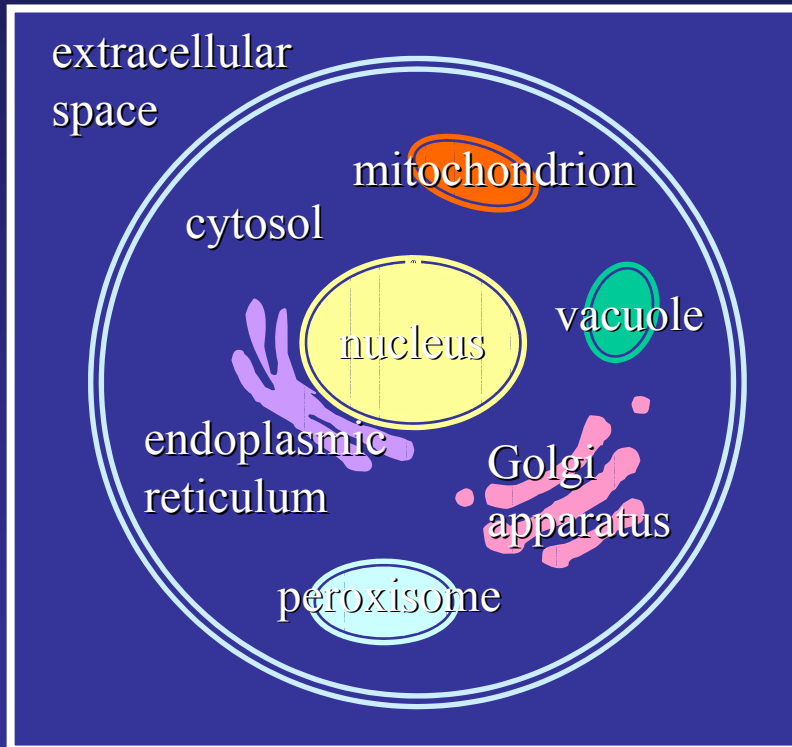
Expanding and updating the yeast metabolic network



Compartmentalization

S. cerevisiae iND750 is the first fully compartmentalized network

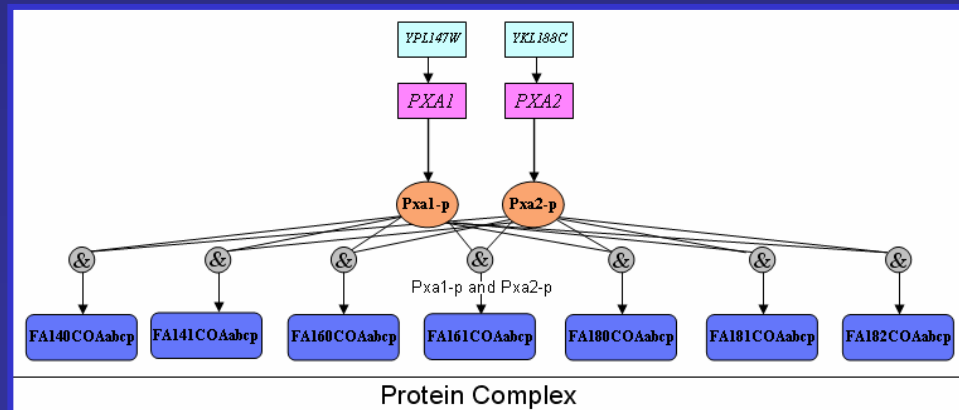
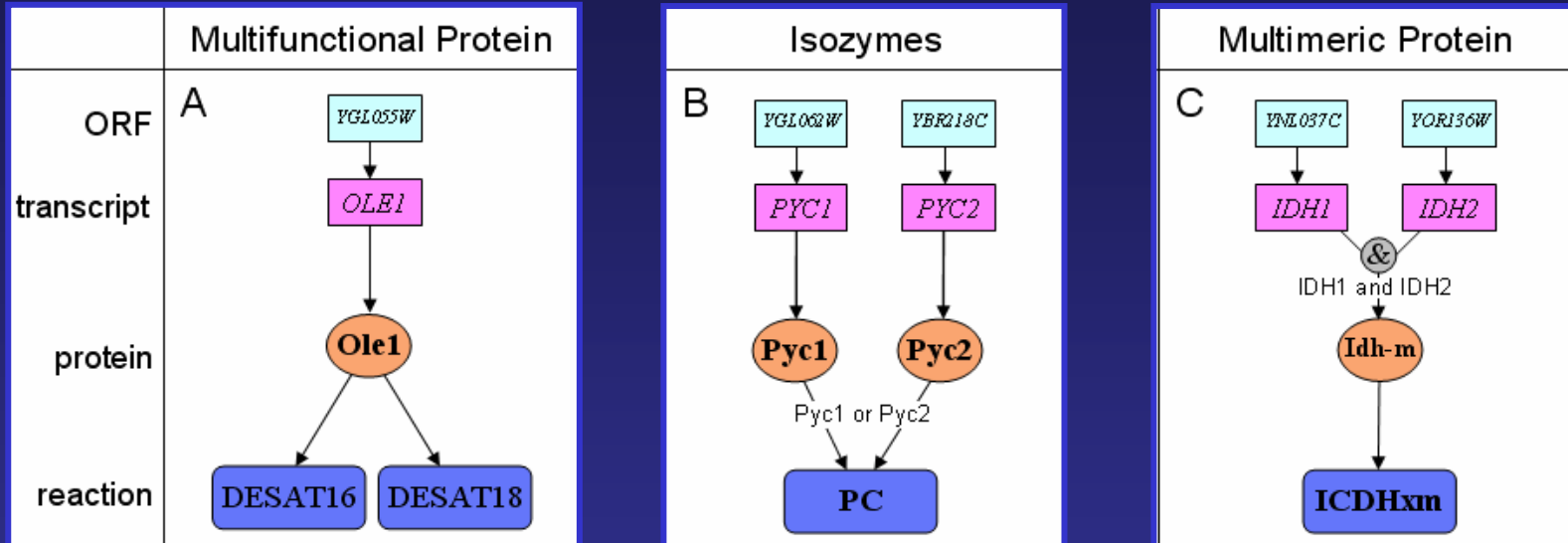
Localizations in *S. cerevisiae* iND750



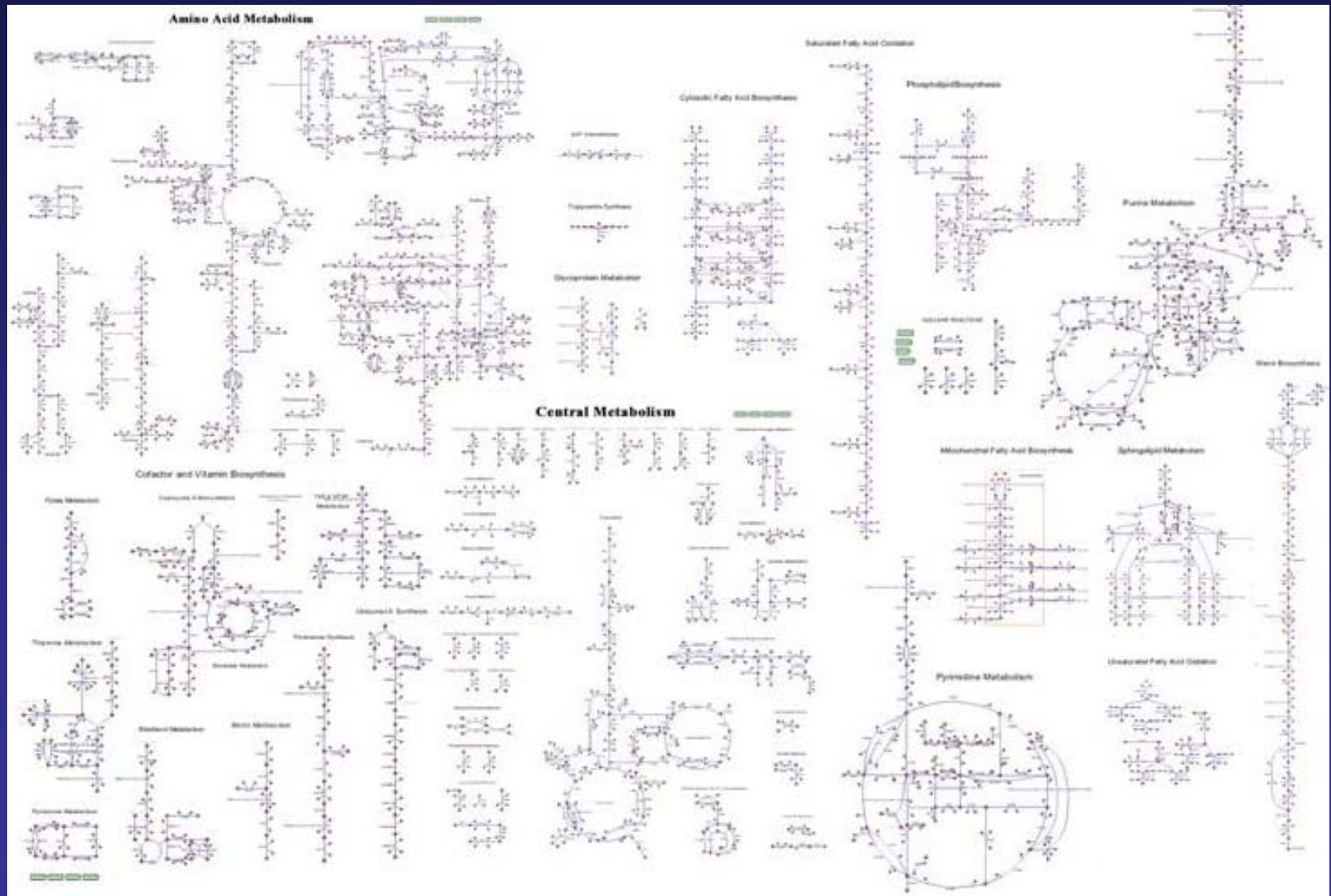
- Assigning localizations is tricky
 - Assumed to be cytosolic by default
- Many intracellular transport reactions had to be inferred
 - Assumed similar transport mechanisms across various intracellular membranes
- Mass and charge are balanced within each compartment

Gene-Protein-Reaction Associations

Boolean logic rules are used to describe gene-protein relationships



S. cerevisiae iND750 Metabolic Network



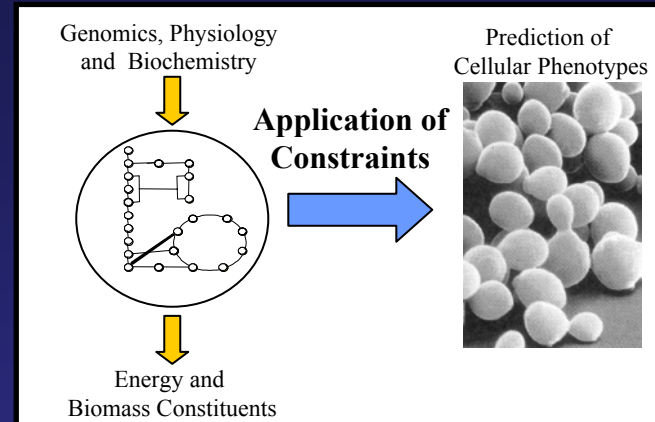
Constraint-Based Analysis

Predicting cellular phenotypes by application of constraints



How often have I said to you that when you have eliminated the impossible, whatever remains, however improbable, must be the truth?

—Sherlock Holmes, [A Study in Scarlet](#)



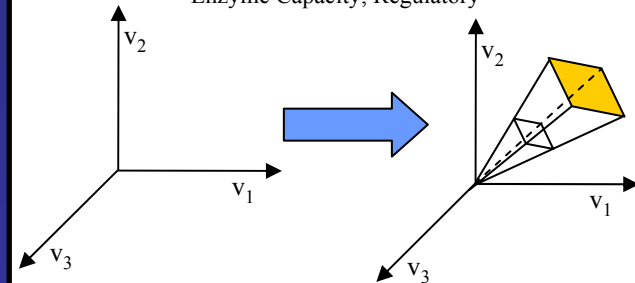
Mathematical Representation of Constraints

$$S \cdot v = 0$$

$$v_{min,i} \leq v_i \leq v_{max,i}$$

Application of Constraints

Stoichiometric, Thermodynamic,
Enzyme Capacity, Regulatory



Validation of *S. cerevisiae* iND750

- Qualitatively compared the growth rates of 682 gene deletion strains to *S. cerevisiae* iND750's predictions
 - Knockout strains were grown on 7 media conditions, resulting in a total comparison of 4,154 metabolic phenotypes!
 - Results were classified as either false positive, false negative, true positive, or true negative
 - iND750 correctly predicted 82.6% growth phenotypes
- ... *but what happened in the 724 cases where the model failed?*

[Steinmetz *et al.*, Nat Genet 2002]

[Giaever *et al.*, Nature 2002]

[Duarte *et al.*, Genome Res 2004]

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Analysis of Failure Modes

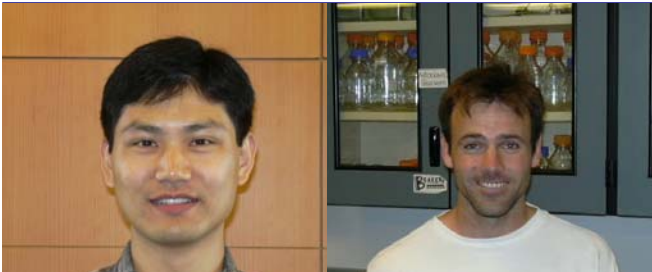
- Each failure mode was evaluated individually to determine the reason for the false prediction
- False predictions were generally **not condition-dependent**
- More than half of the failures can be attributed to **genes involved in other cellular processes (33.7%)** and our assumed **biomass composition (17.5%)**
- **Nuclear** and **mitochondrial** genes had the highest false prediction rates
- Genes in **quinone biosynthesis** and **oxidative phosphorylation** pathways had high false prediction rates

Summary

- Model building is an iterative process, requiring continued updating and testing.
- We can successfully build multi-compartmental metabolic models of eukaryotic cells that require cell-wide mass and charge balances.
- Genome-scale models can be used to compute growth phenotypes of organisms with altered genotypes in various media conditions.
- Failure modes can be used to improve model, identify inconsistencies in knowledge base, and highlight areas where further experimental investigation is required.

Systems Biology Research Group

Principal Investigator: Dr. Bernhard Palsson



Qiang Hua

Eric Knight



Jennie Reed

Scott Becker



Natalie Duarte

Jason Papin



Markus Herrgard

Tim Allen



Andrew Joyce

BK Cho

Christian Barrett

Anu Rangunathan

Baekseok Lee

Nathan Price

Thuy Vo



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