

# Reconstruction of Metabolic Models and Applications

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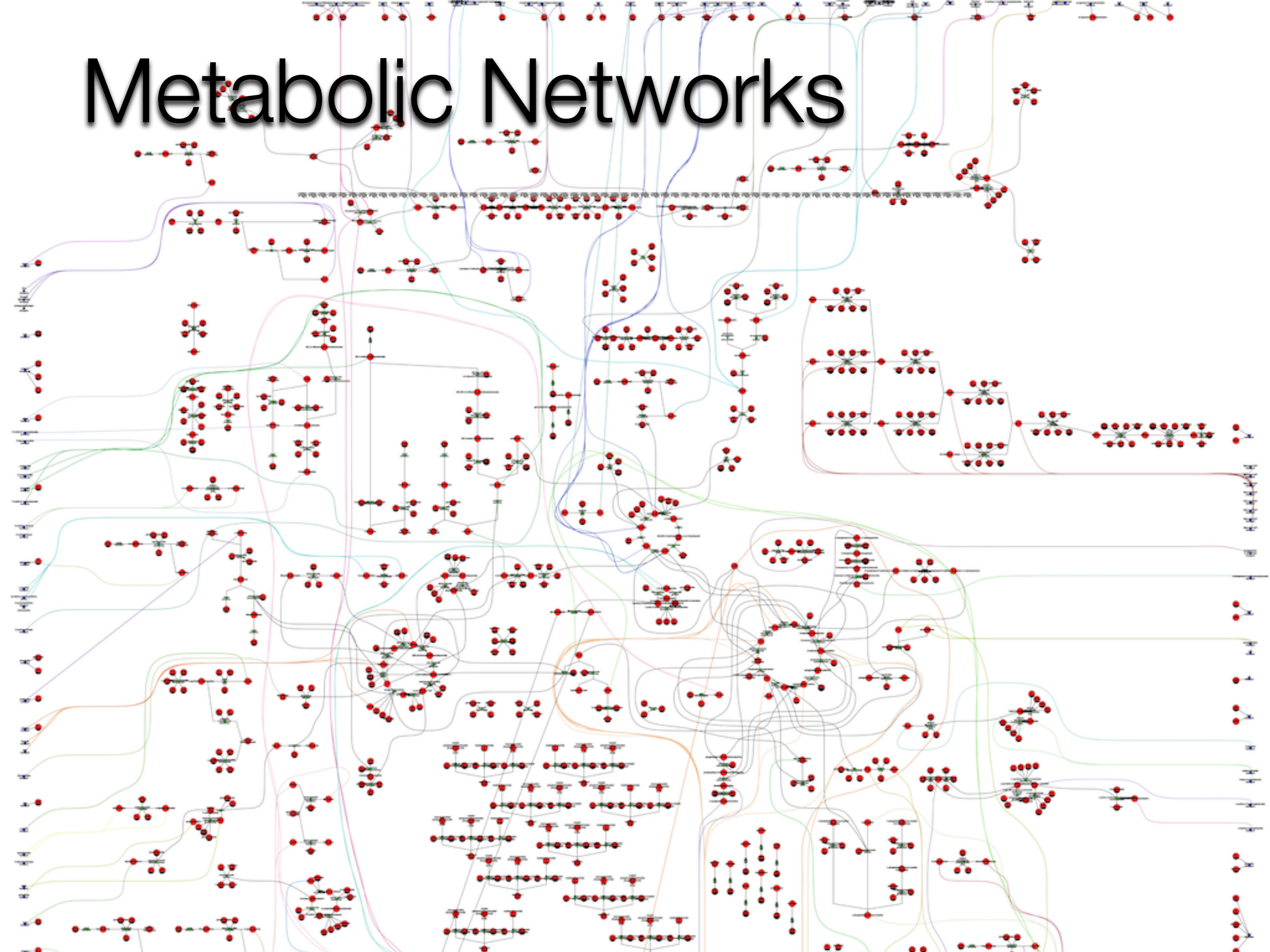
**Center for Genome  
Regulation &**

**Center of Mathematical  
Modeling (U. Chile)**

**— 2014 —**

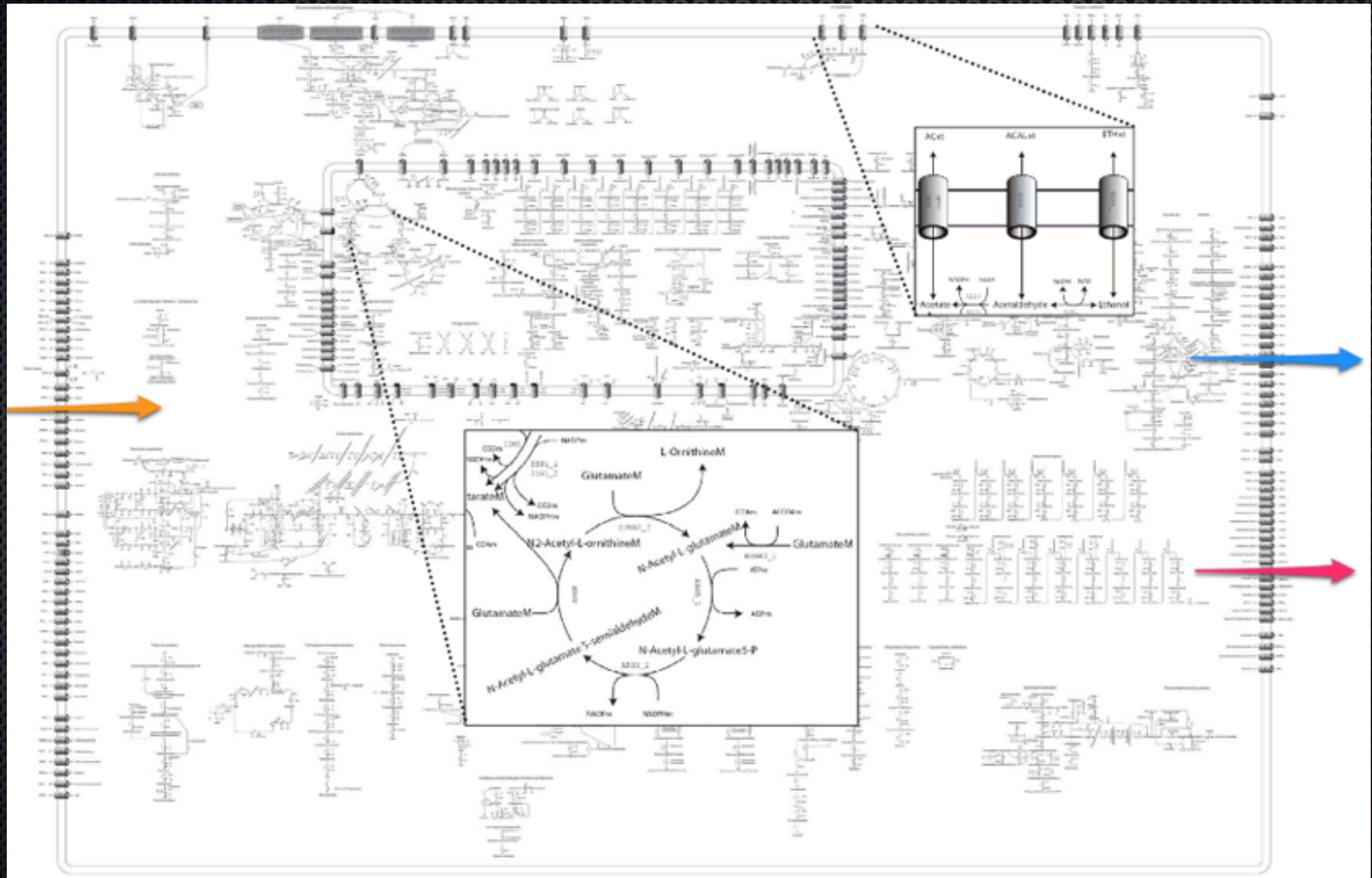


# Metabolic Networks



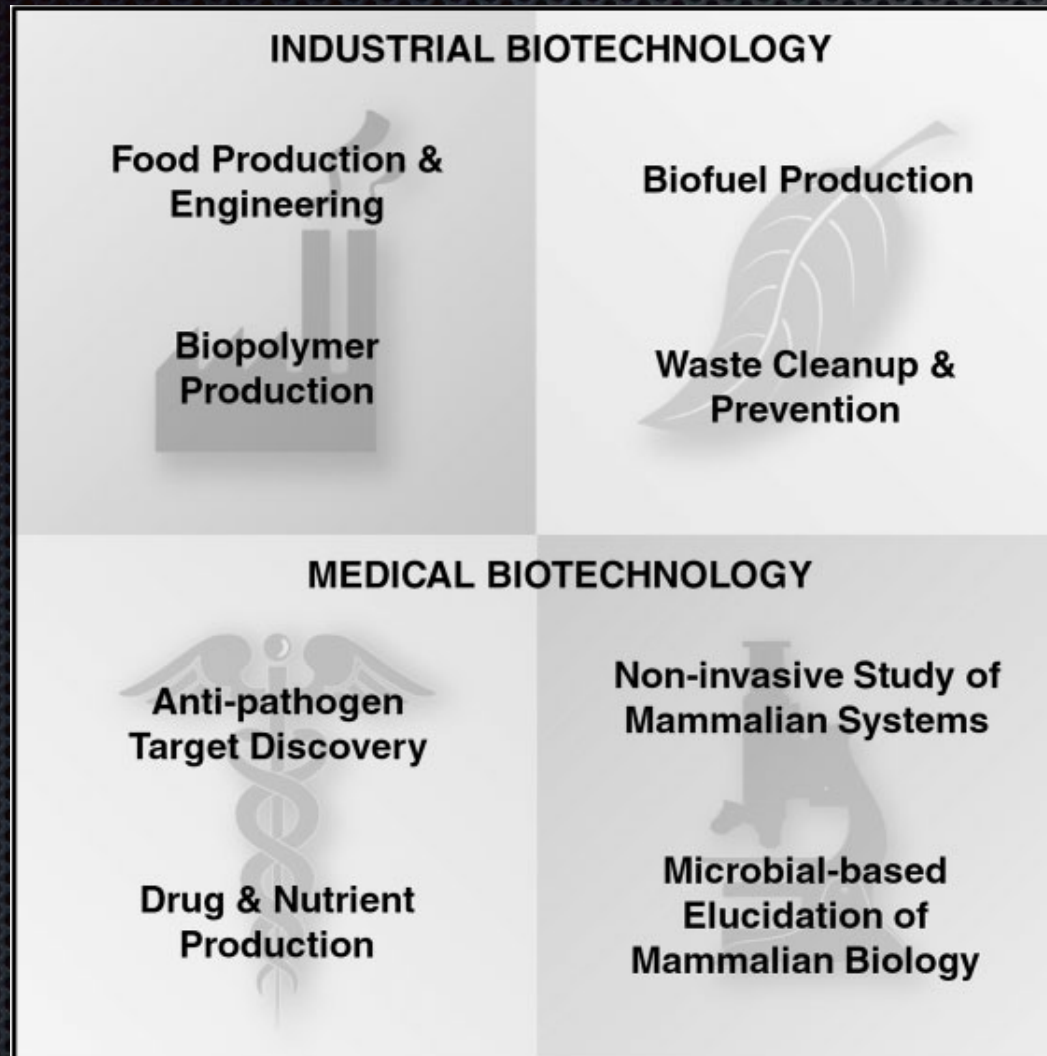


# Genome-scale Metabolic Models





# Scientific & Biotech Applications

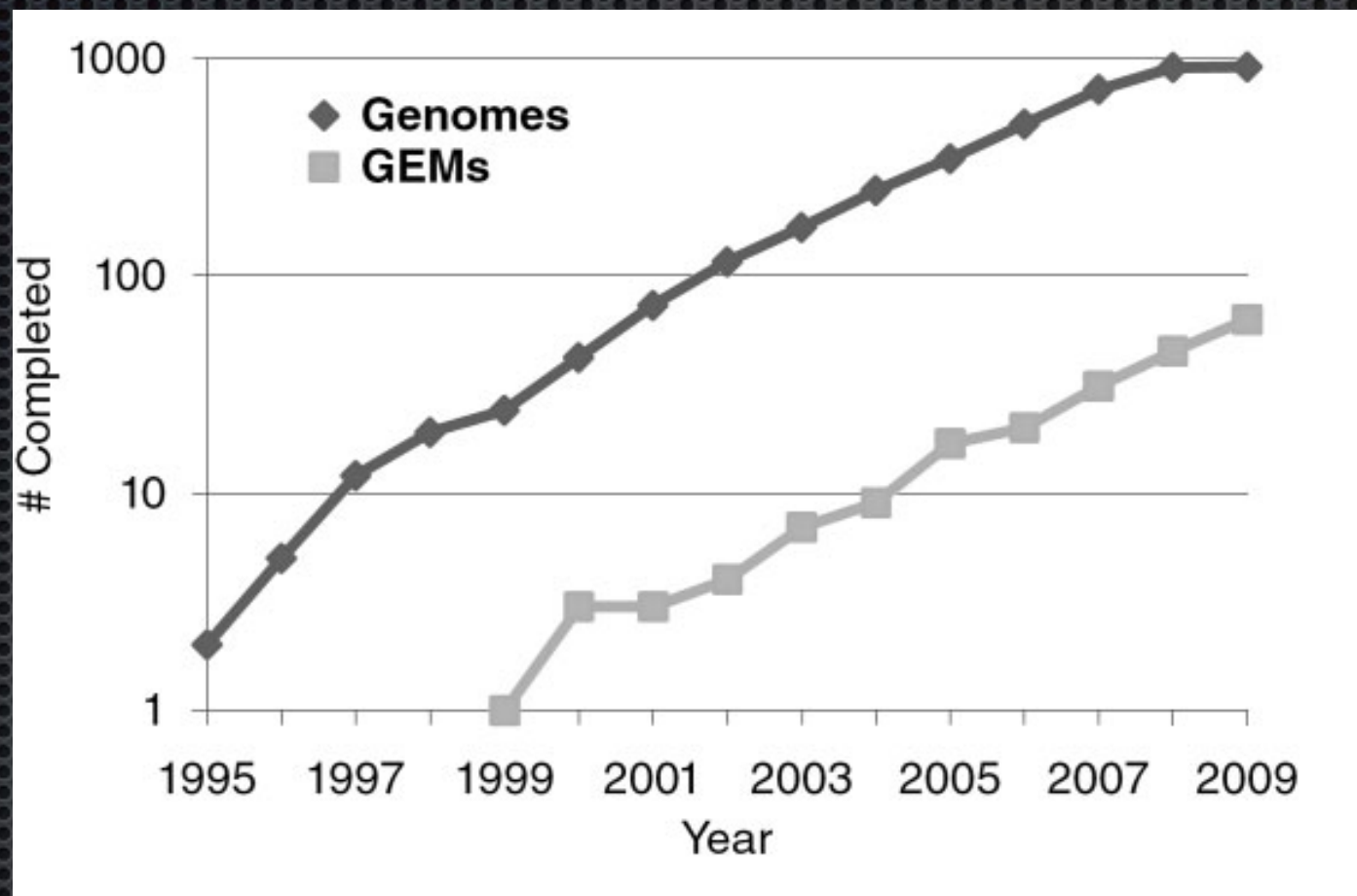


1. Contextualization of data
2. Guidance of metabolic engineering
3. Directing hypothesis-driven discovery
4. Discovery of multi-species relationships
5. Network property discovery

[Milne, 2009]



# Completed genome sequences and genome-scale models



[Milne, 2009]



# Paper 1

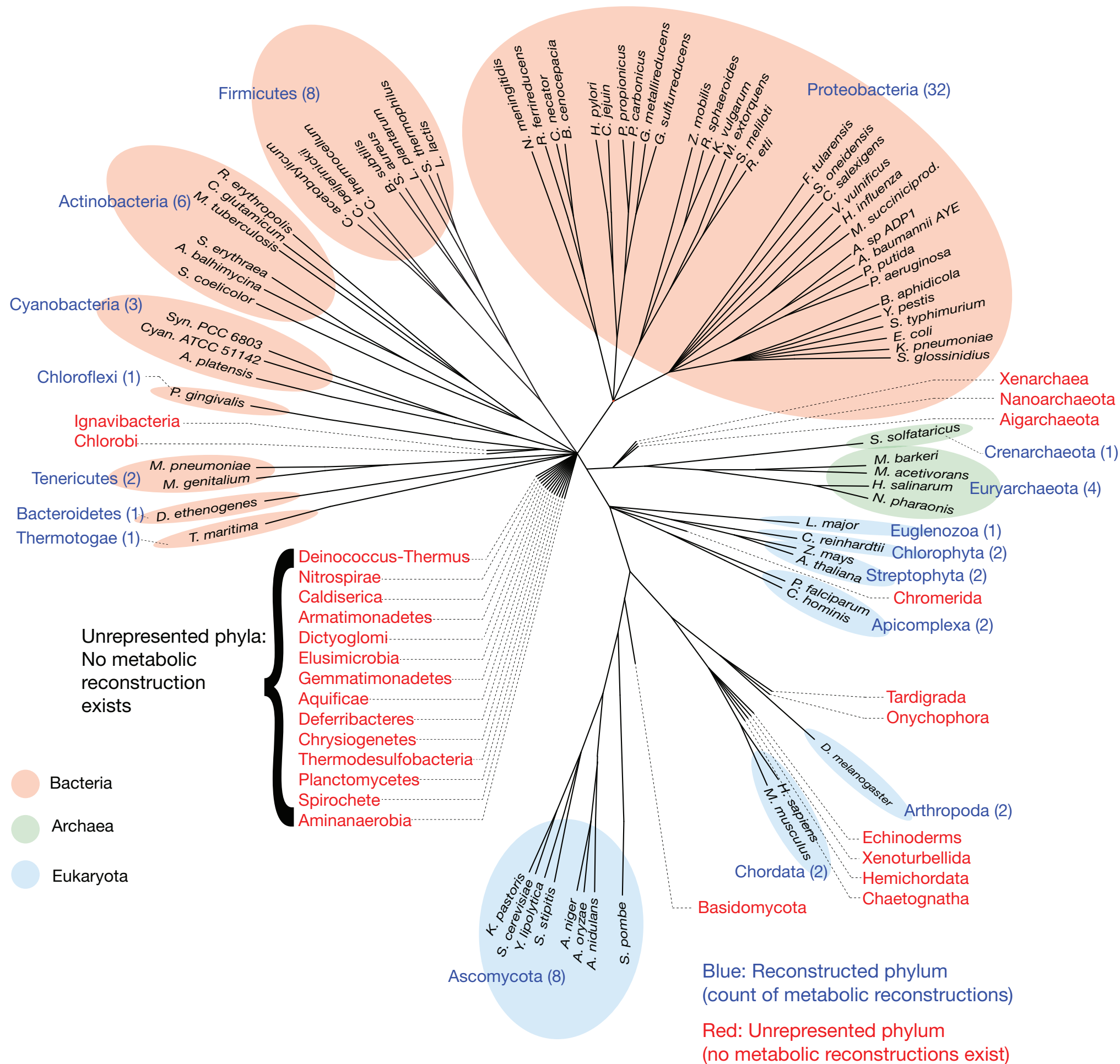
## Optimizing genome-scale network reconstructions

Jonathan Monk<sup>1,3</sup>, Juan Nogales<sup>1-3</sup> & Bernhard O Palsson<sup>1</sup>

Metabolic reconstructions remain limited in their scope and content, and improvements in biochemical knowledge and collaborative research are required.

1. Monk J, Nogales J, Palsson BØ: Optimizing genome-scale network reconstructions. Nat Biotechnol 2014, 32:447–452.

Metabolic reconstructions for 78 species across the tree of life



# Paper 2

**PROTOCOL**

## **A protocol for generating a high-quality genome-scale metabolic reconstruction**

Ines Thiele<sup>1,2</sup> & Bernhard Ø Palsson<sup>1</sup>

<sup>1</sup>Department of Bioengineering, University of California, San Diego, La Jolla, California, USA. <sup>2</sup>Current address: Center for Systems Biology, Faculty of Industrial Engineering, Mechanical Engineering and Computer Science, University of Iceland, Reykjavik, Iceland. Correspondence should be addressed to B.Ø.P. (palsson@ucsd.edu).

Published online 7 January 2010; doi:10.1038/nprot.2009.203

1. Thiele I, Palsson BØ: A protocol for generating a high-quality genome-scale metabolic reconstruction. Nature protocols 2010, 5:93–121.



# de novo reconstruction

[Thiele, Nature  
Protocols, 2010]

## 1. Draft reconstruction

- 1| Obtain genome annotation.
- 2| Identify candidate metabolic functions.
- 3| Obtain candidate metabolic reactions.
- 4| Assemble draft reconstruction.
- 5| Collect experimental data.

## 2. Refinement of reconstruction

- 6| Determine and verify substrate and cofactor usage.
- 7| Obtain neutral formula for each metabolite.
- 8| Determine the charged formula.
- 9| Calculate reaction stoichiometry.
- 10| Determine reaction directionality.
- 11| Add information for gene and reaction localization.
- 12| Add subsystems information.
- 13| Verify gene–protein–reaction association.
- 14| Add metabolite identifier.
- 15| Determine and add confidence score.
- 16| Add references and notes.
- 17| Flag information from other organisms.
- 18| Repeat Steps 6 to 17 for all genes.
- 19| Add spontaneous reactions to the reconstruction.
- 20| Add extracellular and periplasmic transport reactions.
- 21| Add exchange reactions.
- 22| Add intracellular transport reactions.
- 23| Draw metabolic map (optional).
- 24–32| Determine biomass composition.
- 33| Add biomass reaction.
- 34| Add ATP-maintenance reaction (ATPM).
- 35| Add demand reactions.
- 36| Add sink reactions.
- 37| Determine growth medium requirements.

## 4. Network evaluation

- 43–44| Test if network is mass-and charge balanced.
- 45| Identify metabolic dead-ends.
- 46–48| Perform gap analysis.
- 49| Add missing exchange reactions to model.
- 50| Set exchange constraints for a simulation condition.
- 51–58| Test for stoichiometrically balanced cycles.
- 59| Re-compute gap list.
- 60–65| Test if biomass precursors can be produced in standard medium.
- 66| Test if biomass precursors can be produced in other growth media.
- 67–75| Test if the model can produce known secretion products.
- 76–78| Check for blocked reactions.
- 79–80| Compute single gene deletion phenotypes.
- 81–82| Test for known incapacilities of the organism.
- 83| Compare predicted physiological properties with known properties.
- 84–87| Test if the model can grow fast enough.
- 88–94| Test if the model grows too fast.

## 3. Conversion of reconstruction into computable format

- 38| Initialize the COBRA toolbox.
- 39| Load reconstruction into Matlab.
- 40| Verify S matrix.
- 41| Set objective function.
- 42| Set simulation constraints.

## Data assembly and dissemination

- 95| Print Matlab model content.
- 96| Add gap information to the reconstruction output.



# Paper 3

Ebrahim *et al.* *BMC Systems Biology* 2013, **7**:74  
<http://www.biomedcentral.com/1752-0509/7/74>



**SOFTWARE**

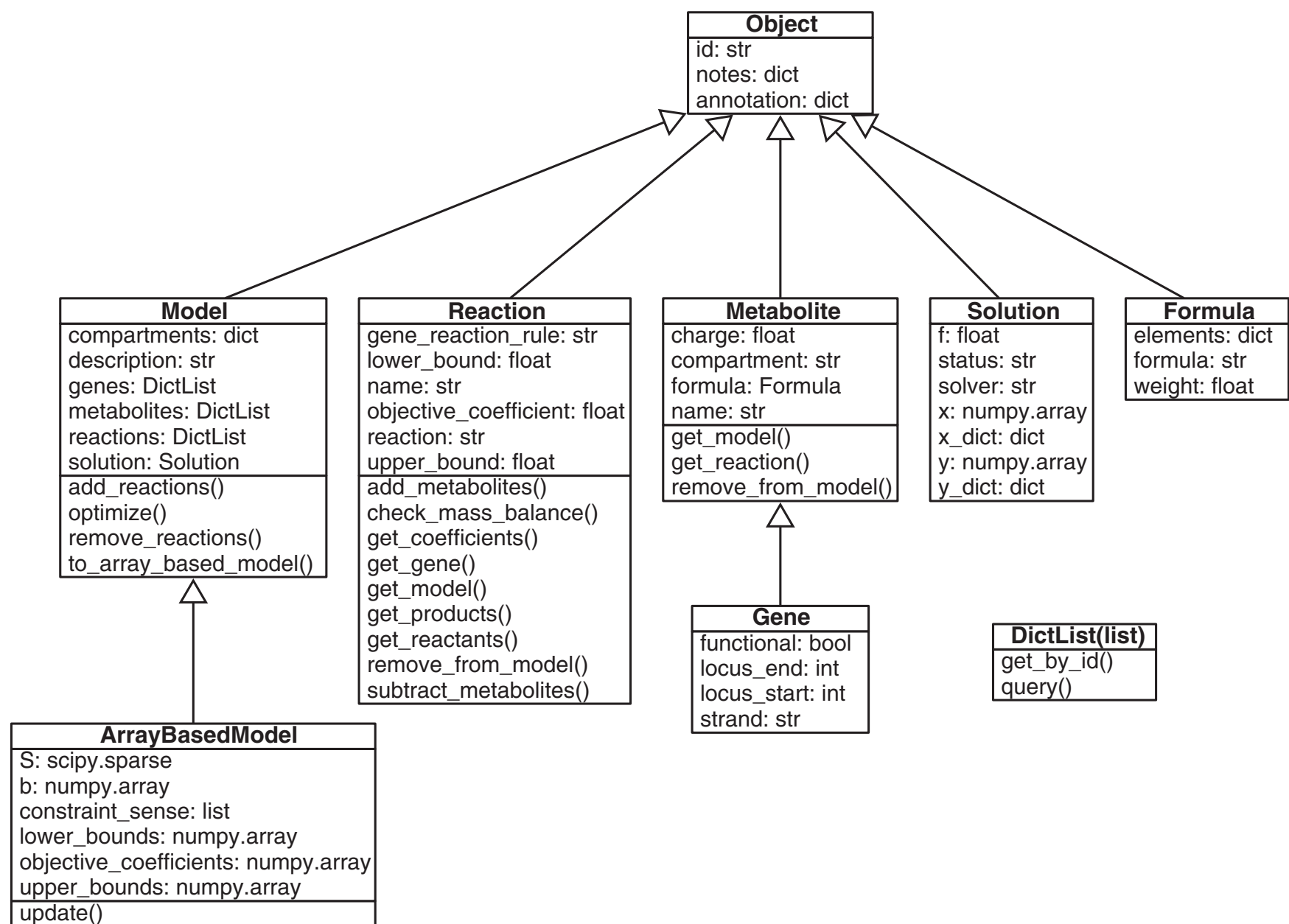
**Open Access**

## COBRApy: COnstraints-Based Reconstruction and Analysis for Python

Ali Ebrahim<sup>1</sup>, Joshua A Lerman<sup>1</sup>, Bernhard O Palsson<sup>1</sup> and Daniel R Hyduke<sup>1,2\*</sup>

1. Ebrahim A, Lerman JA, Palsson BØ, Hyduke DR: COBRApy: COnstraints-Based Reconstruction and Analysis for Python. *BMC systems biology* 2013, **7**:74.





**Figure 1 Core classes in COBRA for Python with key attributes and methods listed.** Additional attributes and methods are described in the documentation.



# Paper 4

Loira et al. *BMC Systems Biology* 2012, **6**:35  
<http://www.biomedcentral.com/1752-0509/6/35>



**RESEARCH ARTICLE**

**Open Access**

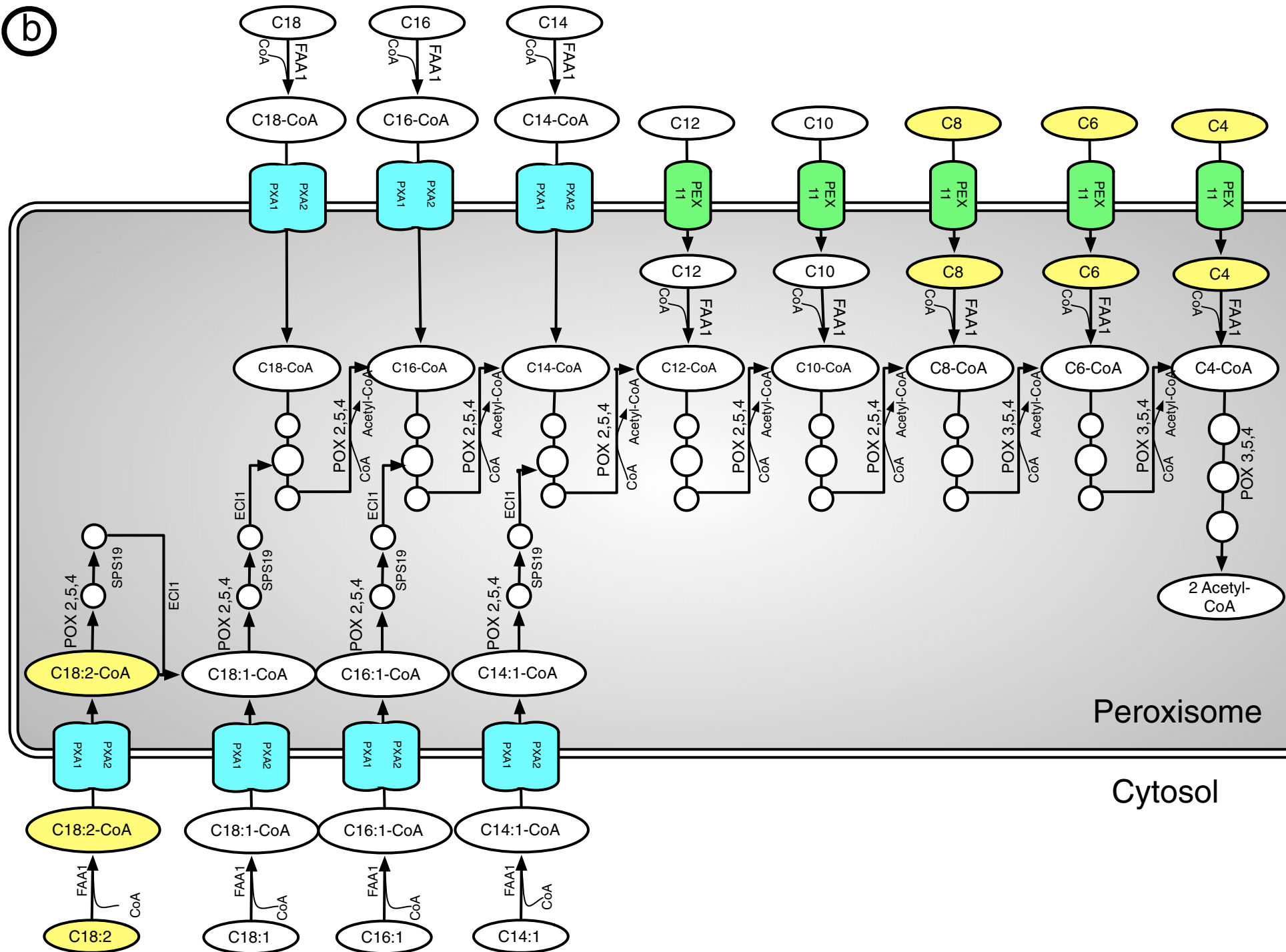
## A genome-scale metabolic model of the lipid-accumulating yeast *Yarrowia lipolytica*

Nicolas Loira<sup>1,4</sup>, Thierry Dulermo<sup>2,3</sup>, Jean-Marc Nicaud<sup>2,3</sup> and David James Sherman<sup>1\*</sup>

1. Loira N, Dulermo T, Nicaud J-M, Sherman DJ: A genome-scale metabolic model of the lipid-accumulating yeast *Yarrowia lipolytica*. *BMC systems biology* 2012, **6**:35.



b





# Paper 5

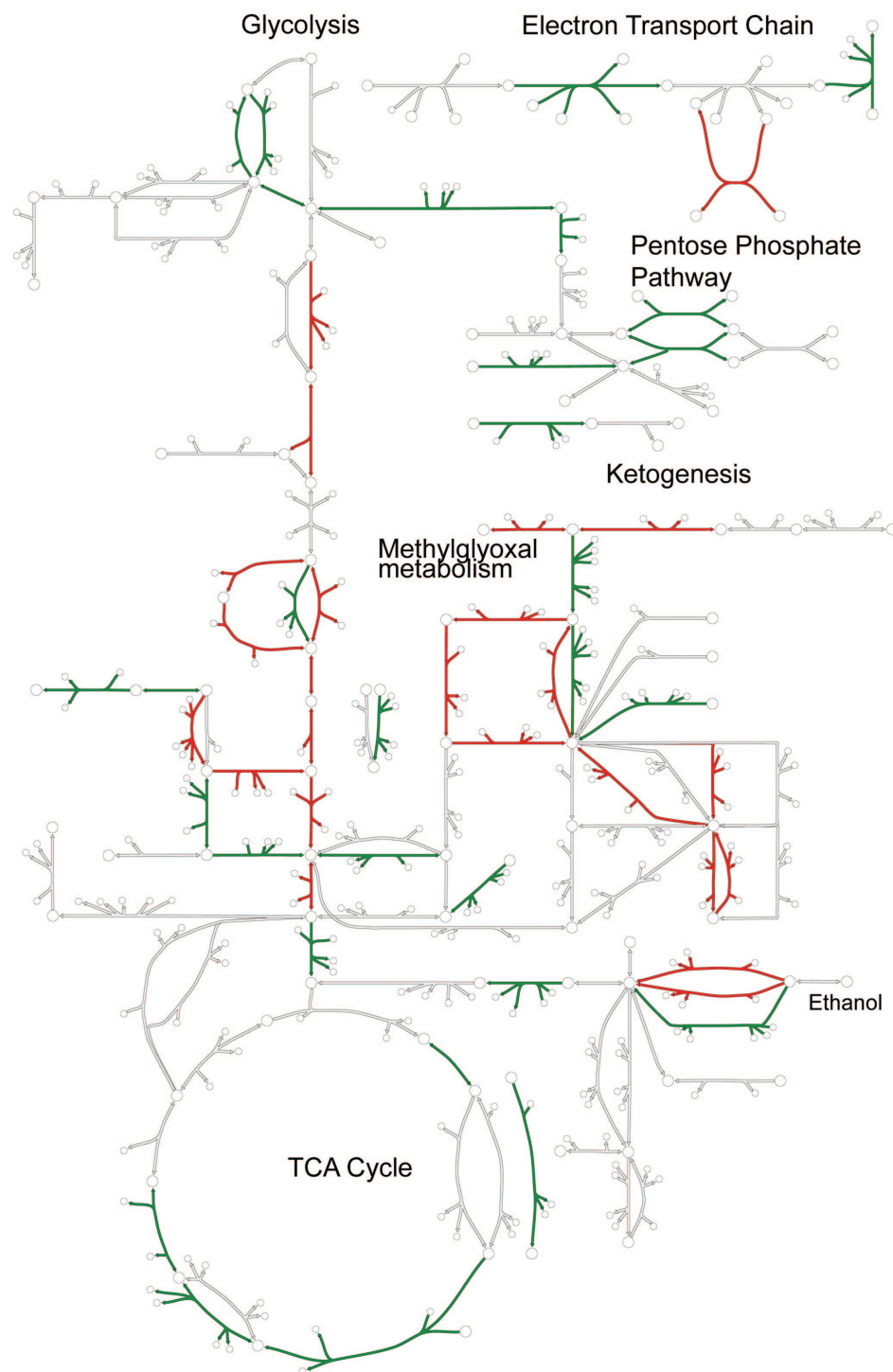
## **Global reconstruction of the human metabolic network based on genomic and bibliomic data**

**Natalie C. Duarte, Scott A. Becker, Neema Jamshidi, Ines Thiele, Monica L. Mo, Thuy D. Vo, Rohith Srivas, and Bernhard Ø. Palsson\***

Bioengineering Department, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0412

1. Duarte NC, Becker SA, Jamshidi N, Thiele I, Mo ML, Vo TD, Srivas R, Palsson BØ: Global reconstruction of the human metabolic network based on genomic and bibliomic data. Proc Natl Acad Sci USA 2007, 104:1777–1782.





Integrated analysis of gene expression data from gastric bypass patients before surgery and 1 year afterward. Expression measurements were to reactions in the global human metabolic network and then visualized on Recon 1's comprehensive collection of human metabolic maps. Reactions are color-coded based on their corresponding gene expression changes (green, down-regulated; red, up-regulated; white, no data available or reaction level conflict). Arrows next to reaction abbreviations indicate the magnitude of expression changes on a log10 scale (gray boxes indicate no data available)



# Posibles temas de investigación

- ✦ Desafíos en la construcción de modelos para organismos eucariontes
- ✦ Usos de modelos metabólicos en salud humana
  - ✦ Mapeo de datos -omicos sobre Recon 1
  - ✦ Diseño de drogas



# Gracias!

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