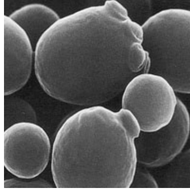


Integrated Genomic and Proteomic Analyses of a Systematically Perturbed Metabolic Network

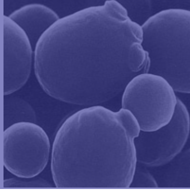
Trey Ideker, Vesteinn Thorrson, Jeffrey A. Ranish, Rowan Christmas, Jeremy Buhler,
Jimmy K. Eng, Roger Bumgarner, David R. Goodlett, Ruedi Aebersold, Leroy Hood

Science, May 4 2001

Chris Bielow   Christian Hoffmann

Wie Zellen denken WS05/06

Motivation



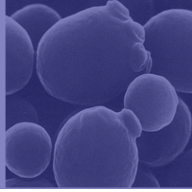
Aufdeckung von Stoffwechselwegen

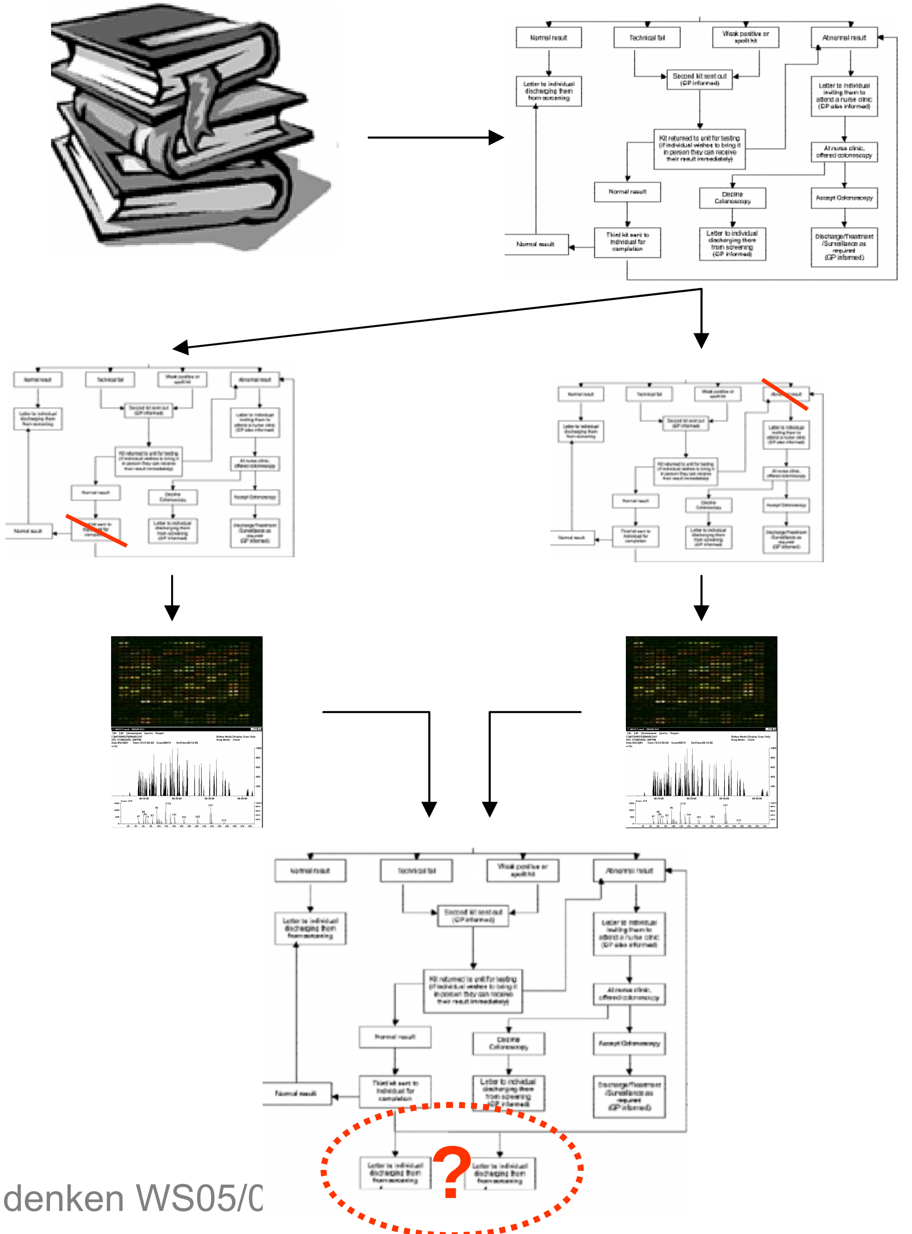
- Genomik: Microarrays, In-situ-Hybridisierung, Real-Time-PCR …
- Proteomik: Massenspektrometrie, Western Blot, ELISA, Yeast-Two-Hybrid …

Neu: Kombination von mRNA & Proteindaten

Ziel: Rückschlüsse auf das Regulationsnetzwerk

Das Modell





Stufe 1: bisher bekanntes Netzwerk beschreiben

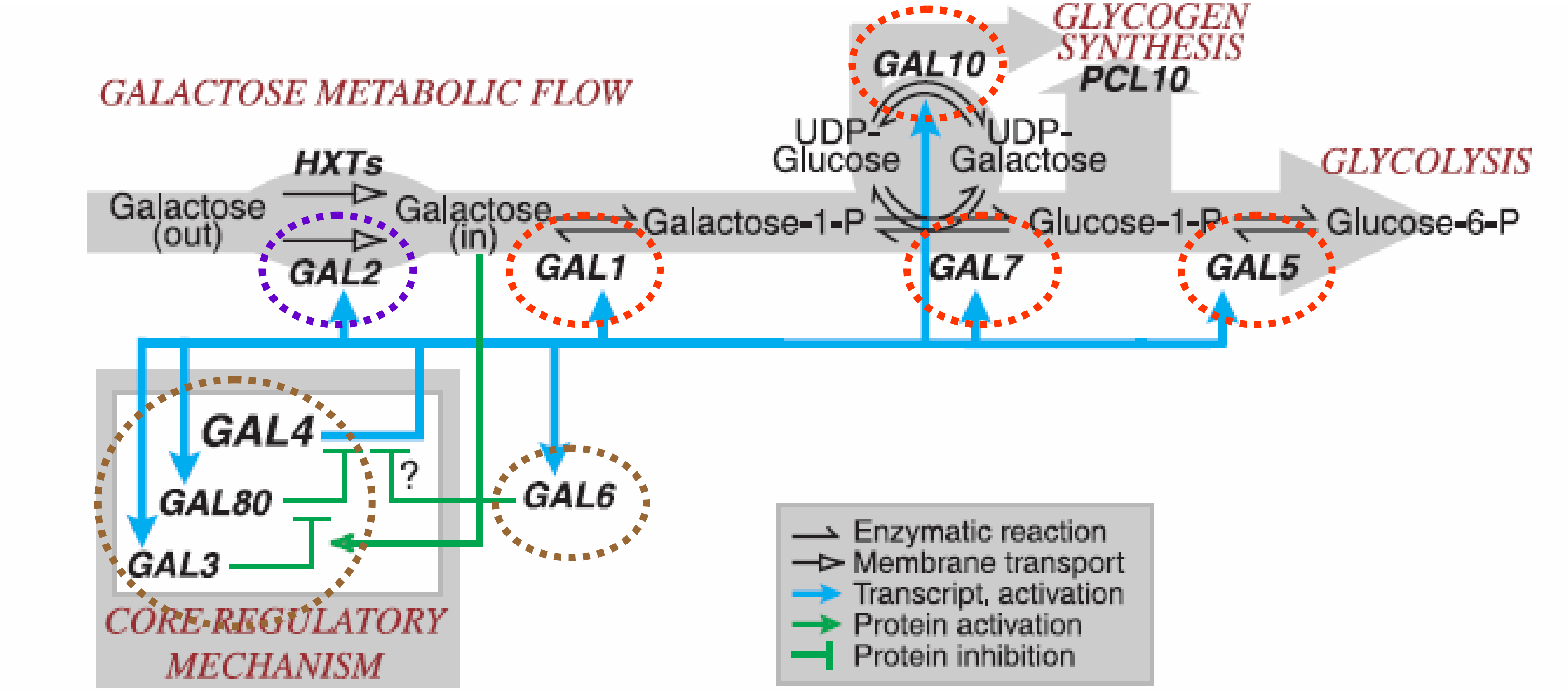
Stufe 2: jede Komponente stören und Veränderungen messen (mRNA, Protein)

Stufe 3:
Veränderungen in Netzwerk integrieren

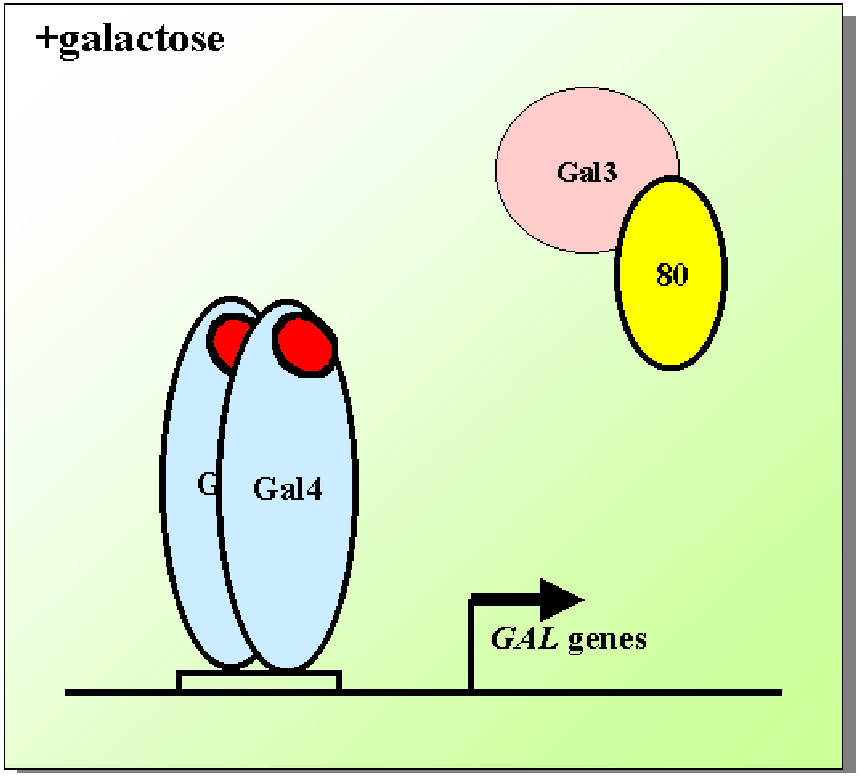
Stufe 4: Hypothese über bisher unbekannte Beobachtungen formulieren und mit weiteren Experimenten verifizieren

Modell des Galaktoseweges

■☐☐☐

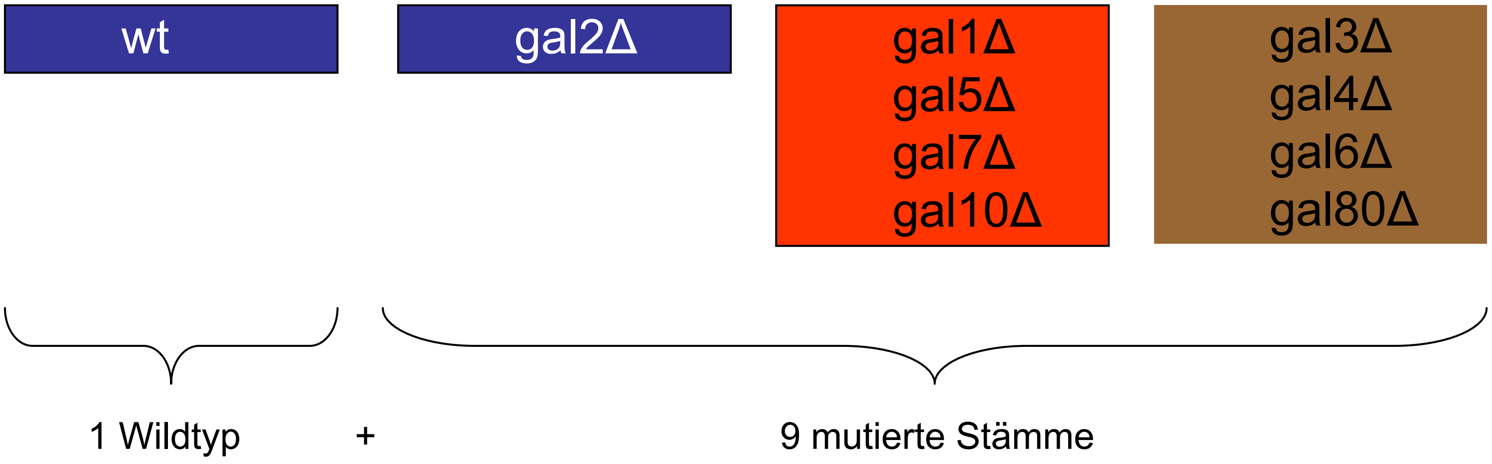


Regulation der Expression



http://web.uni-frankfurt.de/fb15/mikro/melcher/GAL.html

Das Experiment



wt

gal2Δ

gal1Δ
gal5Δ
gal7Δ
gal10Δ

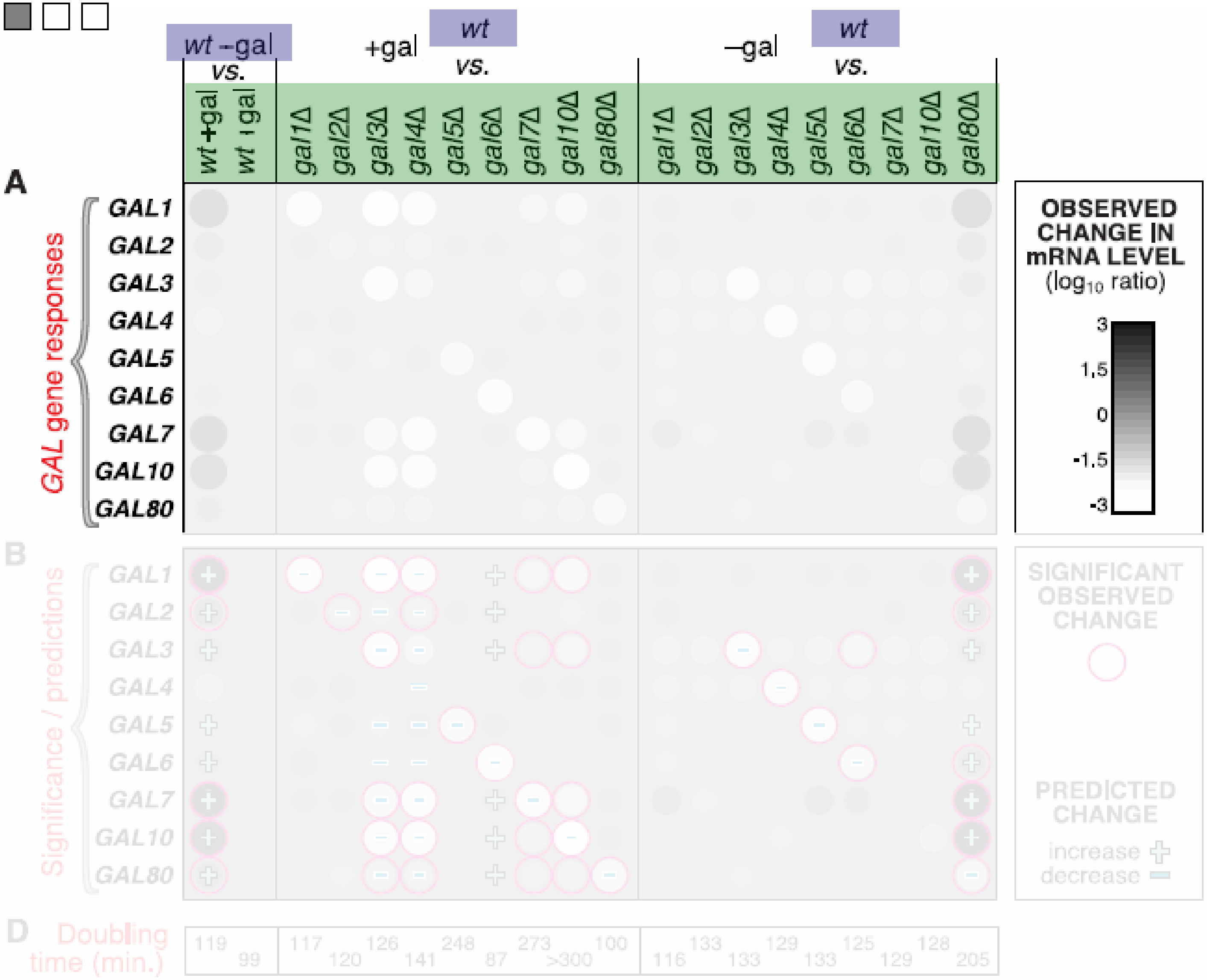
gal3Δ
gal4Δ
gal6Δ
gal80Δ

1 Wildtyp + 9 mutierte Stämme

in 2 verschiedenen Kulturmedien: +GAL
-GAL

→ 20 Experimente

mRNA-Störungsmatrix



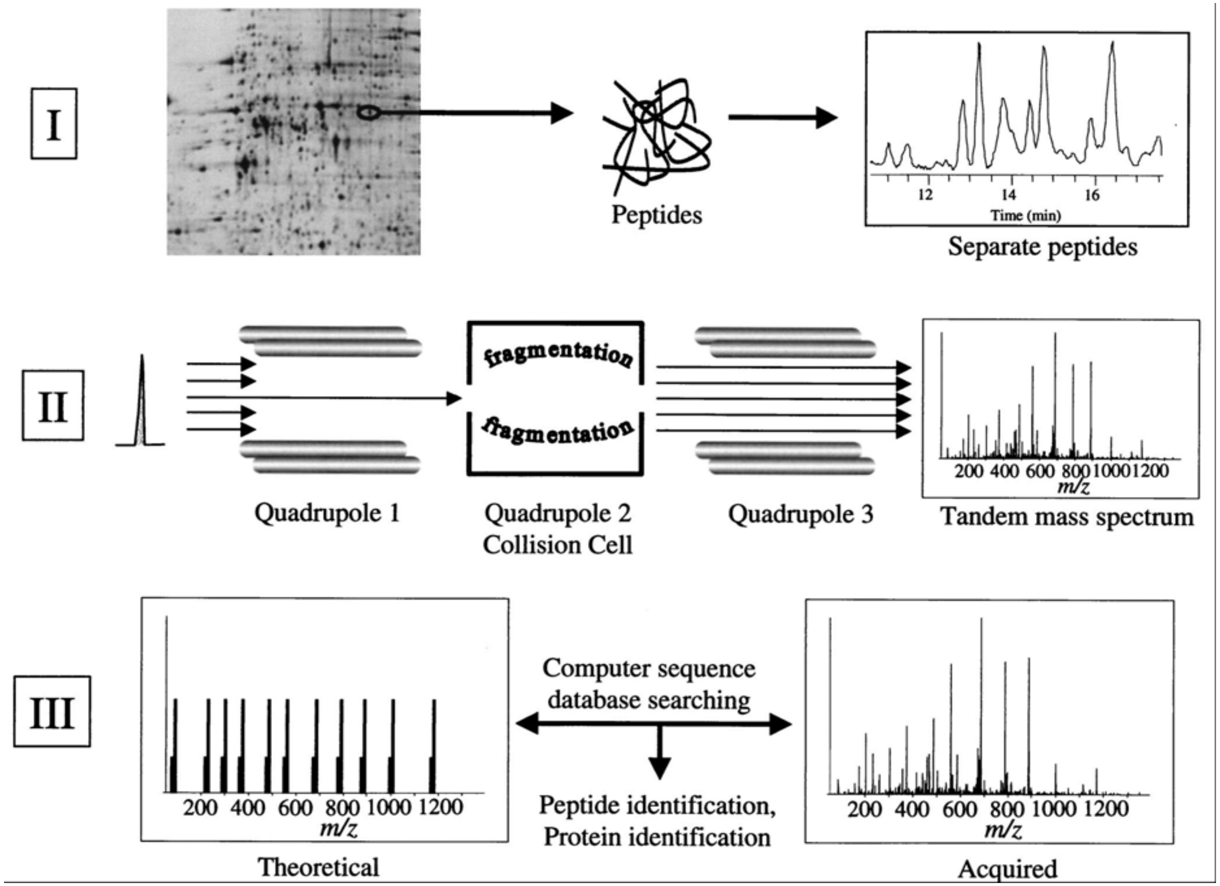
Mutante

÷

Referenz

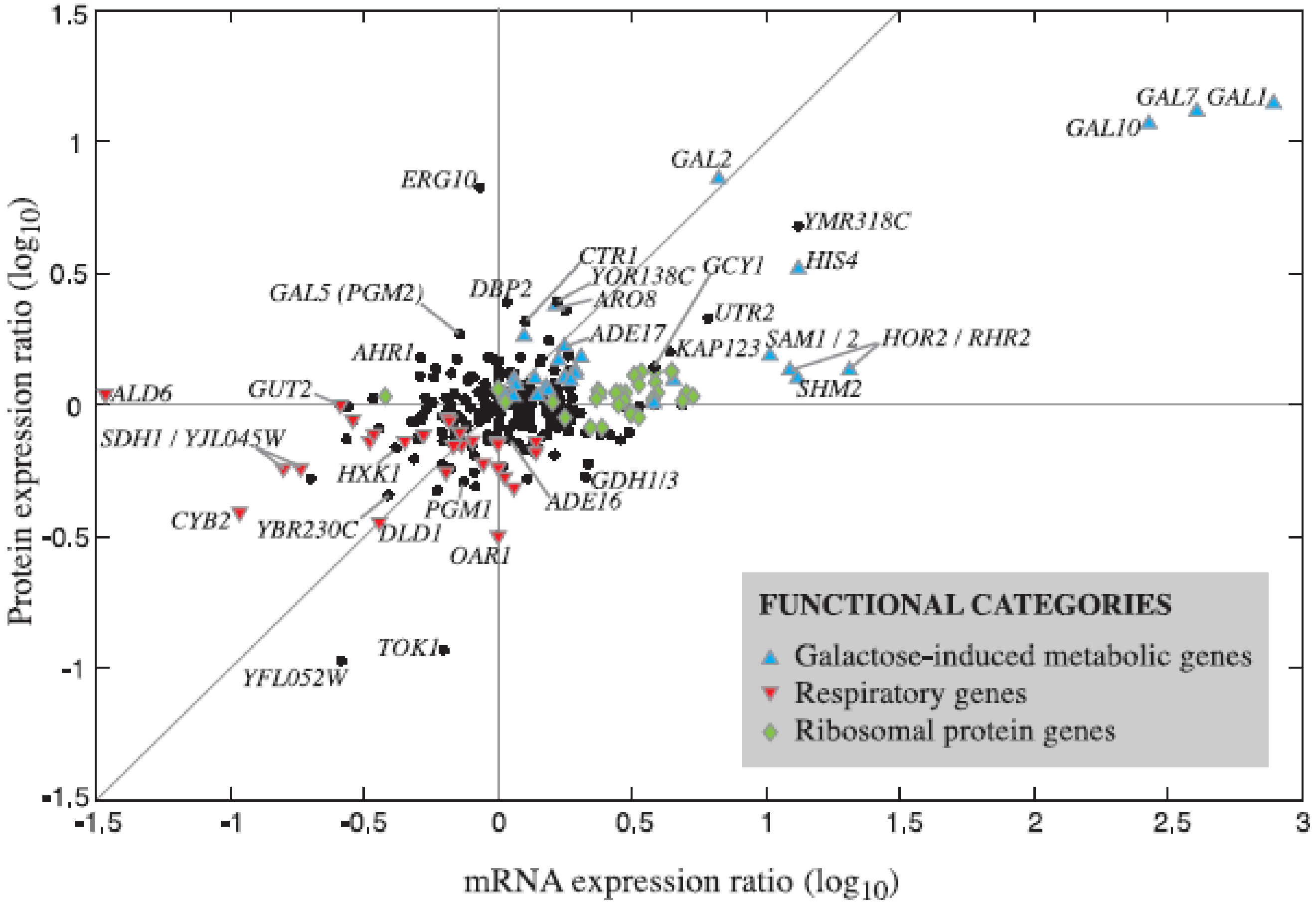
Proteindaten

- 2D-Gel
- HPLC
- MS/MS

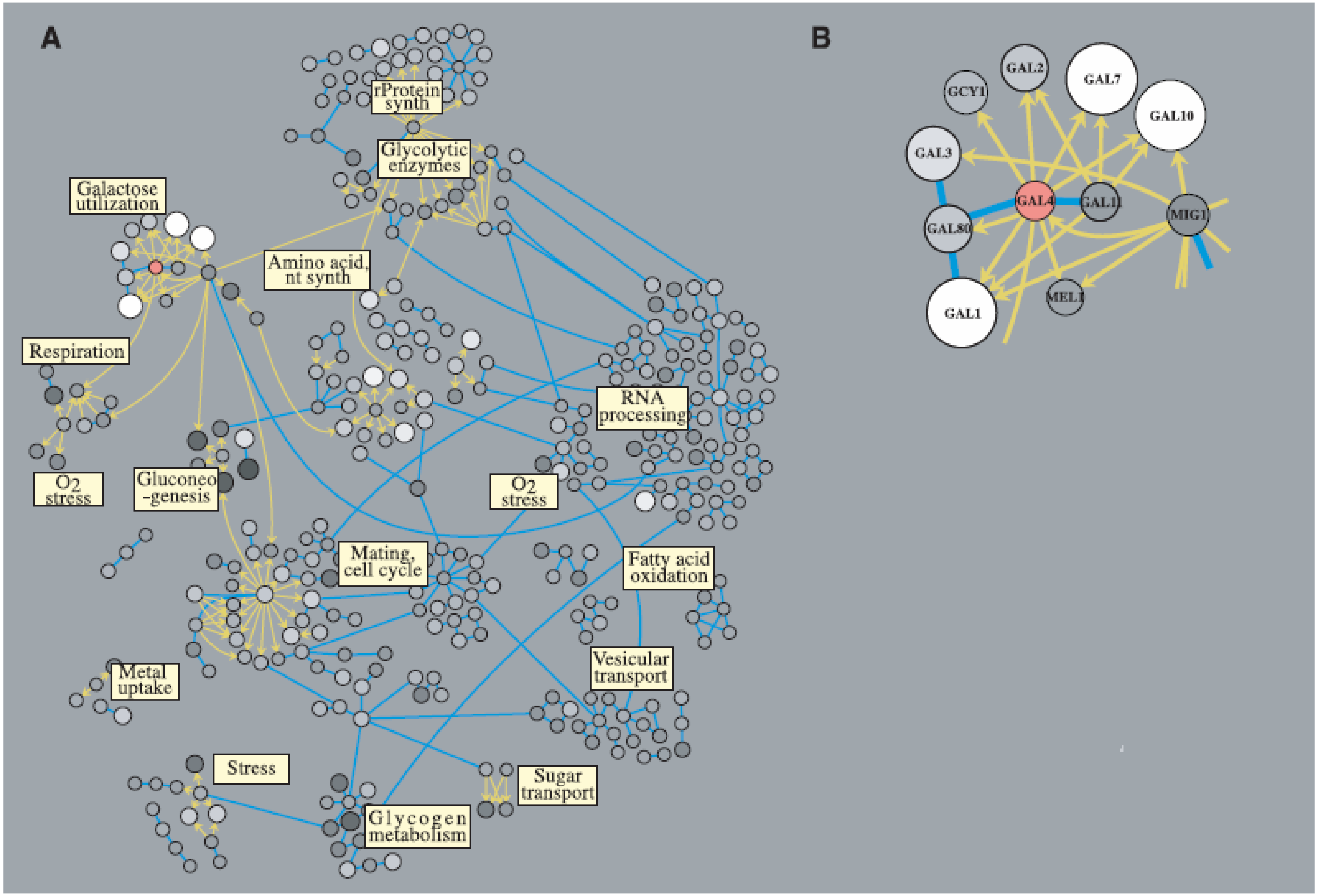


Correlation between protein and mRNA abundance in yeast; S P Gygi and Y Rochon and B R Franza and R Aebersold, *Mol Cell Biol* **Vol19**;

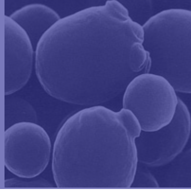
Protein vs DNA

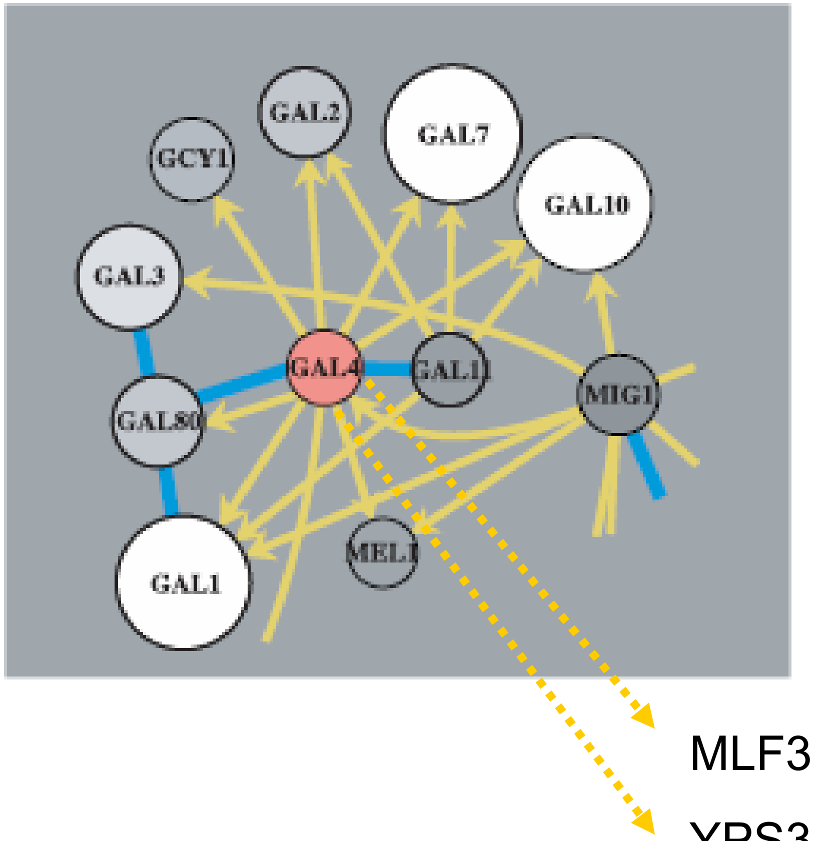


Interaktionsnetzwerk



Interaktionsnetzwerk



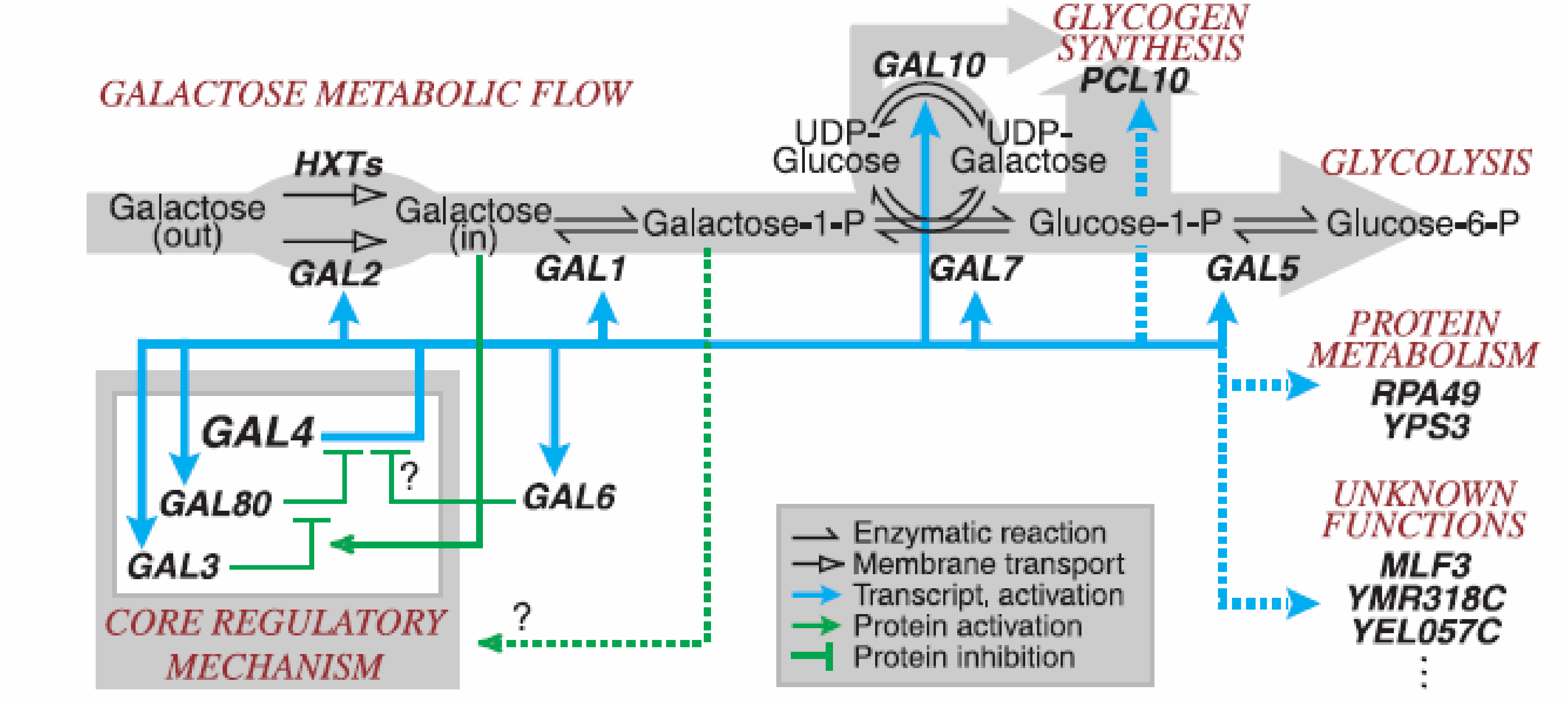


MLF3

YPS3

…

Modell des Galaktoseweges



take home

- Ansatz von Integration von mRNA und Proteindaten richtig (proof-of-principle √)
    - Besseres Verständnis von Regulationsnetzwerken
- mRNA und Proteinexpression sind nicht zwingend korreliert
- Verfeinerungen am Modell bisher *nicht* in der Literatur nachgewiesen

Literatur

- Assessing the limits of genomic data integration for predicting protein networks;

  Long J. Lu and Yu Xia and Alberto Paccanaro and Haiyuan Yu and Mark Gerstein, *Genome Research* **Vol15**;945-53, 2005
- Transient responses and adaptation to steady state in a eukaryotic gene regulation system; Erez Braun and Naama Brenner, *Phys. Biol.* **1** 67–76, 2004
- Testing for Differentially-Expressed Genes by Maximum-Likelihood Analysis of Microarray Data; T Ideker and V Thorsson and A F Siegel and L E Hood, *J Comput Biol* **Vol7**;805-17; 2000
- Transcriptional control of the GAL/MEL regulon of yeast Saccharomyces cerevisiae: mechanism of galactose-mediated signal transduction; P J Bhat and T V Murthy, *MolMicrobiol* **Vol40**;1059-66, 2001
- Complementary profiling of gene expression at the transcriptome and proteome levels in {S}accharomyces cerevisiae; Timothy J Griffin and Steven P Gygi and Trey Ideker and Beate Rist and Jimmy Eng and Leroy Hood and Ruedi Aebersold, *Mol Cell Proteomics* **Vol1**;323-33, 2002
- Correlation between protein and mRNA abundance in yeast; S P Gygi and Y Rochon and B R Franza and R Aebersold, *Mol Cell Biol* **Vol19**;1720-30, 1999