

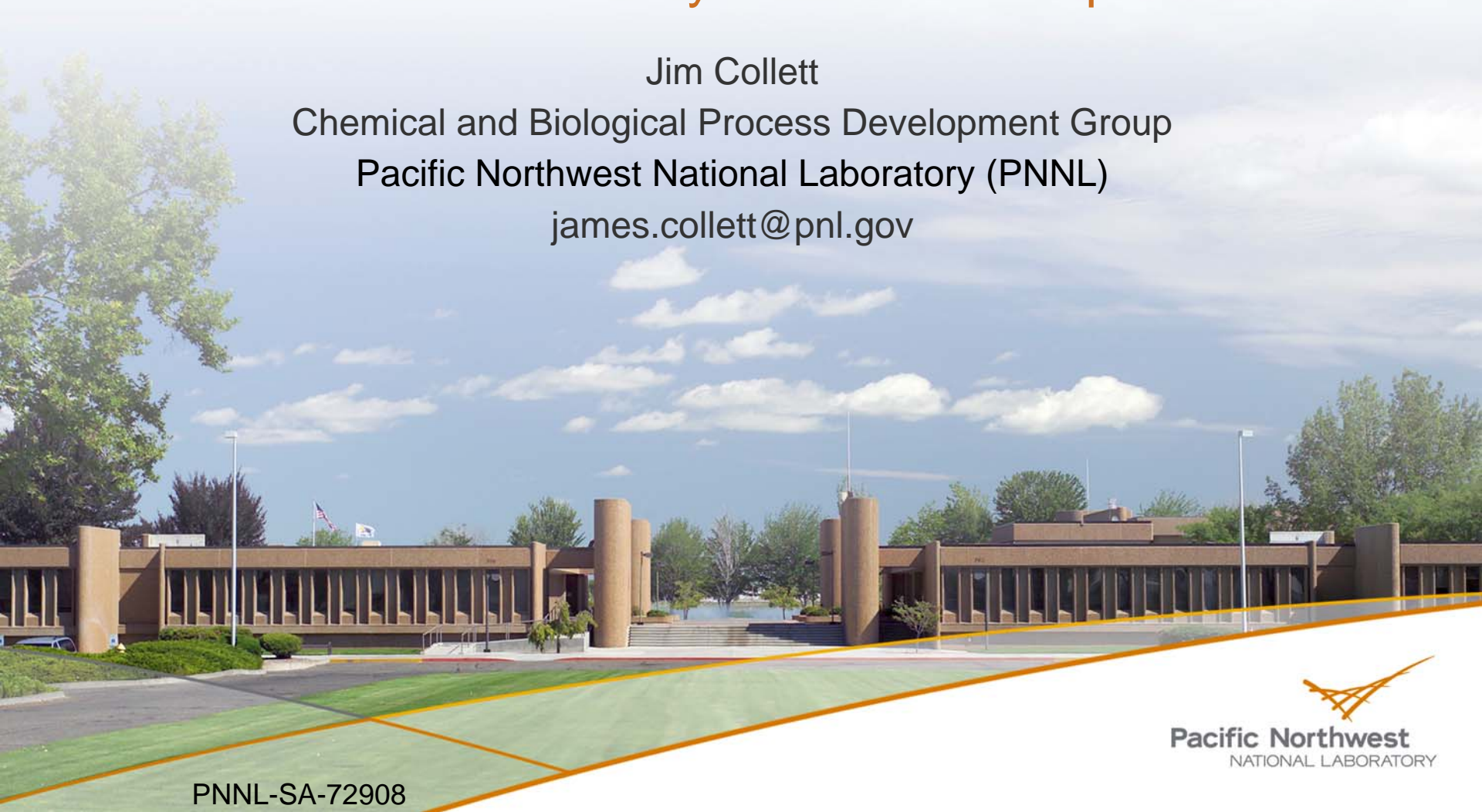
# Integrating flux balance analysis of fungal genome-scale metabolic networks into metabolic engineering practice

## 2010 Pathway Tools Workshop

Jim Collett

Chemical and Biological Process Development Group  
Pacific Northwest National Laboratory (PNNL)

[james.collett@pnl.gov](mailto:james.collett@pnl.gov)

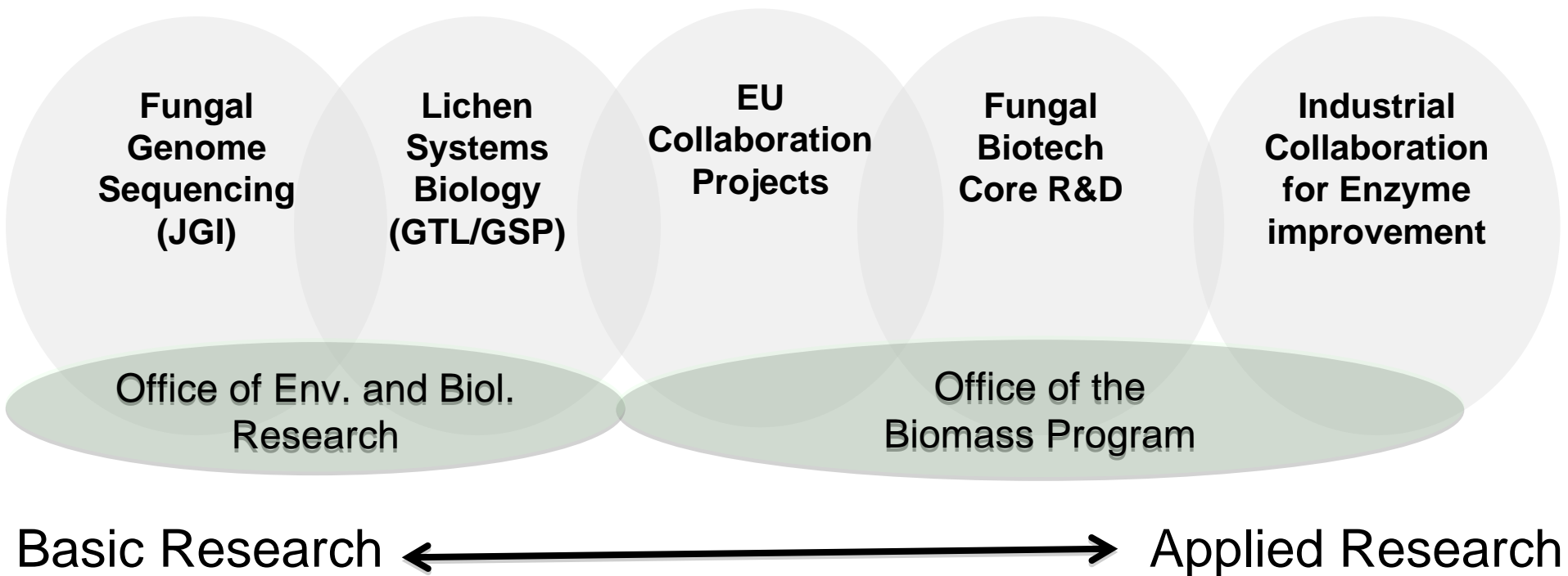


# Bioproducts, Sciences, & Engineering Lab at PNNL

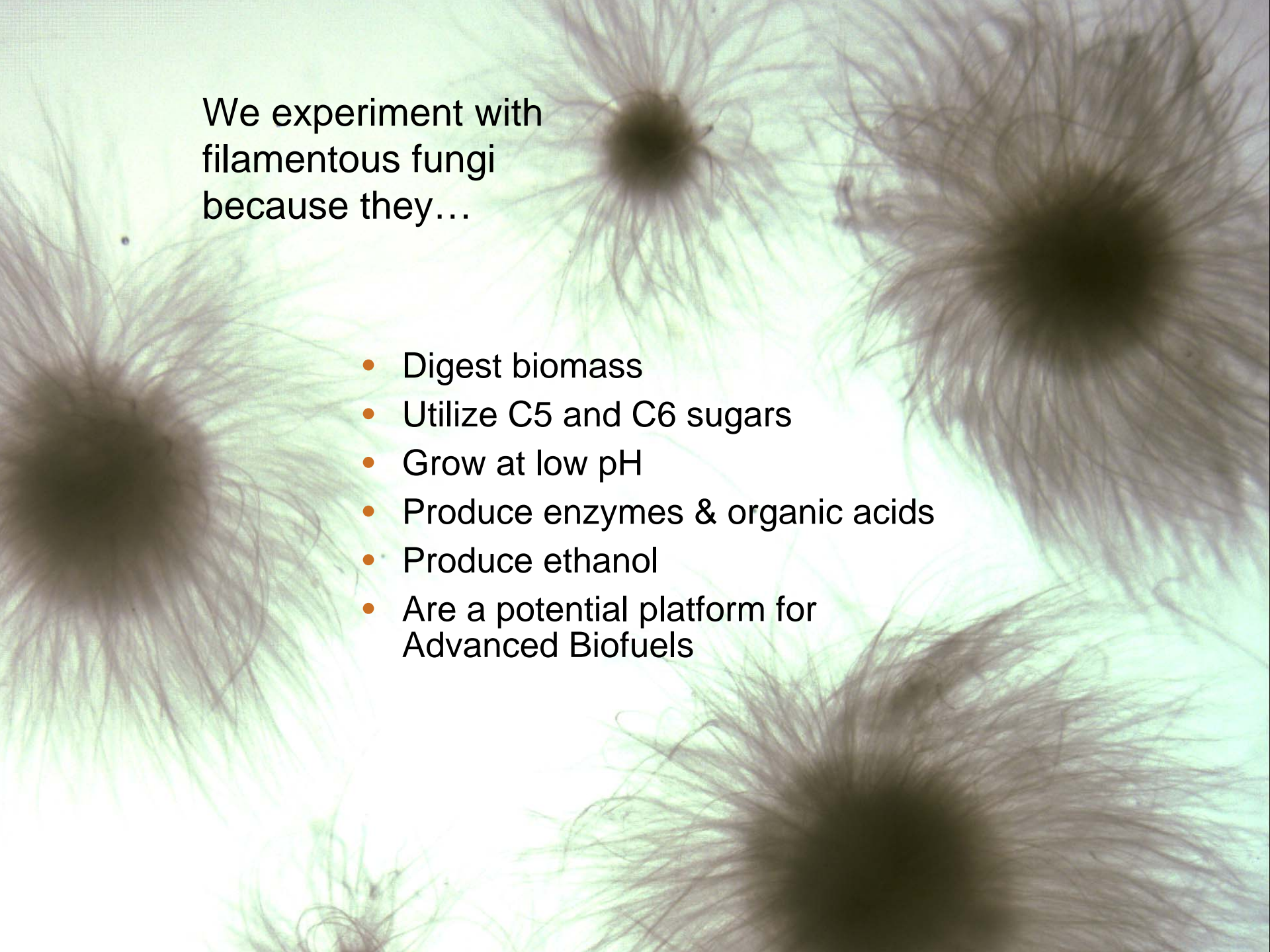


- Thermochemical Conversion
- Biochemical Conversion
- Catalysis and Separations

# PNNL fungal research funded by the DOE





The background of the slide is a microscopic image of filamentous fungi. It shows several dark, circular, fuzzy structures, likely spores or clusters of hyphae, set against a light green and purple background. The overall appearance is that of a dense, fibrous network of microscopic organisms.

We experiment with  
filamentous fungi  
because they...

- Digest biomass
- Utilize C5 and C6 sugars
- Grow at low pH
- Produce enzymes & organic acids
- Produce ethanol
- Are a potential platform for Advanced Biofuels

# PNNL/JGI Fungal Genome Sequencing Projects

Aspergillus aculeatus  
Aspergillus brasiliensis  
**Aspergillus carbonarius (2)**  
**Aspergillus niger**  
Aspergillus tubingensis  
Catenaria anguillulae  
Cochliobolus heterostrophus  
Coemansia reversa  
Conidiobolus coronatus  
Cryphonectria parasitica

Gonapodya sp.  
Neurospora crassa  
Orbilia auricolor  
Orpinomyces sp.  
Phycomyces blakesleeanus  
Piromyces sp.  
Tremella mesenterica  
**Trichoderma atroviride**  
**Trichoderma reesei**  
**Trichoderma reesei**

**Blue = PGDB and curation underway**

**JGI genome-to-PFF pipeline built by Sebastian Jaramillo-Riveri**

# Fungal Genomics Core Research Projects

**Genomics:** Improved transformation for *A. niger* and *T. reesei*. Analysis of *A. niger* polyketide synthase (PKS) genes. SNV analysis of highly mutagenized, cellulose overproducing *T. reesei* strains.

**Proteomics:** Analysis of *A. niger* mutant strains using an Orbitrap mass spectrometer.

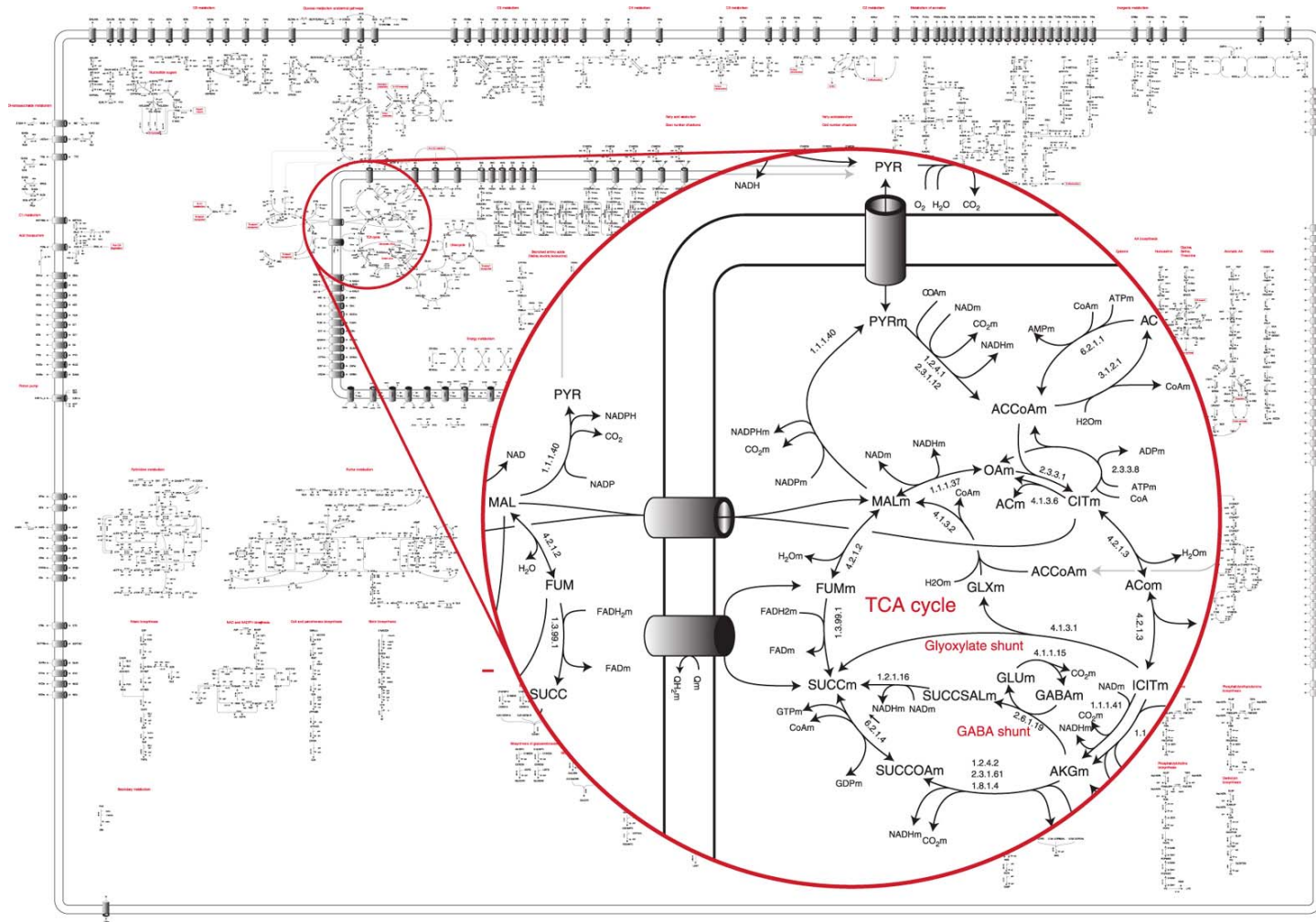
**Hyper-productivity and consolidated bioprocesses:** Itaconic acid production in *A. terreus*.

**Pentose utilization in filamentous fungal:** Study of pentose utilization during *A. oryzae* fermentation.

**Alternative renewable fuels from fungi:** Polyketide, isoprenoid and fatty acid biosynthesis for advanced hydrocarbon biofuels. NMR analysis of candidate biofuel precursor strains.

**Metabolic Process Modeling and Data Integration**

# *Aspergillus niger* genome scale metabolic model from the Nielsen group at DTU/Chalmers



From review of 371 articles

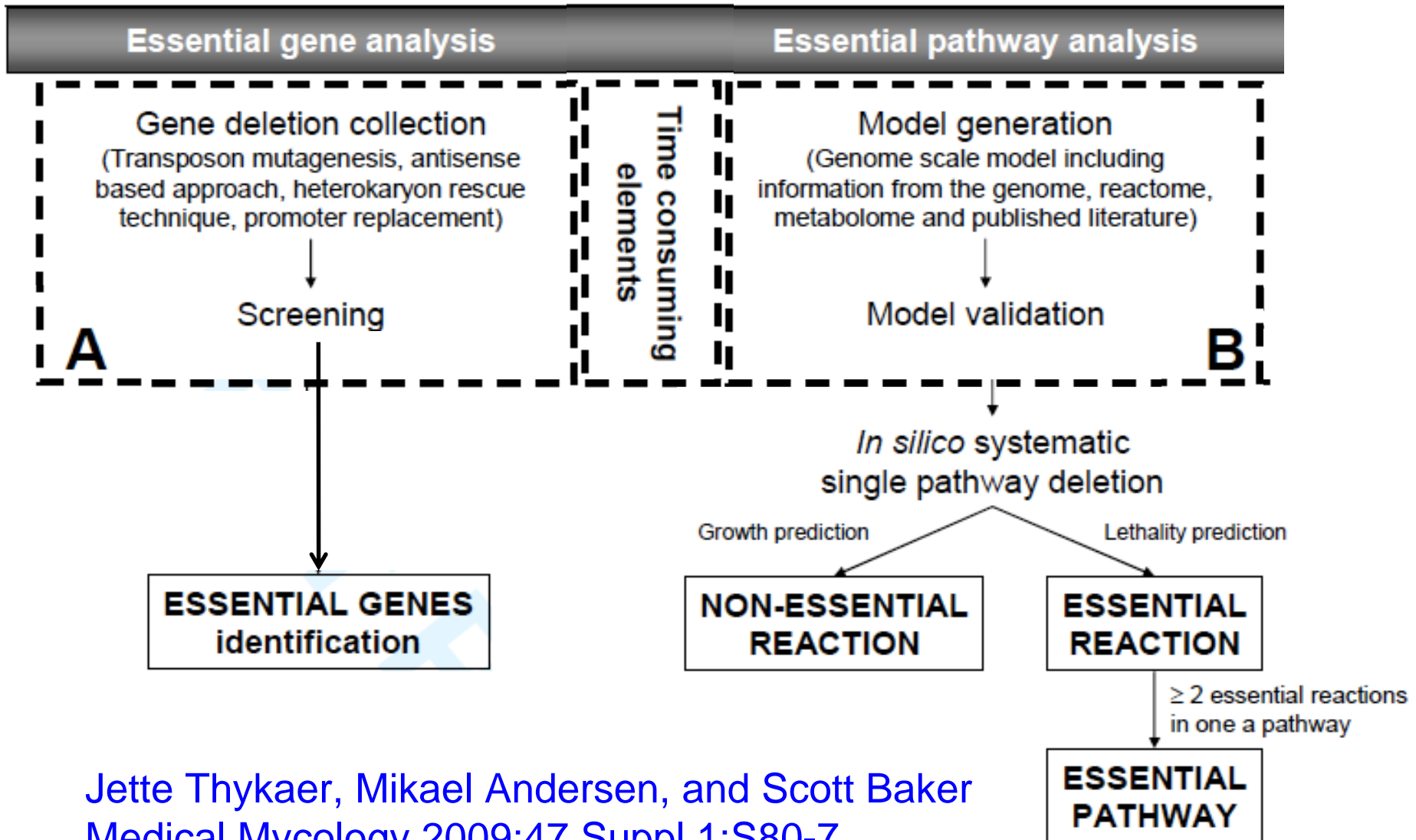
Features:

- 871 ORFs
- 1045 metabolites
- 1190 reactions
- Mitochondrial Compartment

Mikael Rørdam Andersen,<sup>1\*</sup> Michael Lyngge Nielsen,<sup>1</sup> and Jens Nielsen<sup>1a</sup>  
Mol Syst Biol. 2008; 4: 178.



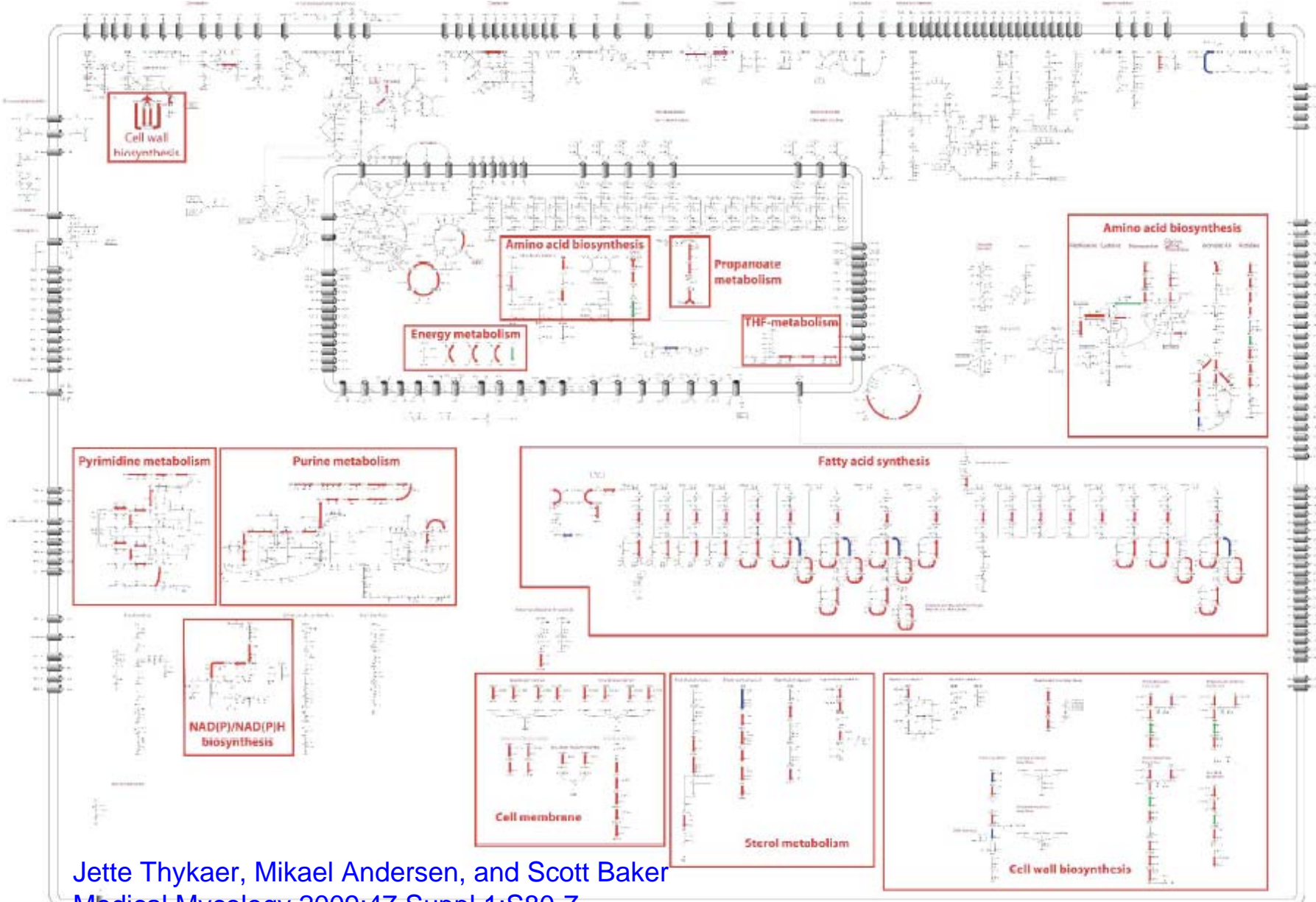
# Using Flux Balance Analysis (FBA) in *A. niger* to predict potential antifungal targets in *Aspergillus fumigatus*



Jette Thykaer, Mikael Andersen, and Scott Baker  
Medical Mycology 2009;47 Suppl 1:S80-7.



*A. niger* genes predicted to be essential by FBA were blasted against the *A. fumigatus* and *Homo sapiens* genomes to find possible orthologs



Jette Thykaer, Mikael Andersen, and Scott Baker  
Medical Mycology 2009;47 Suppl 1:S80-7.

Table 1 Potential antifungal targets in *A. fumigatus*

# Predicted antifungal drug targets

EC no.	Essential enzyme	<i>A. fumigatus</i> gene ID	Additional info
<b>Amino acids biosynthesis</b> *			
5.4.99.5	Chorismate mutase	Afu5g13130	Aromatic
2.4.2.18	Anthranilate phosphoribosyl transferase	Afu4g11980	Aromatic
2.1.1.17	Phosphatidylethanolamine N-methyltransferase	Afu2g15970	Aromatic
4.2.1.51	Prephenate dehydratase	Afu5g05690	Aromatic
2.5.1.54	3-deoxy-7-phosphoheptulonate synthase	Afu1g02110	Aromatic
4.2.1.19	Imidazoleglycerol-phosphate dehydratase	Afu6g04700	His
3.5.4.19	phosphoribosyl-AMP cyclohydrolase	Afu1g14570	His
3.1.3.15	Histidinol phosphatase	Afu4g04030	His
1.1.1.23	Histidinol dehydrogenase	Afu1g17660	His
2.4.2.17	ATP phosphoribosyltransferase	Afu7g04500	His
1.1.1.3	Homoserine dehydrogenase	Afu3g11640	Lys, Gly, Ser, Thr
2.7.2.4	Aspartate kinase	Afu5g05590	Lys, Gly, Ser, Thr
1.2.1.11	aspartate-semialdehyde dehydrogenase	Afu3g06830	Lys, Gly, Ser, Thr
2.3.3.14	Homocitrate synthase	Afu4g10460	Lys
1.1.1.86	Ketol-acid reductoisomerase	Afu3g14490	Val, Leu, Ile
2.3.1.31	homoserine O-acetyltransferase	Afu5g07210	Met
2.1.1.13	Methionine synthase	Afu4g07360	Met
<b>Propanoate metabolism</b>			
4.1.3.30	2-methylisocitrate lyase	Afu6g02860	
4.2.1.79	2-methylcitrate hydrolyase	Afu6g03730	
<b>Fatty acid biosynthesis</b> *			
2.1.1.71	Methylene-fatty-acyl-phospholipid synthase	Afu1g09050	
2.3.1.38	[ACP]acetyltransferase	Afu3g04220	
2.3.1.85	Fatty-acid synthase	Afu3g04210	
<b>Pyrimidine and purine metabolism</b>			
1.8.1.9	Thioredoxin reductase	Afu6g09740	
2.4.2.10	Orotate phosphoribosyltransferase 1	Afu2g11290	
4.1.1.21	Phosphoribosylaminoimidazole carboxylase	Afu4g12600	
<b>Cell wall biosynthesis</b> *			
2.4.1.34	1,3-beta-Glucan synthase	Afu5g05770	
3.1.3.12	Trehalose-phosphatase	Afu3g05650	
<b>Sterol biosynthesis</b> *			
2.5.1.21	Squalene synthase	Afu7g01220	
2.7.4.2	Phosphomevalonate kinase	Afu5g10680	
<b>NADH/NADPH metabolism</b>			
2.4.2.19	Nicotinate mononucleotide pyrophosphorylase	Afu3g05730	
<b>Urea and metabolism of amino groups</b>			
2.3.1.35	Glutamate N-acetyltransferase	Afu5g08120	
<b>Manitol biosynthesis</b>			
1.1.1.17	Mannitol-1-phosphate 5-dehydrogenase	Afu2g10660	

Jette Thykaer, Mikael Andersen,  
and Scott Baker  
Medical Mycology 2009;47 Suppl  
1:S80-7.

# Ethanol overproduction by *Aspergillus oryzae* as a model for pentose utilization in consolidated biofuel production

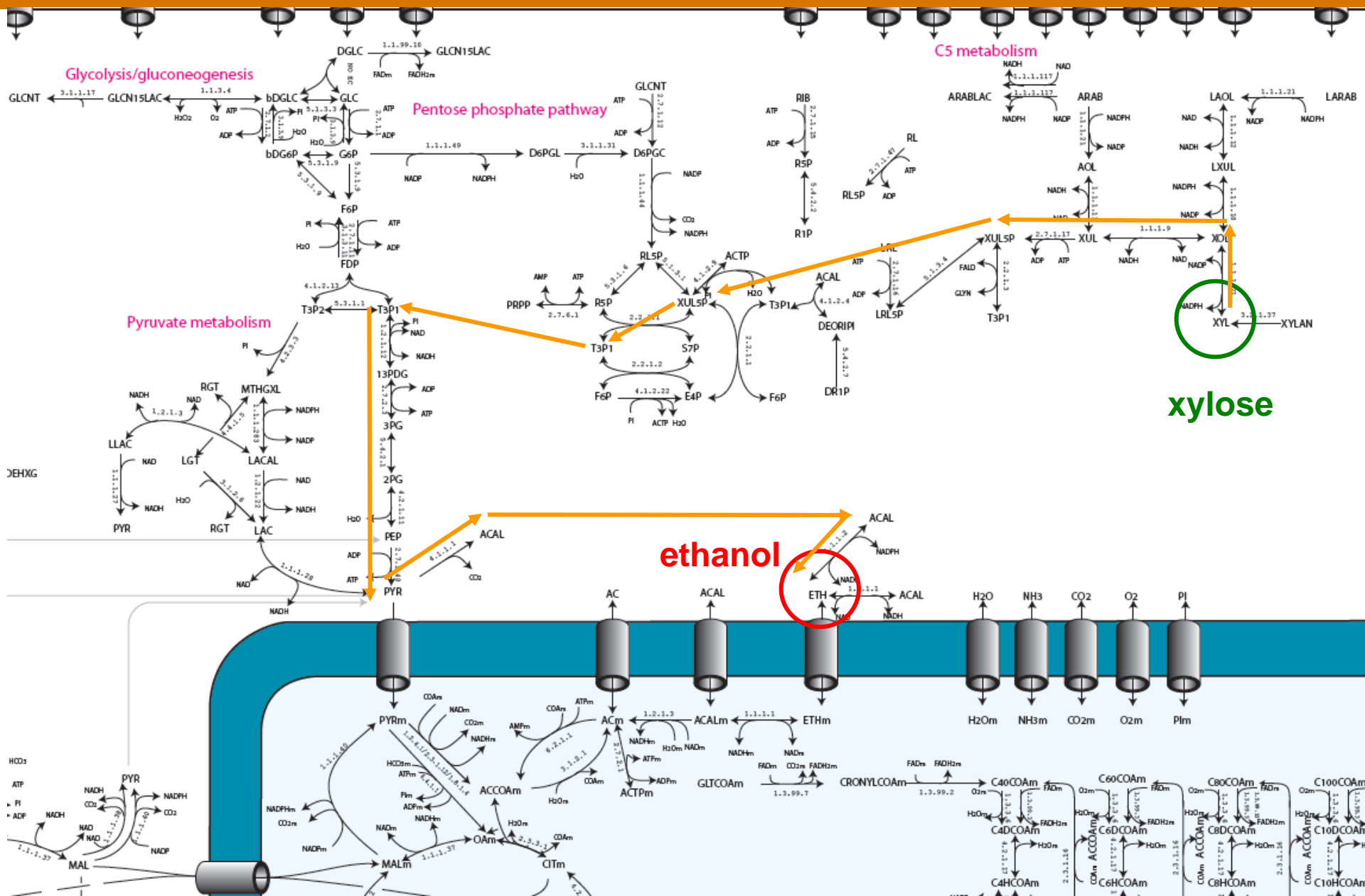


- *A. oryzae* has been used for over 1000 years to saccharify rice for sake brewing.
- It's the national fungus of Japan!





# Flux balance analysis (FBA) to optimize ethanol production in *A. oryzae*





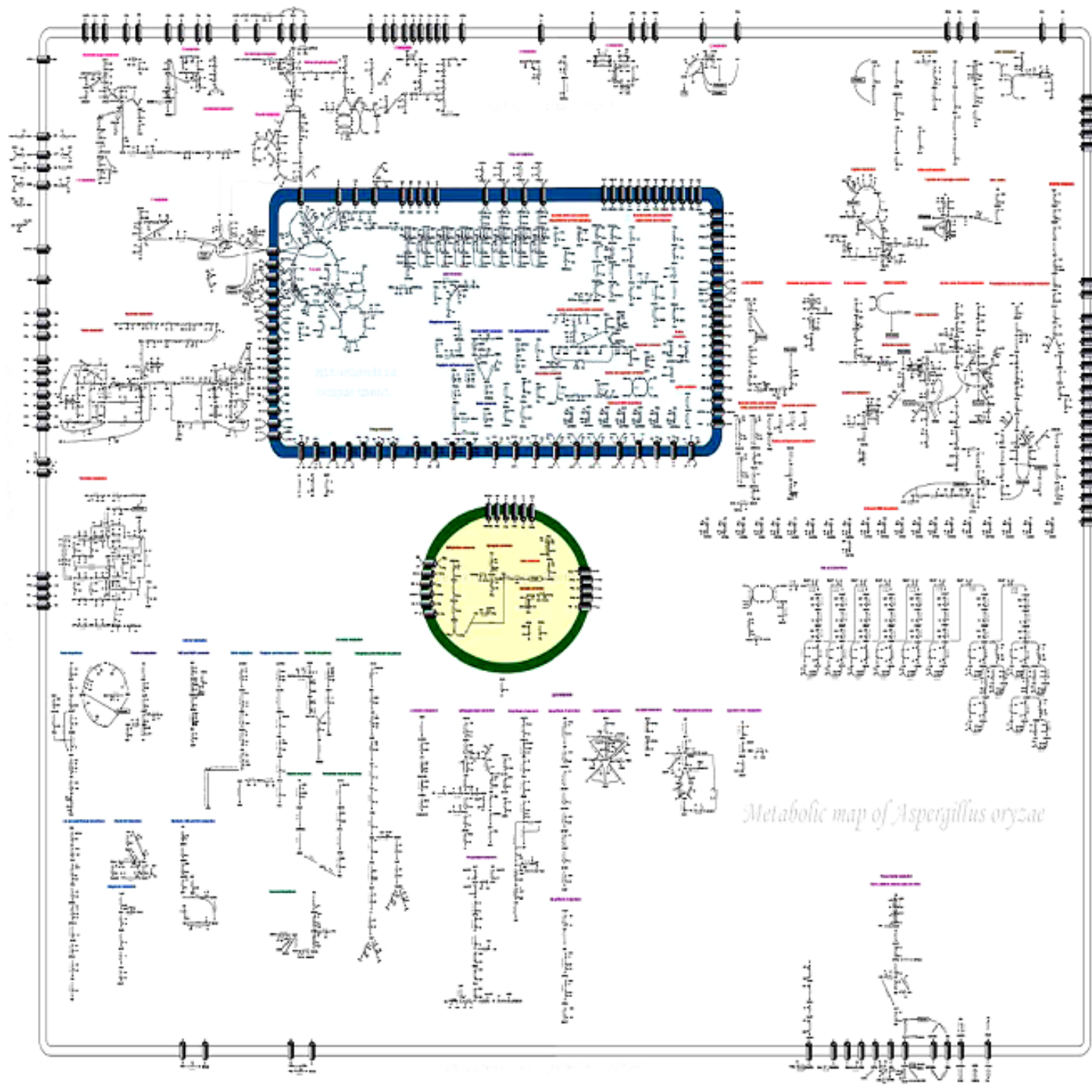
# *Aspergillus oryzae* RIB 40

Genome-scale  
metabolic  
network model

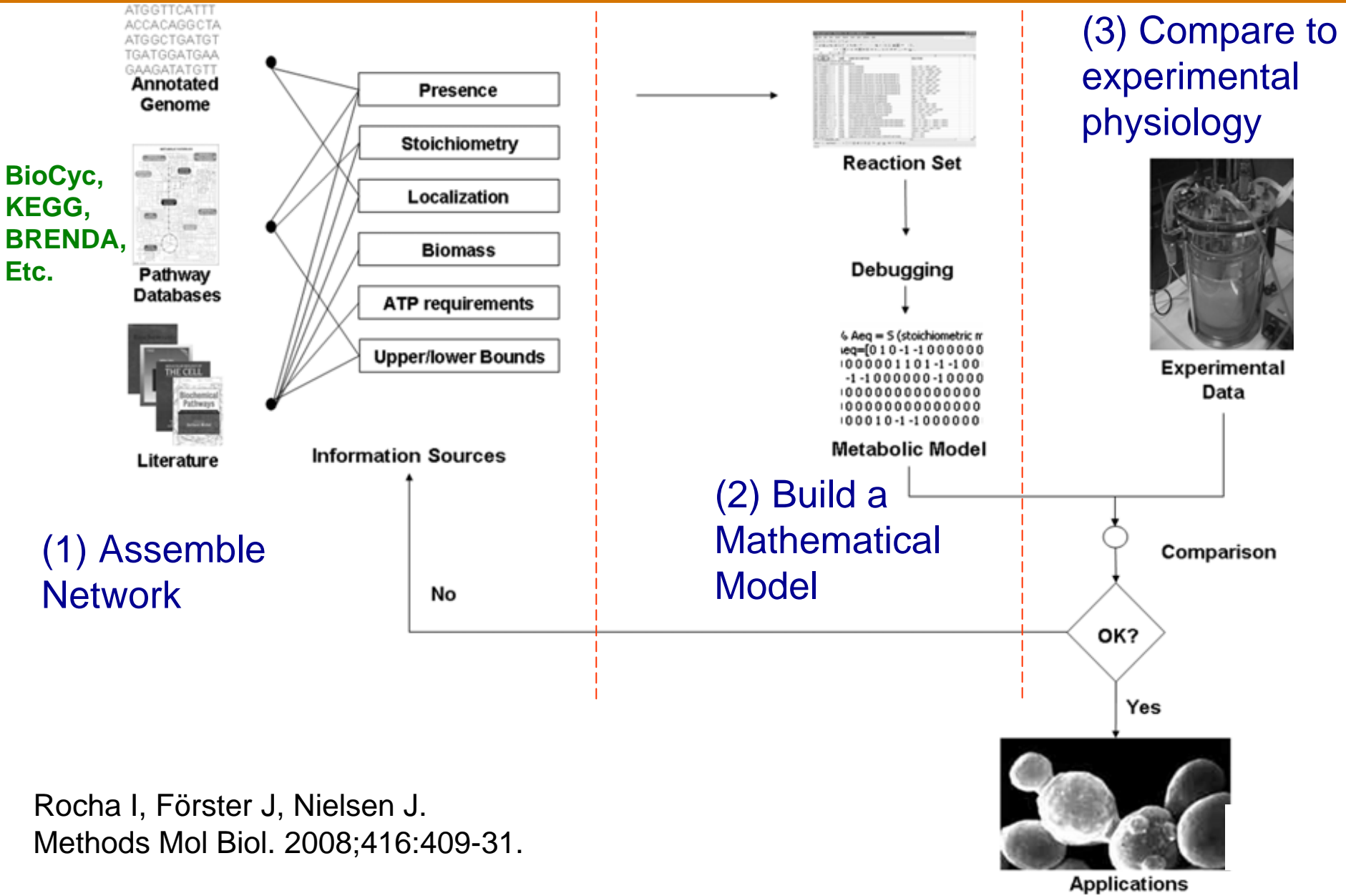
Nielsen group,  
Chlamers/DTU

- 729 enzymes
- 1314 genes
- 1073 metabolites
- 1846 reactions
- Mitochondrial & Peroxisome Compartments

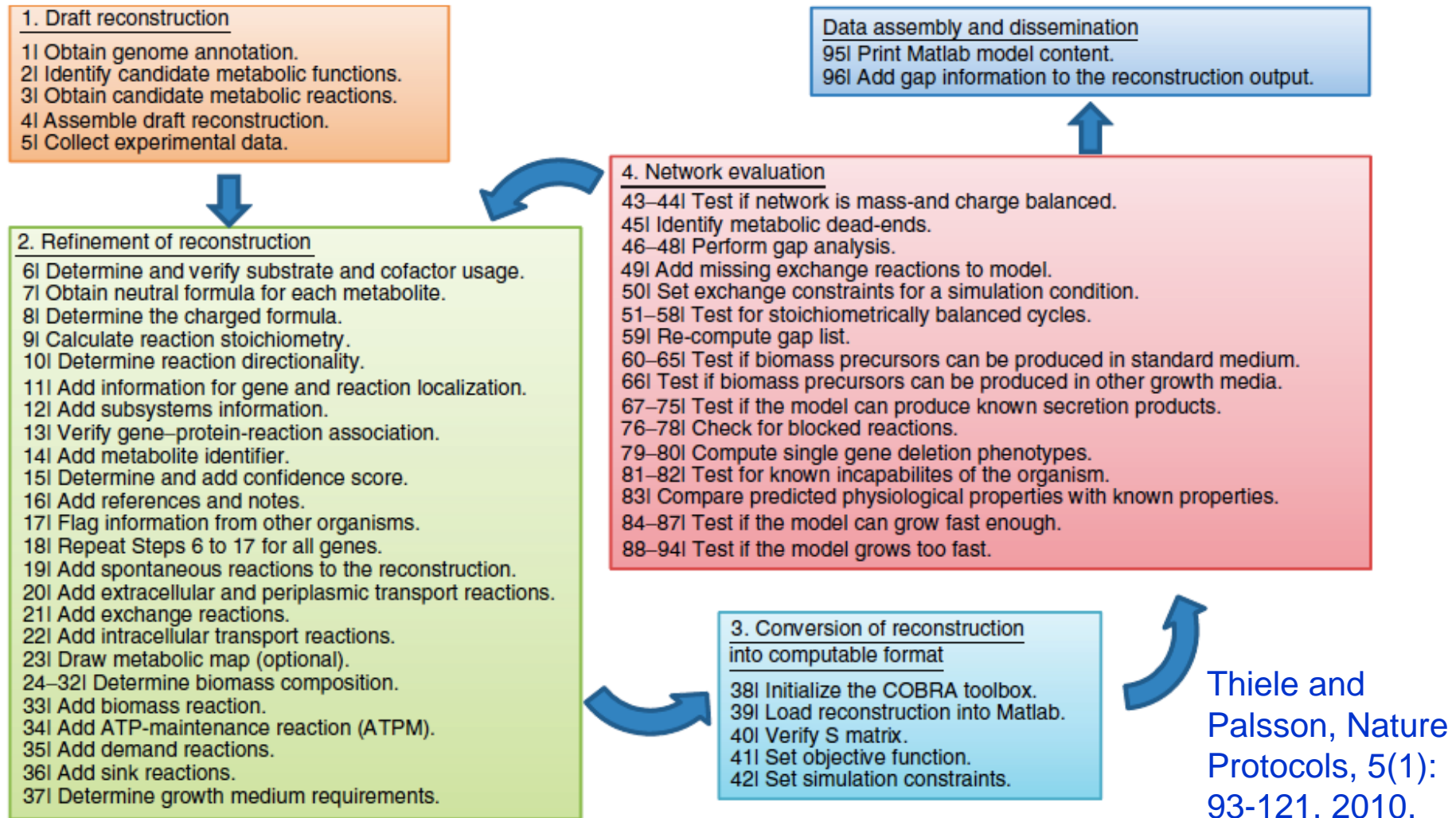
• Vongsangnak, *et al.*  
BMC Genomics 2008



# Stoichiometric network reconstruction and analysis



# Stoichiometric network reconstruction and analysis



**Figure 1** | Overview of the procedure to iteratively reconstruct metabolic networks. In particular, Stages 2–4 are continuously iterated until model predictions are similar to the phenotypic characteristics of the target organism and/or all experimental data for comparison are exhausted.

# Estimated time requirements for constraint-based reconstruction and analysis (COBRA) from Thiele and Palsson

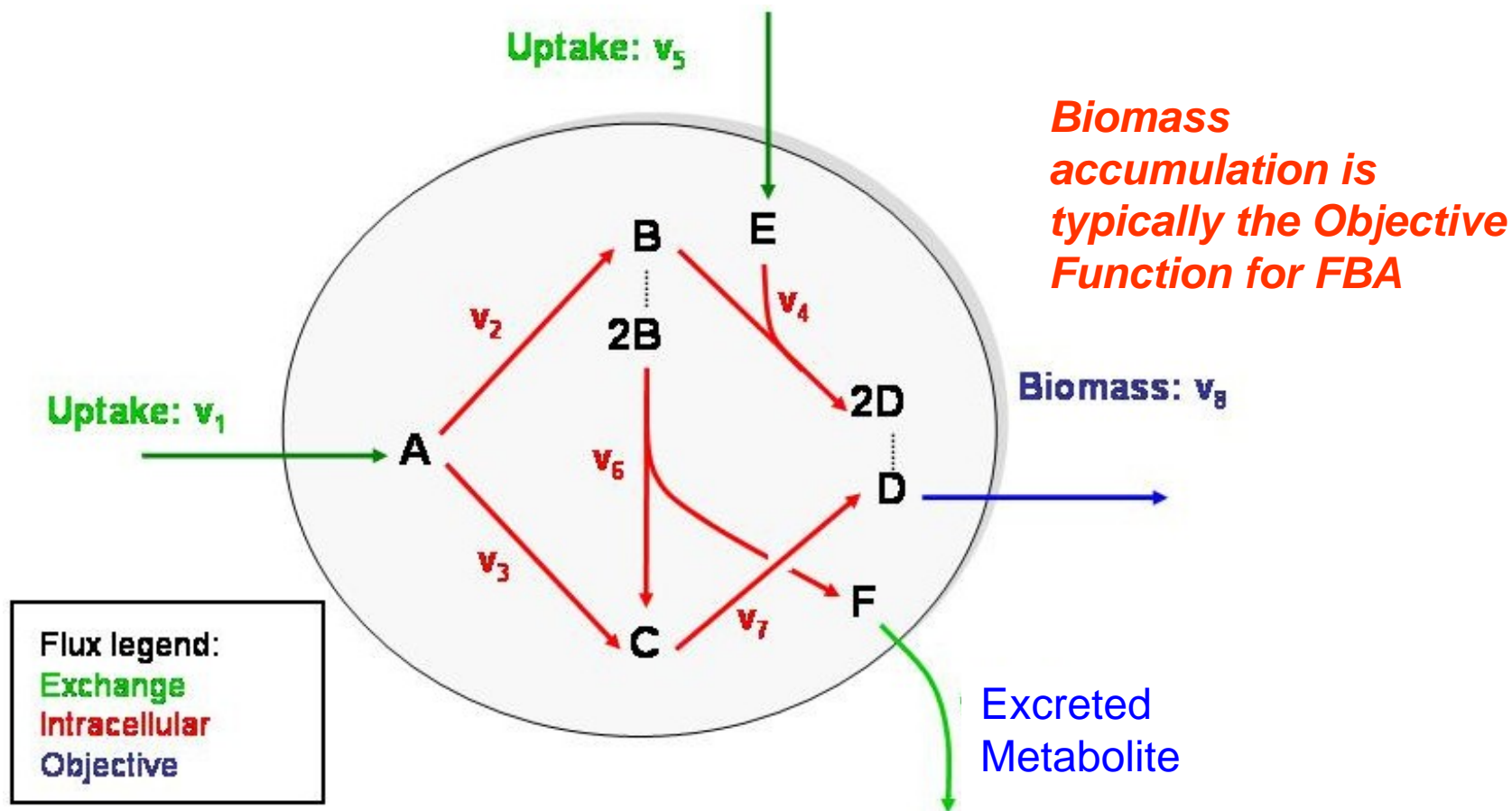
Draft reconstruction	days to weeks
Collect experimental data	ongoing throughout process
Manual reconstruction refinement	months to a year
Determine biomass composition	days to weeks
Mathematical model generation	days to a week
Network evaluation (debugging mode)	week to months
Data assembly and dissemination	days to weeks

Nature Protocols, 5(1): 93-121, 2010.



# Concept of Flux Balance Analysis (FBA)

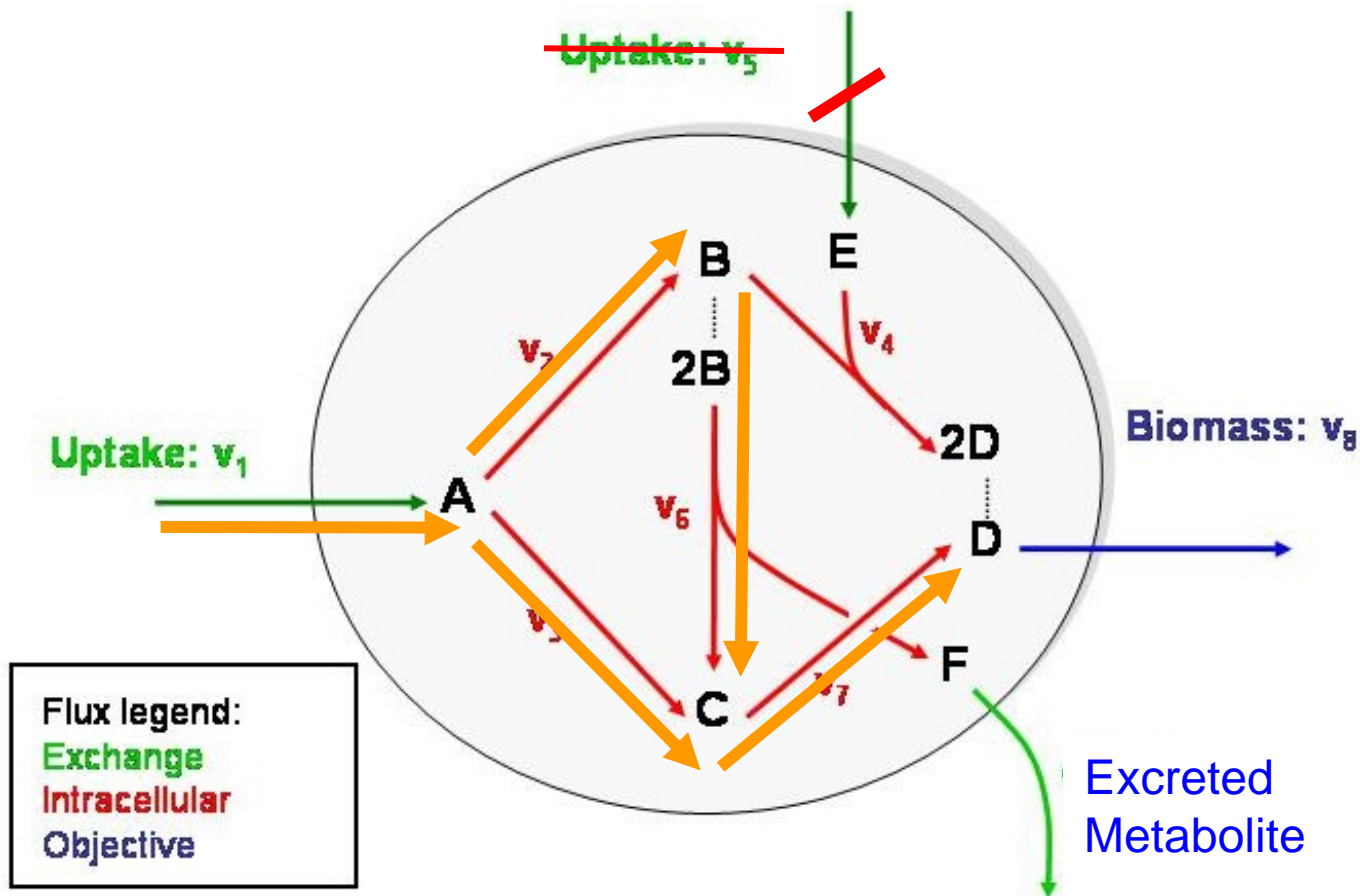
*A steady-state model where all inputs and outputs sum to zero.*



<http://bio.freelogy.org/w/images/1/14/Metabolic-network.JPG>

<http://bio.freelogy.org/wiki/User:JeremyZucker>

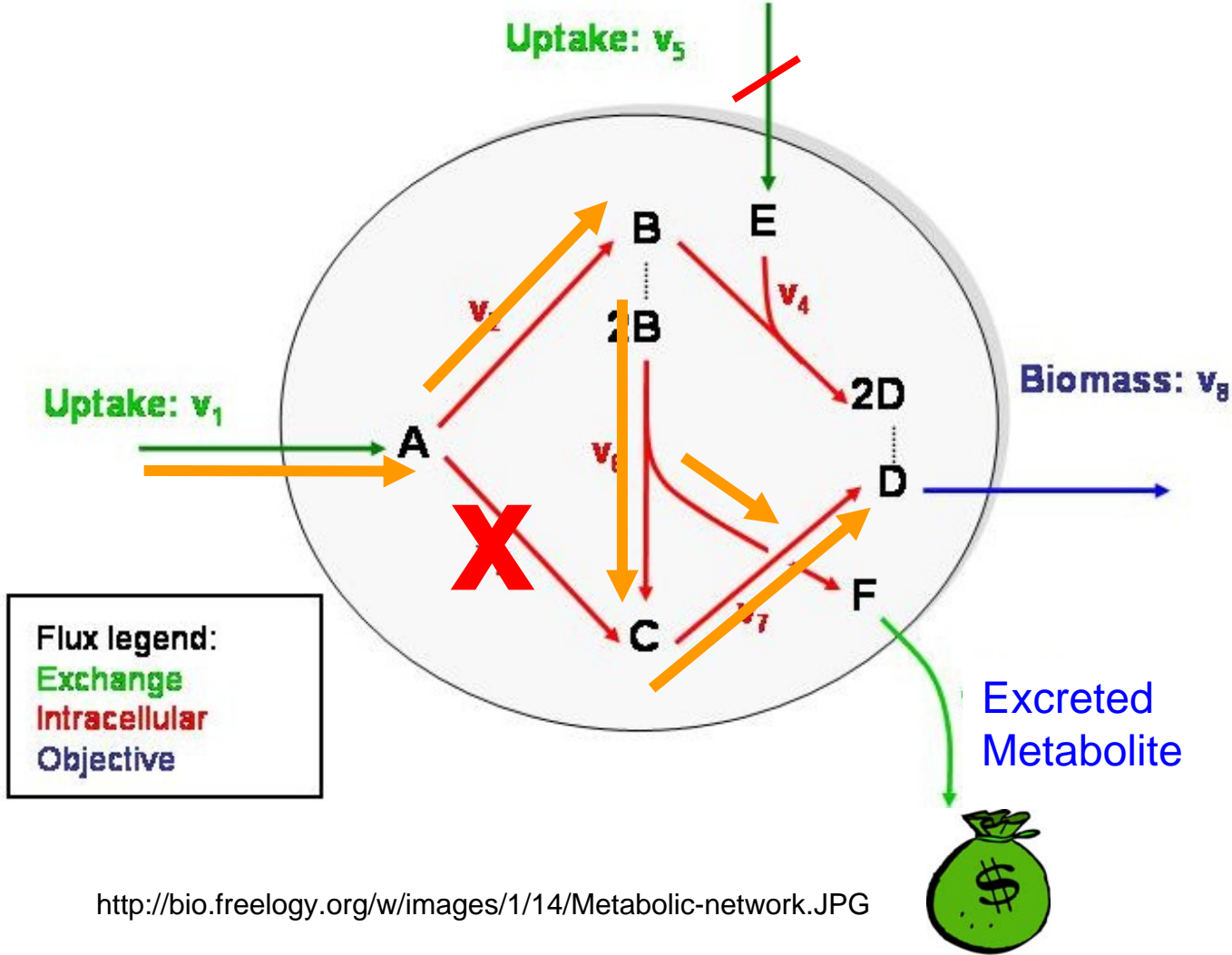
# Constraining an uptake flux



<http://bio.freelogy.org/w/images/1/14/Metabolic-network.JPG>



# Gene deletion to optimize excretion of a specific metabolite



<http://bio.freelogy.org/w/images/1/14/Metabolic-network.JPG>



# Software packages for FBA and related methods

- COBRA Toolbox (MATLAB)
- CellNetAnalyzer (MATLAB)
- OptFlux (v2.2 Windows; v1.37 Windows, Linux)
- MetaFluxNet (Windows)
- Systems Biology Research Tool (Multi-platform Java)

# Using the COBRA Toolbox in MATLAB

The screenshot displays the MATLAB 7.6.0 (R2008a) environment. The workspace window shows a list of files in the current directory, including XML and XLS files related to COBRA models. The Command History window shows a series of MATLAB commands used to optimize a COBRA model, such as `optimizeCbModel`, `printFluxVector`, `diary`, `readCbModel`, `changeRxnBounds`, `changeObjective`, and `optimizeCbModel`. The Editor window shows the source code for the `writeCbModel` function, which is used to write COBRA models in various formats. The Command Window shows the output of the optimization, including the objective value (0.0016) and the fluxes for various reactions.

```
workspace
All Files
Herrgard_yeast_consensus_model.xml XML File 3928 KB 12/17/09 10:00...
iWV1314_NADP2NADP2.xml XML File 3530 KB 4/15/10 1:38 PM
iWV1314simple.xls XLS File 277 KB 10/19/10 2:01 ...
iWV1314simple.xml XML File 2234 KB 3/3/09 2:54 PM
iWV1314simple_format_M...xml XML File 3532 KB 2/11/10 1:45 PM
iWV1314simple_format_M_CX.xml XML File 3539 KB 3/20/10 1:54 PM

Command History
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
diary off
diary('20100507_GlucFerm_02_gradient_none_removed_out.xls')
model = readCbModel()
%Allow for unlimited uptake of NH3, O2, H3PO4, H2SO3 and 1.134 for glucose uptake
model = changeRxnBounds(model,{'2164' '2166' '2167' '2168' '2169' '1865'},[1000 1000]);
%Allow for excretion of CO2 and a lower bound on ATP maintenance
model = changeRxnBounds(model,{'2163' '1865'},[-1000 1.9],'');
%Set the objective to maximize growth
model = changeObjective(model,{'2324'},1);
%Optimize fluxes for aerobic growth on glucose
solving = optimizeCbModel(model)
%Begin O2 gradient series
model = changeRxnBounds(model,'2166',8,'u');
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
model = changeRxnBounds(model,'2166',4,'u');
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
model = changeRxnBounds(model,'2166',2,'u');
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
model = changeRxnBounds(model,'2166',1,'u');
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
model = changeRxnBounds(model,'2166',0.5,'u');
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
model = changeRxnBounds(model,'2166',0.25,'u');
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
model = changeRxnBounds(model,'2166',0.125,'u');
solving = optimizeCbModel(model)
printFluxVector(model, solving.x,true,true,-1,'',true)
model = changeRxnBounds(model,'2166',0.0625,'u');

Editor - writeCbModel.m
function writeCbModel(model,format,fileName)
%writeCbModel Write out COBRA models in various formats
% writeCbModel(model,format,fileName)
%
% model Standard COBRA model structure
% format File format to be used ('text','xls' or 'sbml')
% fileName File name for output file (optional, default opens dialog box)
% Markus Herrgard 2/15/07

Command Window
New to MATLAB? Watch this Video, see Demos, or read Getting Started.
2107 -> 821[e] 0.0009159
2168 -> 788[e] 0.00715815
2178 -> 847[e] 1.134
2322 787[e] -> 1000
2324 112[c] -> 0.0817887
2325 382[c] -> 2.0886
>> %limit O2 uptake and optimize fluxes
>> model = changeRxnBounds(model,'2166',0.03125,'u');
>> solving = optimizeCbModel(model)

solving =

    f: 0.0016
    x: [2323x1 double]
    stat: 1
    solver: 'tomlab_cplex'
    time: 0.0161

>> printFluxVector(model, solving.x,true,true,-1,'',true)
2053 787[e] <=> -1000
2163 759[e] <=> -1.8733
2164 -> 815[e] 0.00970734
2166 -> 816[e] 0.03125
2167 -> 821[e] 0.00110866
2168 -> 788[e] 0.000139459
2178 -> 847[e] 1.134
2289 310[c] -> 1.83437
2307 34[c] -> 0.0280319
2322 787[e] -> 1000
2324 112[c] -> 0.00159345
2325 382[c] -> 1.90375
>> model = changeRxnBounds(model,'2053',0,'');
>> solving = optimizeCbModel(model)

solving =
```

Becker SA, *et al.* Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox. *Nature Protocols* 2007;2(3):727-38

# FBA model structure in COBRA Toolbox/MATLAB

Composed of vectors and matrices for:

- reaction stoichiometry
- genes
- proteins (enzymes)
- Gene-protein-reaction (GPR) associations
- objective function selection
- reaction flux constraints

	GLC11	HEX1	PGI	PFK	FBP	FBA	TPI	EX_glc
glc-D[e]	-1	0	0	0	0	0	0	-1
glc-D	1	-1	0	0	0	0	0	0
atp	0	-1	0	-1	0	0	0	0
H	0	1	0	1	0	0	0	0
adp	0	1	0	1	0	0	0	0
g6p	0	1	-1	0	0	0	0	0
f6p	0	0	1	-1	1	0	0	0
fdp	0	0	0	1	-1	-1	0	0
pi	0	0	0	0	1	0	0	0
h2o	0	0	0	0	-1	0	0	0
g3p	0	0	0	0	0	1	1	0
dhap	0	0	0	0	0	1	-1	0

First steps of glycolysis pathway

Becker SA, Feist AM, Mo ML, Hannum G, Palsson BØ, Herrgard Mjbased. Nature Protocols 2007;2(3):727-38.

# Simulating metabolism under an $O_2$ uptake gradient to predict optimal ethanol production level in *A. oyrzae*

## Exchange Flux Constraints (mmol gDW<sup>-1</sup> hr<sup>-1</sup>)

- $NH_3$ ,  $H_3PO_4$ ,  $H_2SO_3$       Uptake unlimited
- Glucose      Uptake of 1.134
- $O_2$       Uptake stepwise gradient  
from 0.0001 to 10
- ATP      Maintain intracellular 1.9

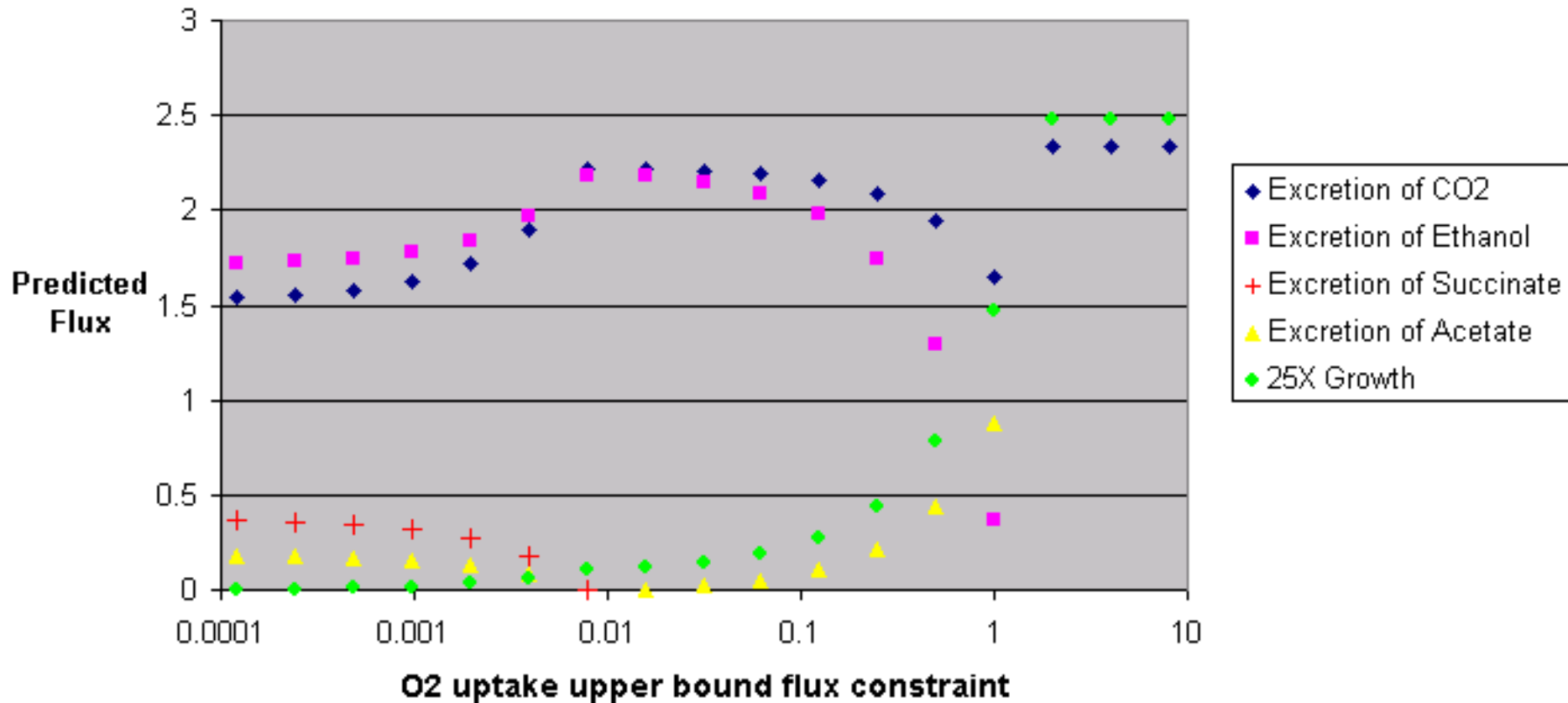
## Objective Function

Set as “Growth” to maximize combined fluxes for generating cell biomass constituents (DNA, RNA, amino acids, lipids, carbohydrates, etc.)

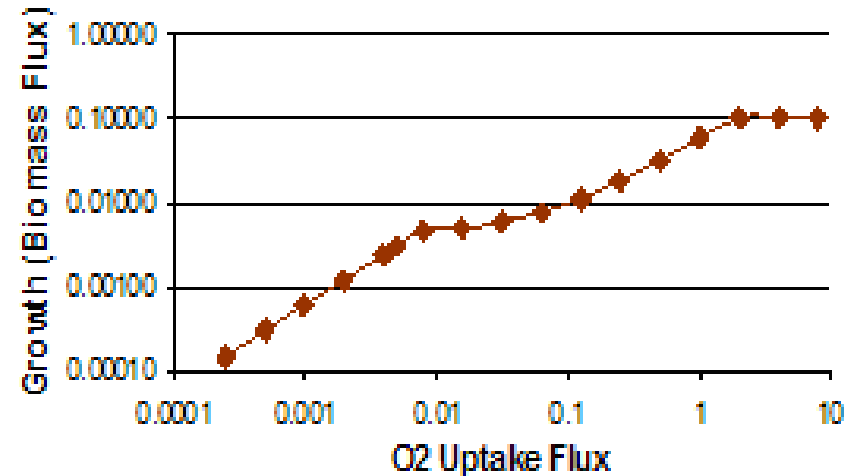
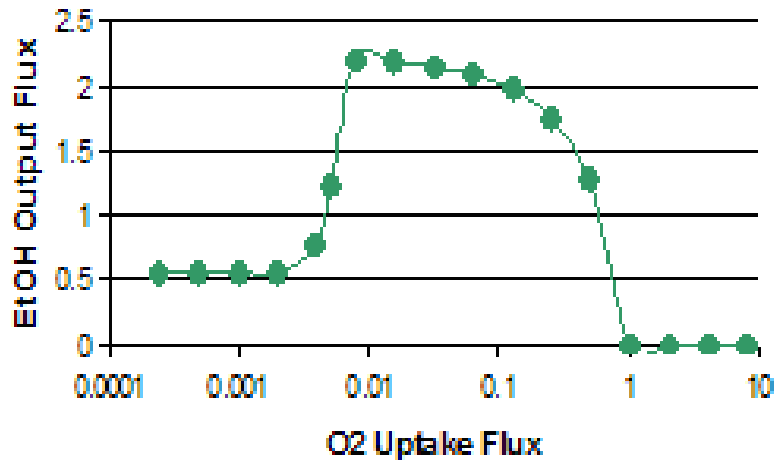


# FBA simulation of *A. oryzae* fermentation on glucose

FBA non-zero exchange flux and growth predictions made with COBRA Toolbox for *A. oryzae* iWV1314 model - Glucose with O<sub>2</sub> gradient (mmol g DW<sup>-1</sup> h<sup>-1</sup>)

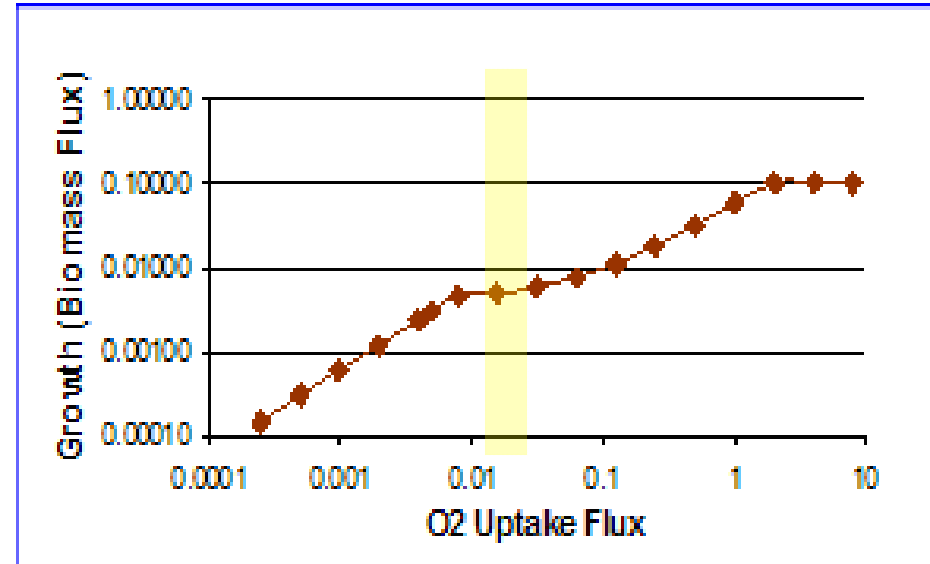
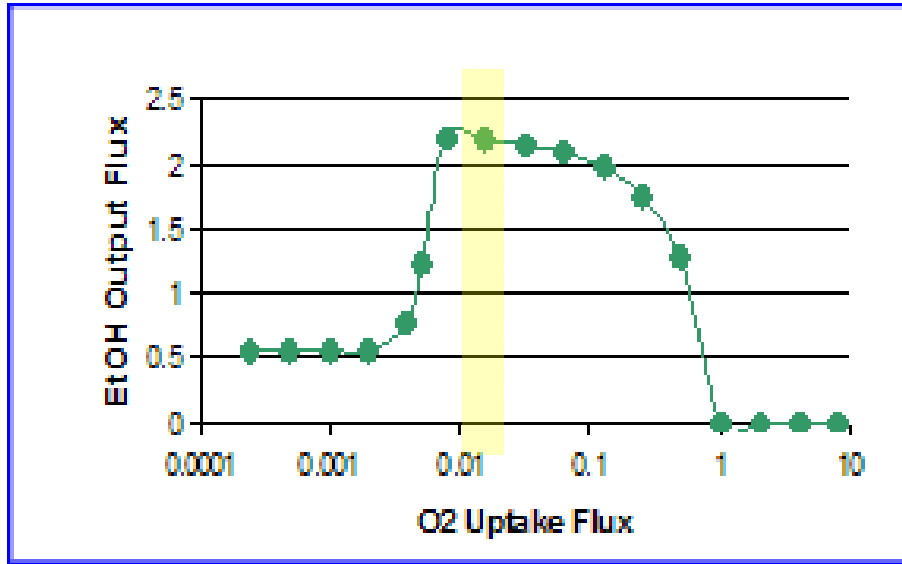


# Predicted ethanol excretion maximum correlates with a plateau in growth in FBA simulation



X and Y flux values = in  $\text{mmol g(DW)}^{-1} \text{ hr}^{-1}$

A genome-wide gene deletion series was conducted under simulated microaerobic conditions ( $0.02 \text{ mmol g}_{\text{DW}}^{-1} \text{ hr}^{-1}$ )

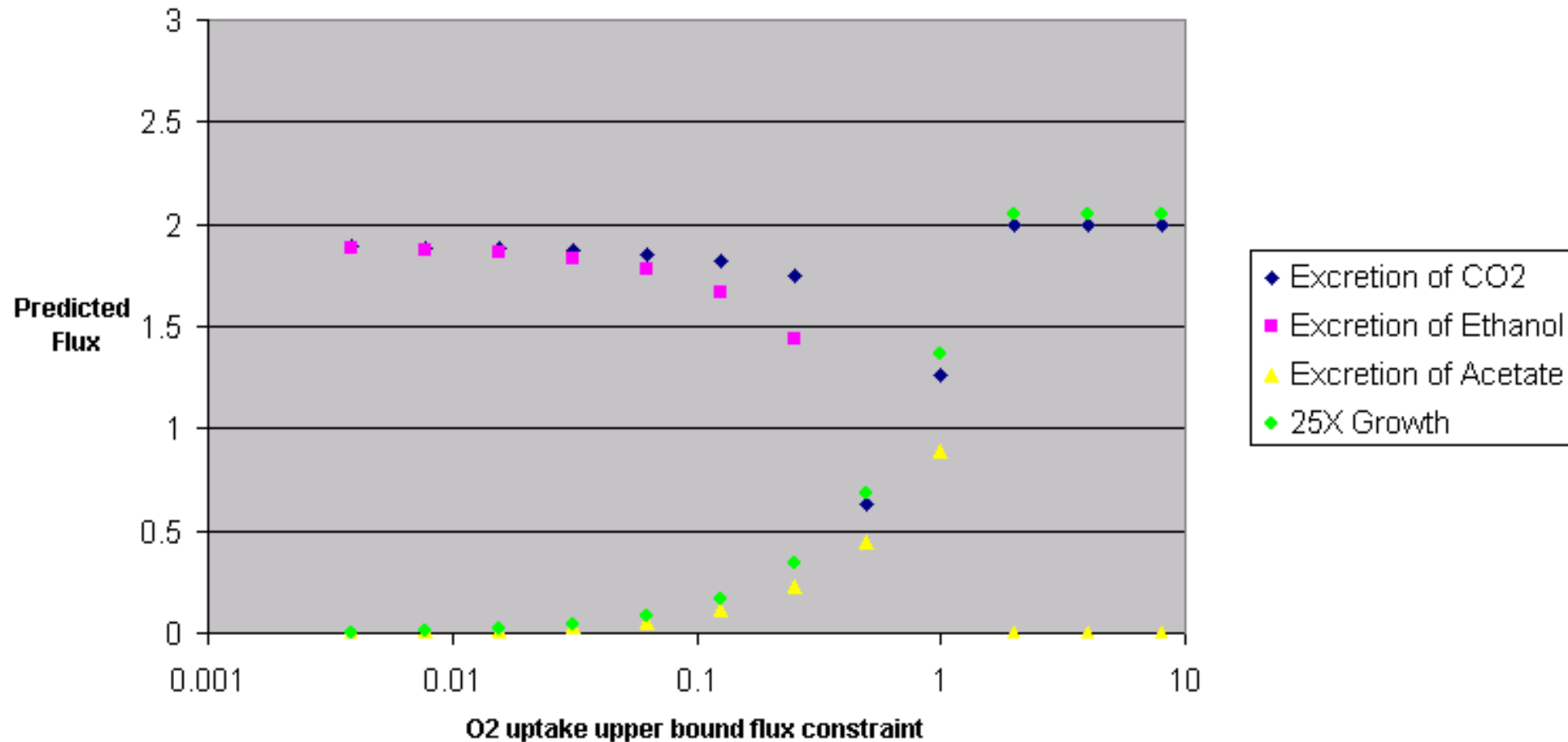


X and Y flux values = in  $\text{mmol g}(\text{DW})^{-1} \text{ hr}^{-1}$

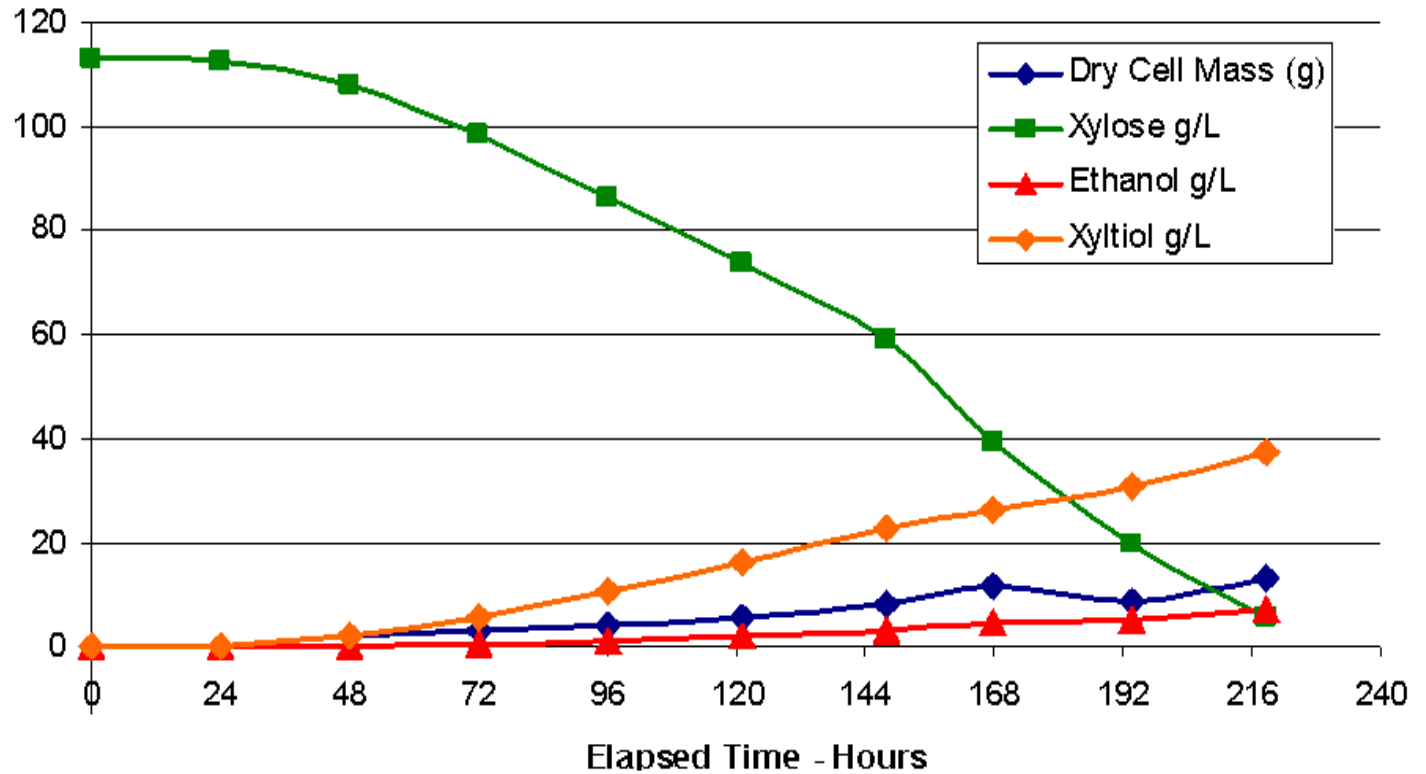
Unconfirmed result: 11 gene deletions were predicted to boost ethanol excretion by 1-5%.

# FBA simulation of *A. oryzae* fermentation on xylose

FBA non-zero exchange flux and growth predictions made with COBRA Toolbox for *A. oryzae* iWV1314 model - Xylose with O<sub>2</sub> gradient (mmol g DW<sup>-1</sup> h<sup>-1</sup>)



# A. oryzae fermentation results on xylose





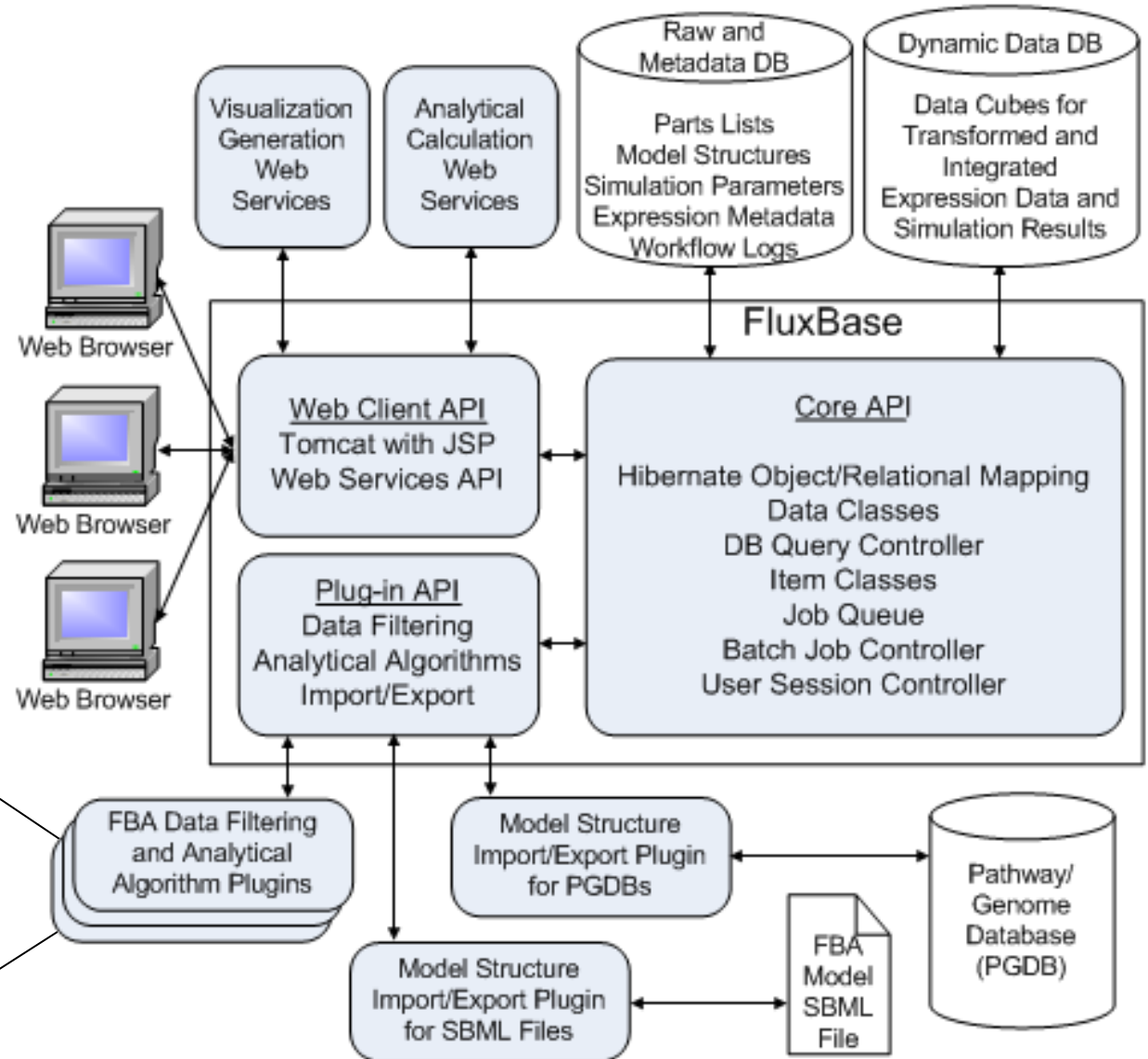
# General “end-user” impressions of currently available FBA models and software

- “Formatted in SBML” != compatible across software packages.
- Model validation by growth rate may not guarantee accurate flux predictions for metabolites of interest.
- More basic research is needed on how to determine the true objective function of organisms under stress, far from idealized growth conditions.
- Metabolic reconstructions should ideally be community projects rather than competing products published by individual labs.
- FBA software should be more like an IDE (i.e., Eclipse) to support the “write-run-debug-run” cycle of model development and refinement.
- More automated tools for diagnosing errors in malfunctioning models are needed.

# Suggested architecture for a collaborative metabolic network reconstruction & analysis and PGDB data management system

Plug-in component architecture modeled after the open source, Java/Tomcat BioArray Software Environment (BASE) package

<http://base.thep.lu.se/>



- COBRA Toolbox
- CellNetAnalyzer
- OptFlux
- MetaFluxNet
- Systems Biology Research Tool

# Data management features in BASE that would be useful in a collaborative FBA/PGDB computing environment

BASE 2.7.0 @ funken -- Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://funken.pnl.gov:8080/base2/

File View Array LIMS Administrate Extensions Help

## Array designs

New... Delete Restore Share... Take ownership... Columns... Import... Export...

1 (3 hits, 30 per page)

	Name	Platform	File features	Owner	Shared to
1	AsprgDTUa520520F.cdf	Affymetrix	43776	Scott Baker	MG Team
2	DTU Aspergillus Tri-species Chip	Affymetrix	43776	Scott Baker	MG Team
3	PNNLTOL1c520468F	Affymetrix	60436	Jim Collett	Biomarkers Initiative

1 (3 hits, 30 per page)

The development of BASE is currently supported by Lund University through SCIBLU. Previous patrons of the BASE project were the Knut and Alice Wallenberg Foundation and the Swedish Cancer Society. This server administered by: [Jim Collett](#)

Find: [ ] Next Previous Highlight all Match case

User- and group-level permissions and item ownership facilitate provenance control in projects with very large datasets and complex analytical workflows.

# Analytical workflow features in BASE that would be useful in a collaborative FBA/PGDB computing environment

BASE 2.7.0 @ fungen -- Mozilla Firefox

File Edit View History Bookmarks Tools Help

http://fungen.pnl.gov:8080/base2/

File View Array LIMS Administrate Extensions Help

## Experiments ▸ A. niger Manganese Effects ▸ APT Summarize

**Properties**

Edit... Delete Copy... Help...

Permissions on this item: Read, Use, Write, Delete

<b>Transformation</b>	<b>Plugin &amp; parameters</b>
<b>Name</b> APT Summarize	<b>Plugin</b> APT Summarize plug-in
<b>Experiment</b> A. niger Manganese Effects	<b>Plugin configuration</b> - none -
<b>Description</b>	<b>Bioassay set name</b> New bioassayset
<b>Job</b>	<b>Experiment analysis</b> rma
<b>Job</b> Run plugin: APT Summarize plug-in	<b>Raw bioassays</b> DTU_Aniger_H2O-1, DTU_Aniger_H2O-2, DTU_Aniger_H2O-3, DTU_Aniger_minusMn-1, DTU_Aniger_minusMn-2, DTU_Aniger_minusMn-3, DTU_Aniger_plusMn-1, DTU_Aniger_plusMn-2, DTU_Aniger_plusMn-3
<b>Started</b> 2009-10-02 17:39:34	
<b>Ended</b> 2009-10-02 17:42:27	
<b>Server</b> fungen	

**Items related to this transformation**  
None.

**Sub analysis tree**

Delete Restore Columns... Export...

- view / presets -	Name	Spots/Values	Reporters	Plugin	Date	Tools
<input type="checkbox"/>	APT Summarize			APT Summarize plug-in	2009-10-02 17:42:27	
<input type="checkbox"/>	All Probes	393984	43776			
<input type="checkbox"/>	Filter: score(3) == 3000			JEP filter plugin	2009-10-26 17:28:59	
<input type="checkbox"/>	AFFX probes only	558	62			
<input type="checkbox"/>	Filter: score(6) == 6000			JEP filter plugin	2009-10-05 16:23:38	
<input type="checkbox"/>	A. niger probes (JGI prefix)	100098	11122			

## Tracking the roots of cellulase hyperproduction by the fungus *Trichoderma reesei* using massively parallel DNA sequencing

Stéphane Le Crom<sup>a,b,c,1</sup>, Wendy Schackwitz<sup>d,1</sup>, Len Pennacchio<sup>d</sup>, Jon K. Magnuson<sup>e</sup>, David E. Culley<sup>e</sup>, James R. Collett<sup>e</sup>, Joel Martin<sup>d</sup>, Irina S. Druzhinina<sup>f</sup>, Hugues Mathis<sup>g</sup>, Frédéric Monot<sup>g</sup>, Bernhard Seiboth<sup>f</sup>, Barbara Cherry<sup>h</sup>, Michael Rey<sup>h</sup>, Randy Berka<sup>h</sup>, Christian P. Kubicek<sup>f</sup>, Scott E. Baker<sup>d,e,2</sup>, and Antoine Margeot<sup>g,2</sup>

<sup>a</sup>Institut National de la Santé et de la Recherche Médicale, U784, 46 rue d'Ulm, 75230 Paris Cedex 05, France; <sup>b</sup>Institut Fédératif de Recherche 36, Plate-forme Transcriptome, 46 rue d'Ulm, 75230 Paris Cedex 05, France; <sup>c</sup>École Normale Supérieure, 46 rue d'Ulm, 75230 Paris Cedex 05, France; <sup>d</sup>Department of Energy Joint Genome Institute, 2800 Mitchell Avenue, Walnut Creek, CA 94598; <sup>e</sup>Pacific Northwest National Laboratory, P.O. Box 999, Richland, WA 99352; <sup>f</sup>Institute of Chemical Engineering, Technische Universität Wien, Getreidemarkt 9/166, A-1060 Vienna, Austria; <sup>g</sup>IFP, Département Biotechnologie, Avenue de Bois-Préau, 92852 Rueil-Malmaison Cedex, France; and <sup>h</sup>Novozymes, Inc., 1445 Drew Avenue, Davis, CA 95618

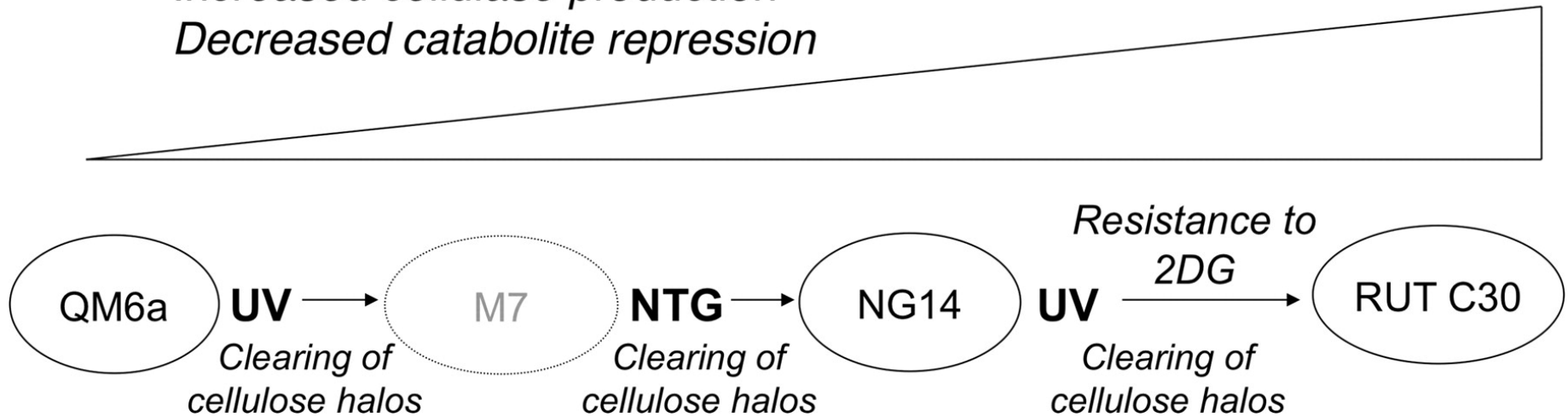
Edited by Joan Wennstrom Bennett, Rutgers University, New Brunswick, NJ, and approved July 27, 2009 (received for review May 28, 2009)

Le Crom, Schackwitz, et al. 2009. PNAS 106 (38): 16151-6

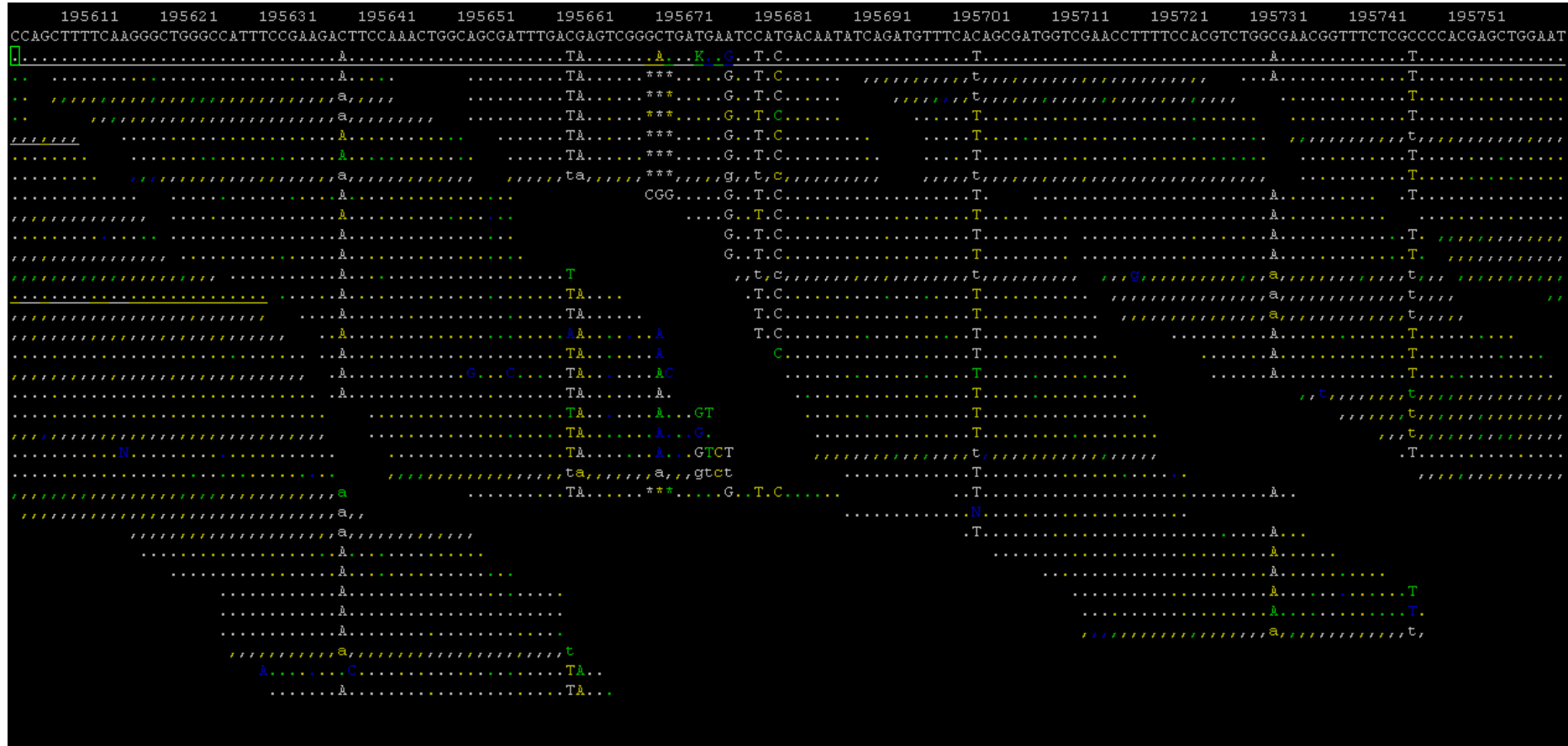


# Genealogy of mutagenized *T. reesei* strains

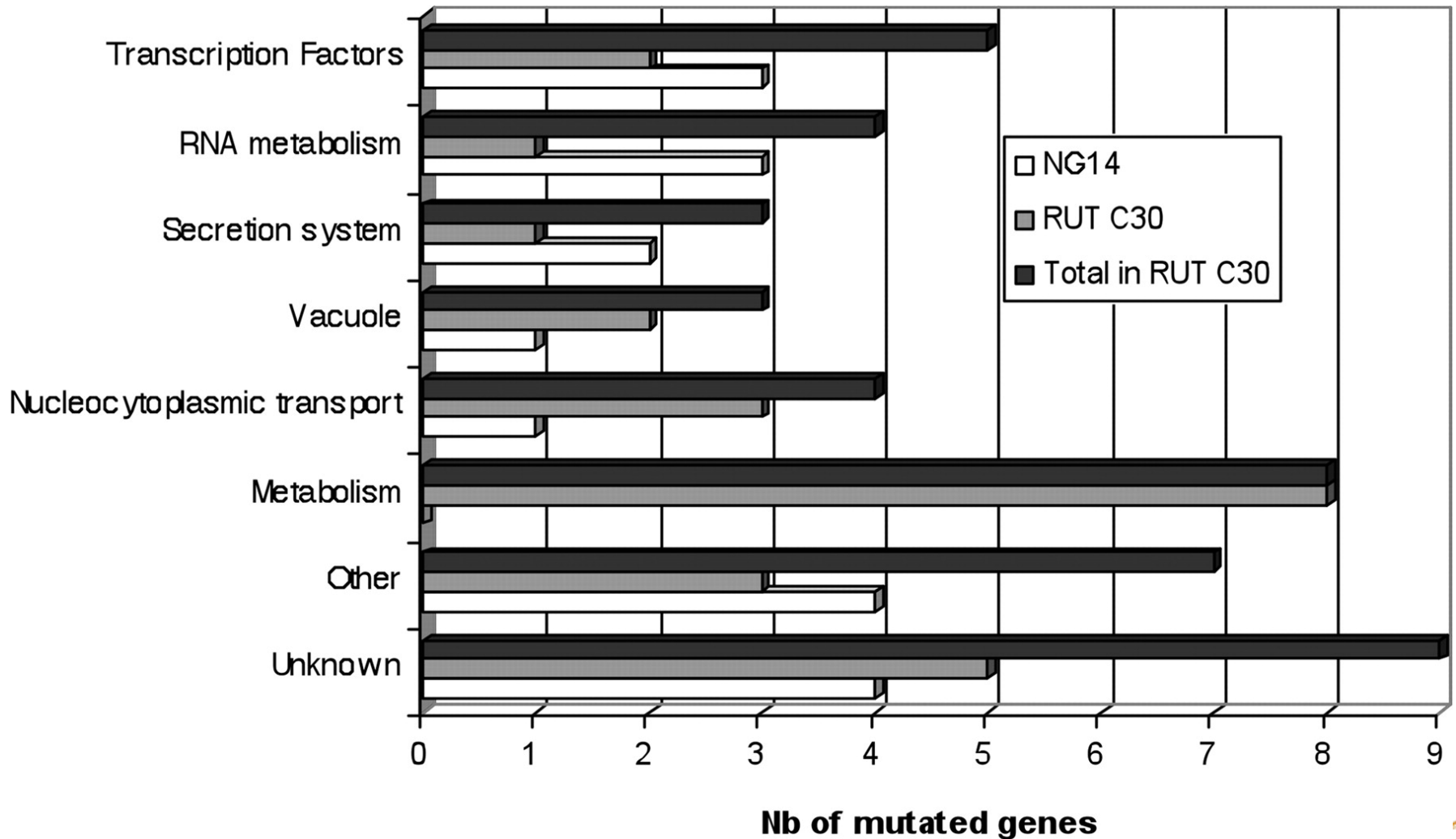
*Increased cellulase production*  
*Decreased catabolite repression*



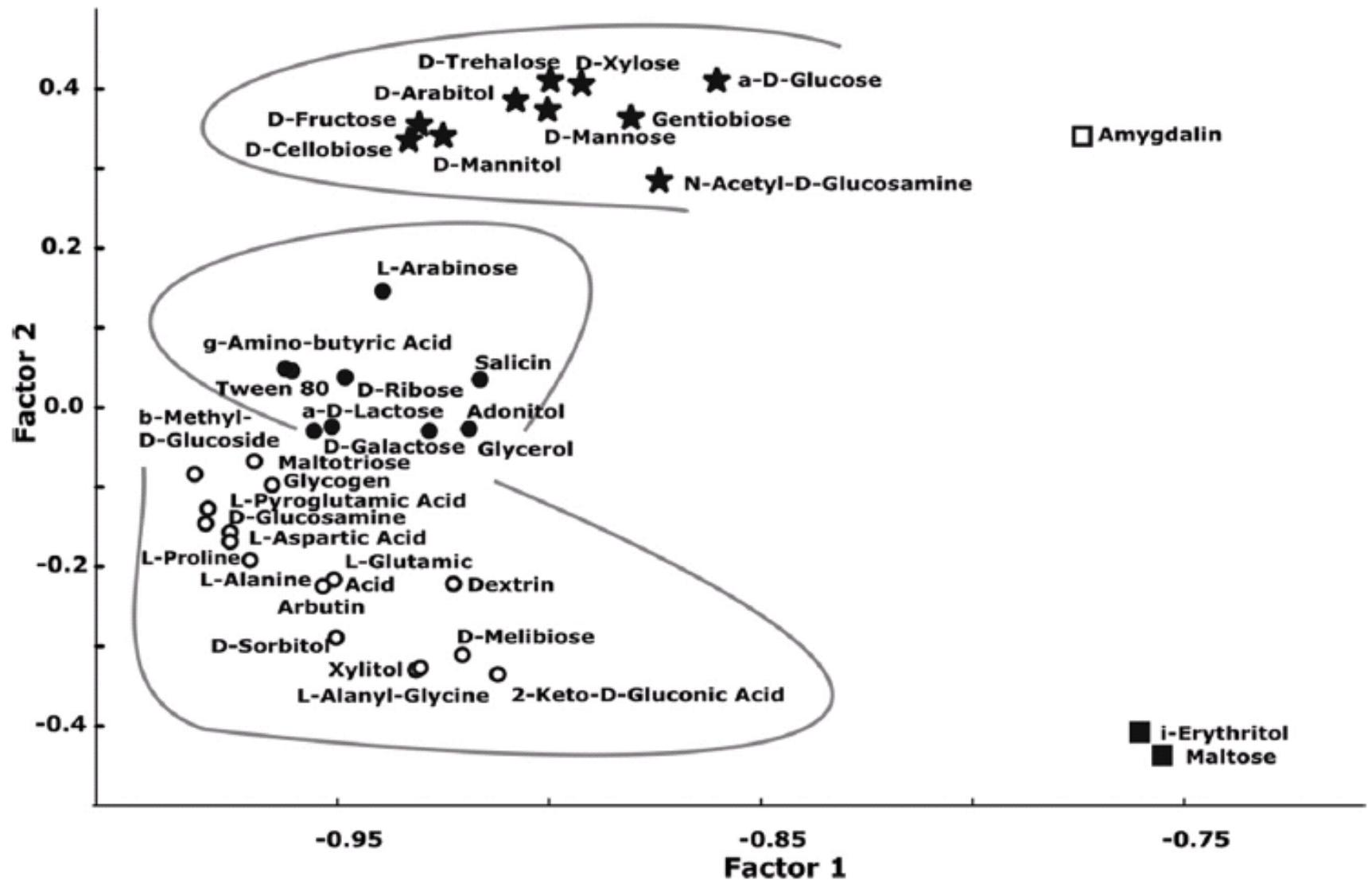
# Reads from *T. reesei* strains NG14 and RUT C30 aligned with QM6a to identify SNVs and indels



# Gene categories of mutagenic events



# Biomass growth profiling on 95 carbon substrates using the Biolog phenotyping system



# Plans for using P-Tools 14. 5+ to correlate SNVs with KO experiments, and to help generate FBA models

Pathway Tools version 14.0

File Overviews Pathway Reaction Protein RNA Gene Compound Chromosome Groups Tools Help

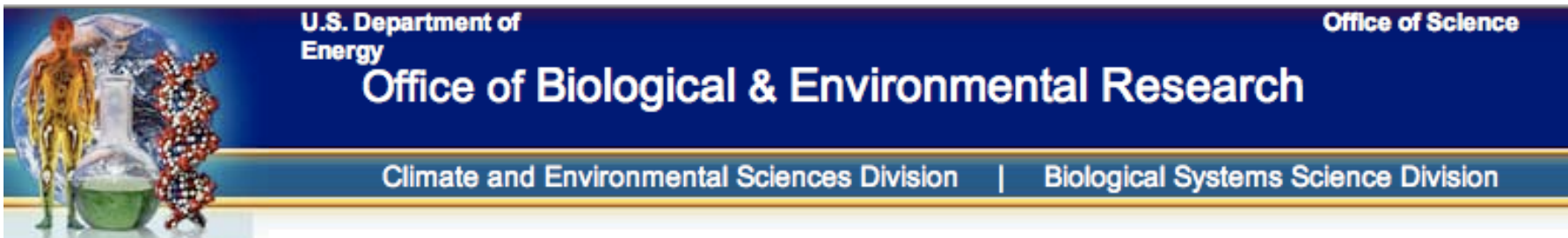
Trichoderma reesei Home Back Forward History Next Answer Clone Save DB

FBA growth and flux predictions may be correlated to the matrix of carbon assimilation phenotypes.

Overview Mode  
Command: [ ]



# Acknowledgements



## PNNL Fungal Biotech Team

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