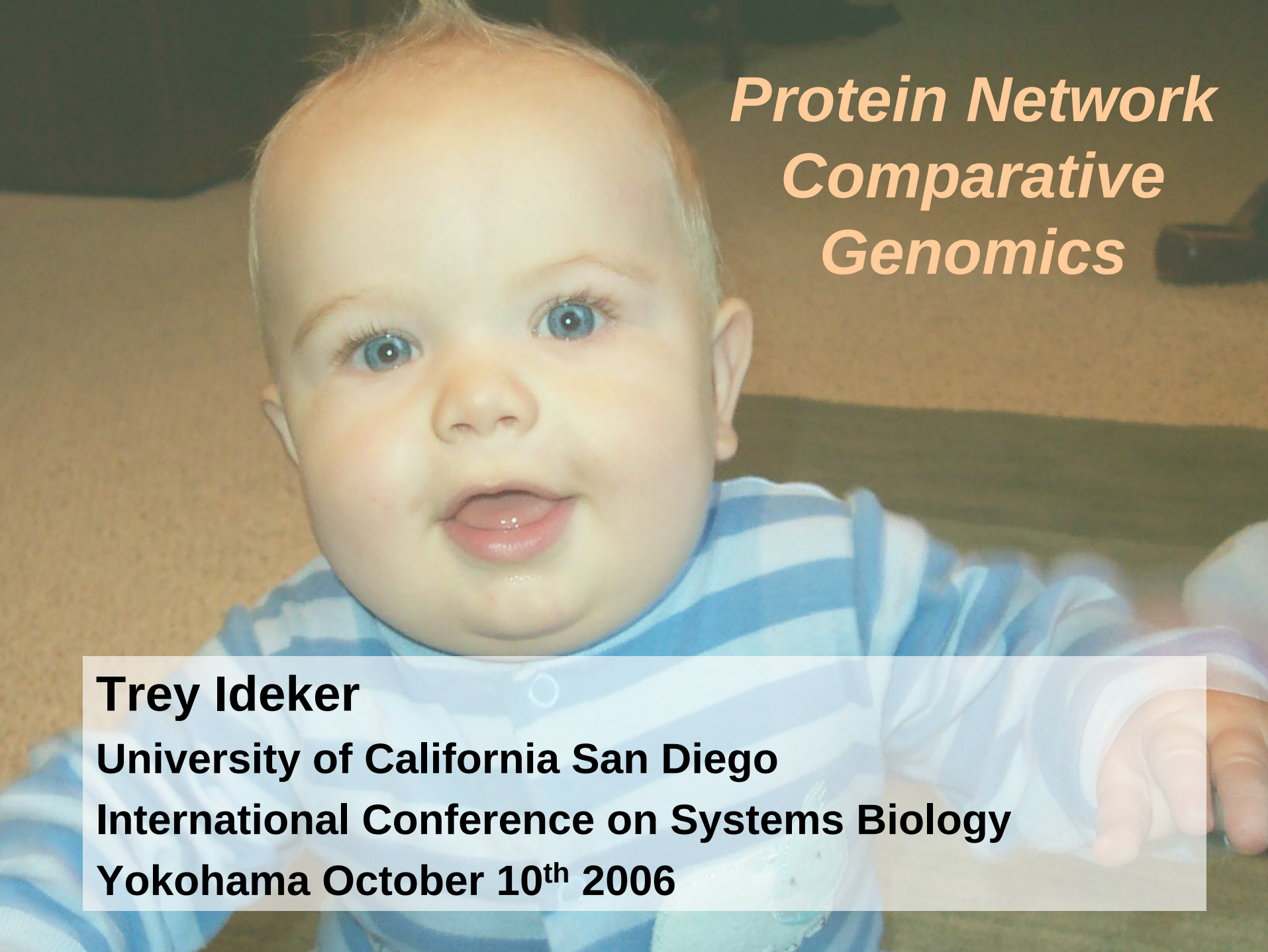


Protein Network Comparative Genomics

Trey Ideker

University of California San Diego

International Conference on Systems Biology

Yokohama October 10th 2006

From protein sequences… to protein networks

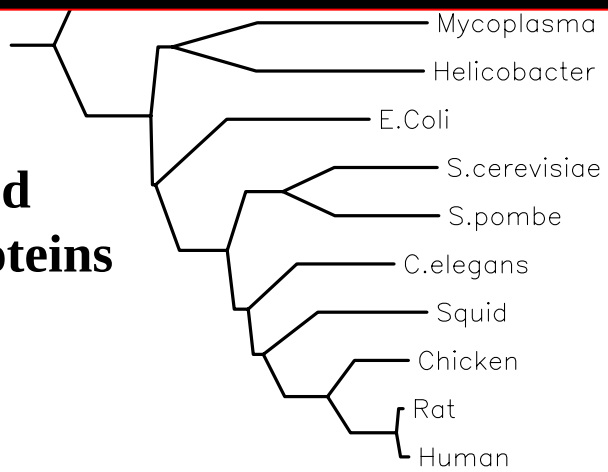
Query Sequence

GACTGCATTAC

Two goals:

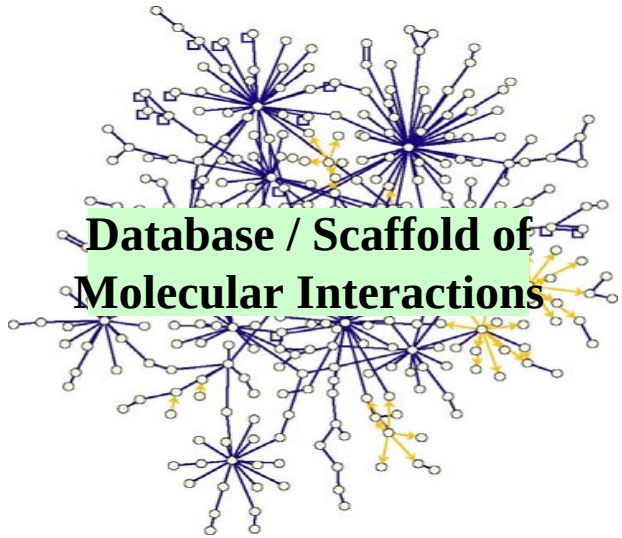
1) Screen out false positives and non-functional interactions

2) Place into pathway models



Conserved genes/proteins

Global query



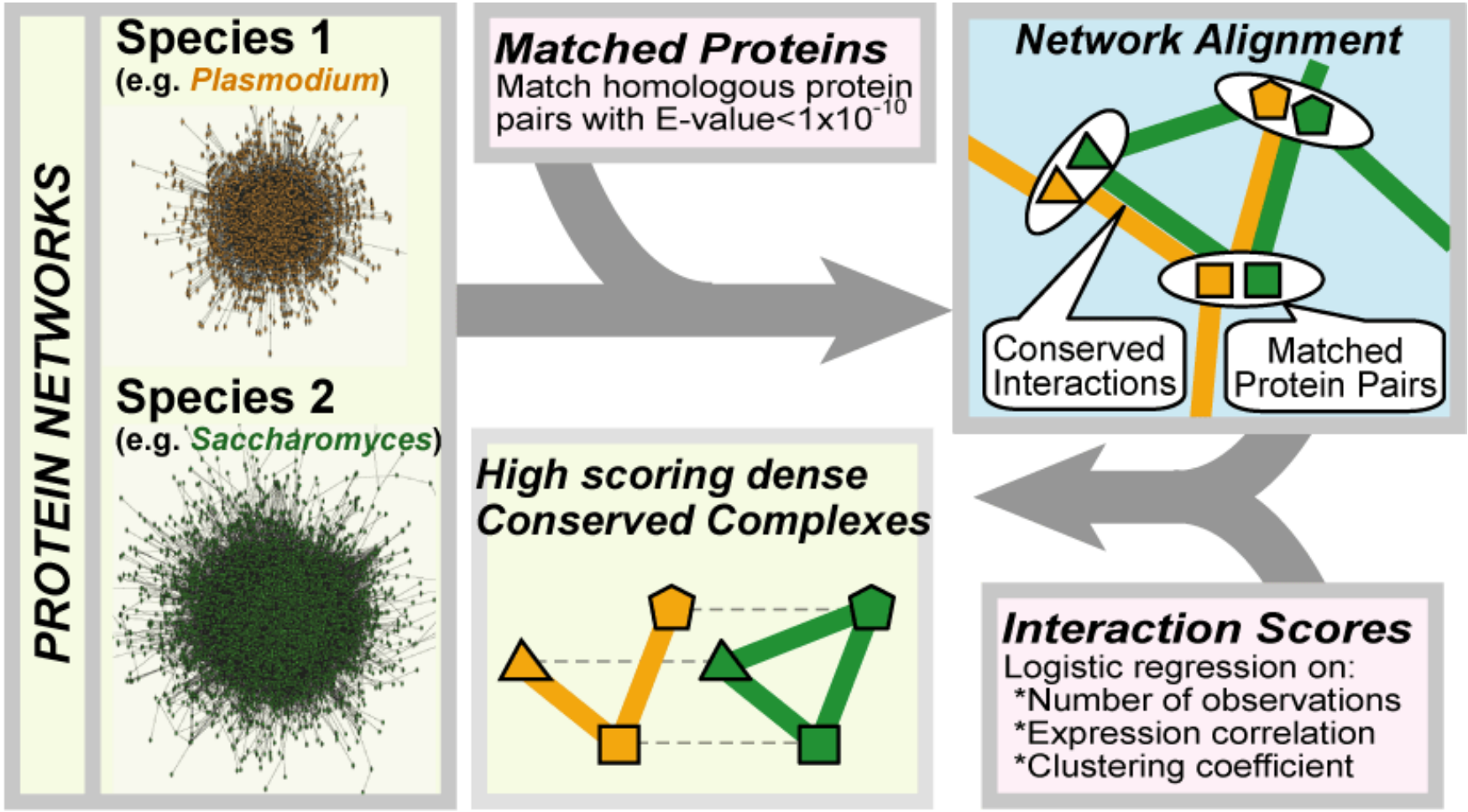
Database / Scaffold of Molecular Interactions

Interaction pathway and complexes associated with query data

Cross-comparison of networks:

(1) Conserved regions in the presence vs. absence of stimulus

(2) Conserved regions across different species



Kelley et al. *PNAS* 2003

http://www.pathblast.org

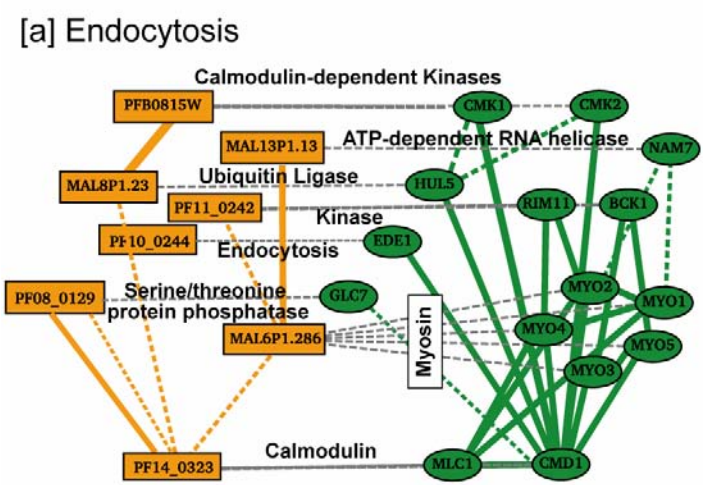
Sharan et al. *PNAS* 2005

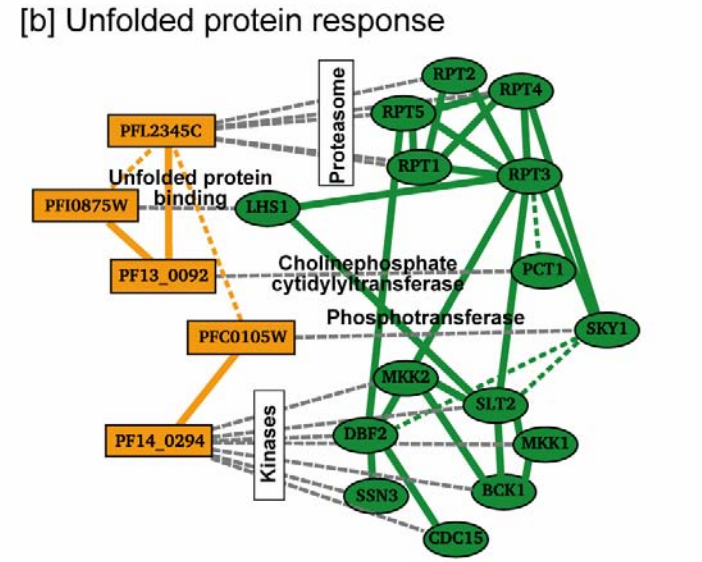
Sharan et al. *Nat Biotech* 2006

Sharan et al. *RECOMB* 2004

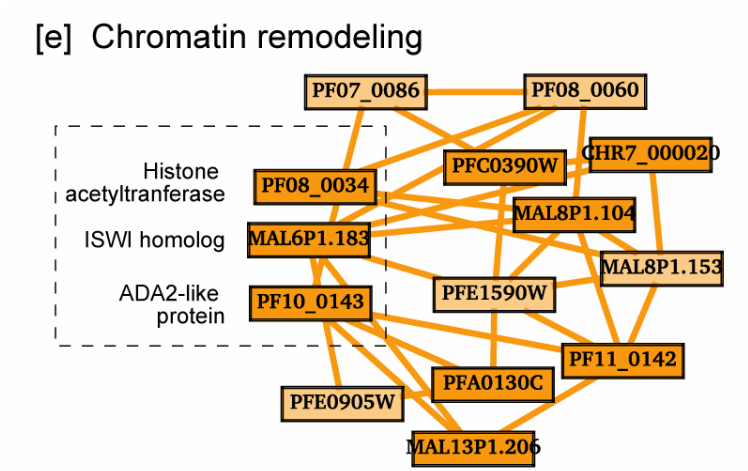
Scott et al. *RECOMB* 2005

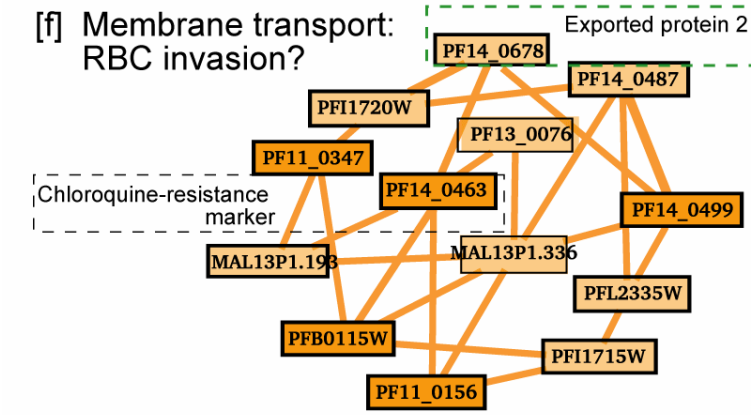
Plasmodium: a network apart?





Conserved *Plasmodium* / *Saccharomyces* protein complexes





Plasmodium-specific protein complexes

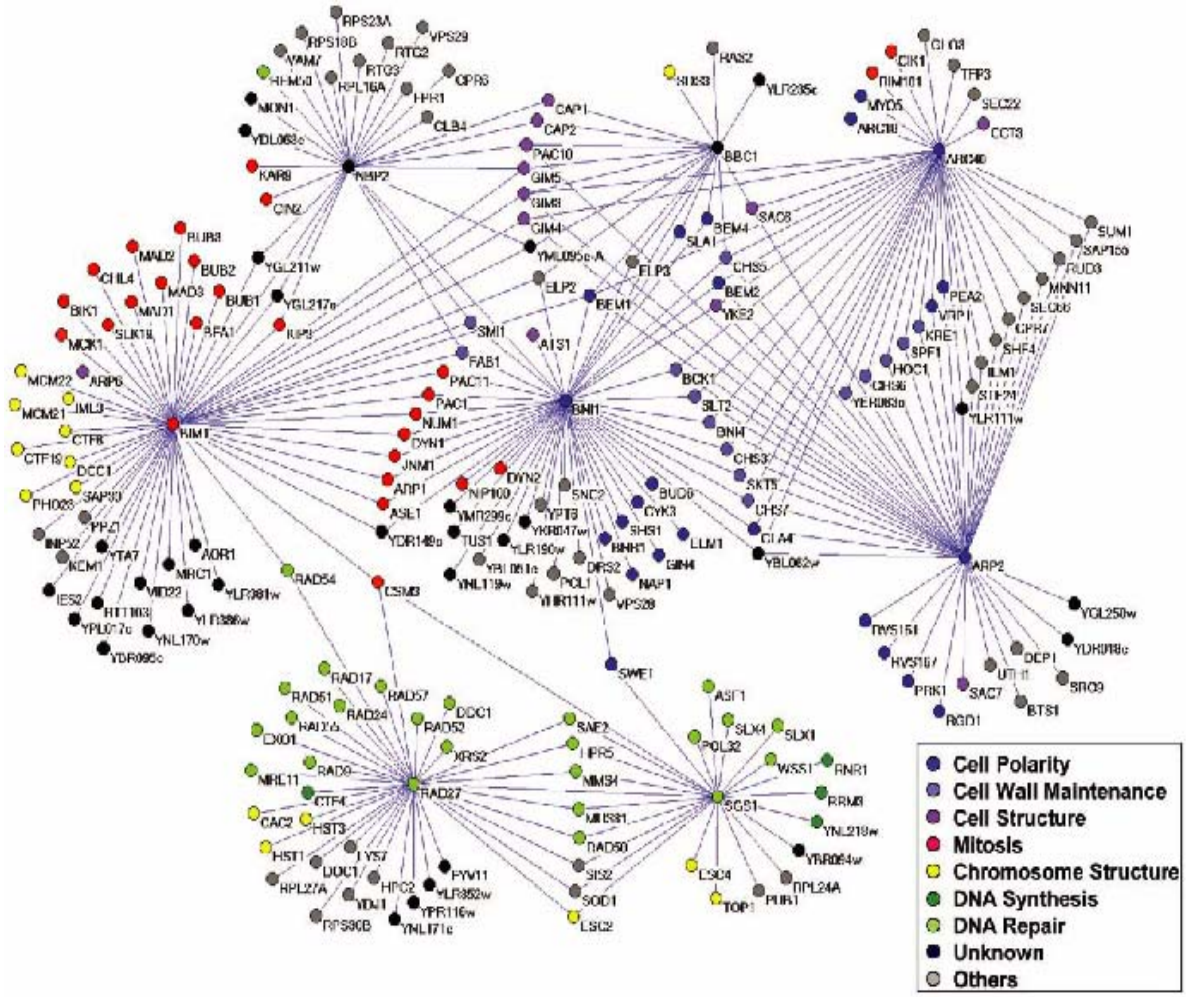
Suthram et al. *Nature* 2005
La Count et al. *Nature* 2005

Finding physical pathways to explain genetic interactions

Genetic Interactions:

- Classical method used to map pathways in model species
- Highly analogous to multi-genic interaction in human disease and combination therapy
- Thousands are being uncovered through systematic studies

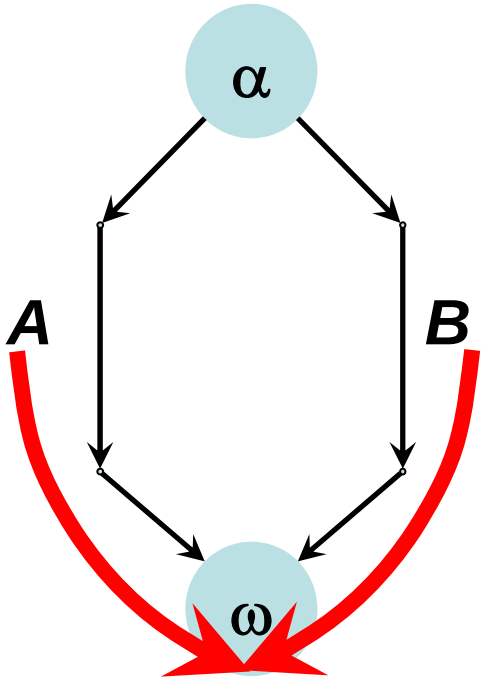
Thus as with other types, the number of known genetic interactions is *exponentially increasing…*



Adapted from Tong *et al.*, *Science* 2001

Interpretation of genetic interactions (Guarente *T.I.G.* 1990)

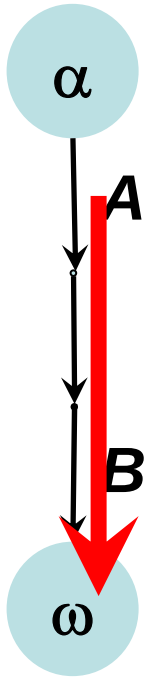
Parallel Effects (Redundant or Additive)



Single A or B mutations typically *abolish* their biochemical activities

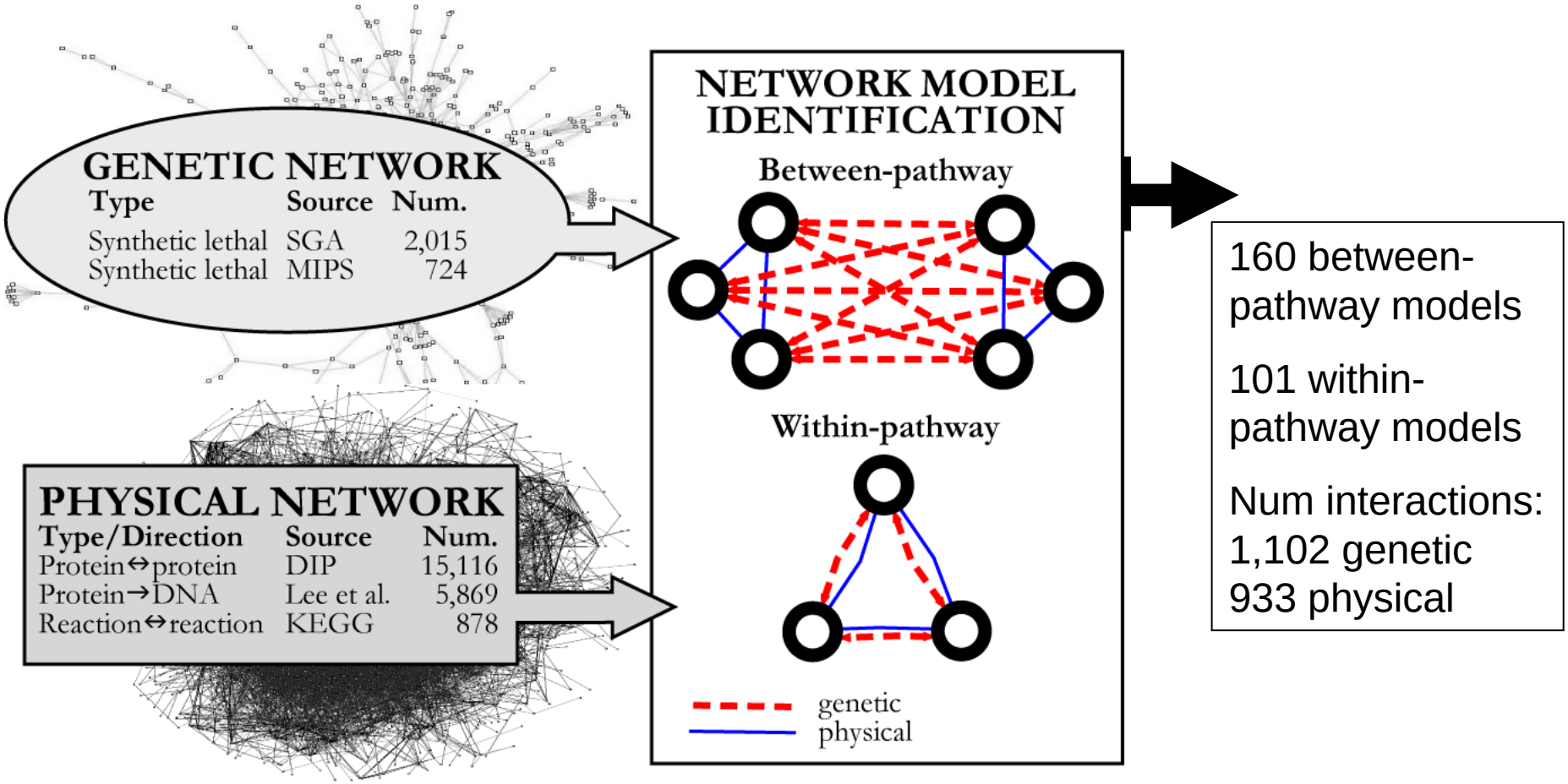
GOAL: Identify downstream physical pathways

Sequential Effects (Additive)



Single A or B mutations typically *reduce* their biochemical activities

Integration of genetic and physical interactions



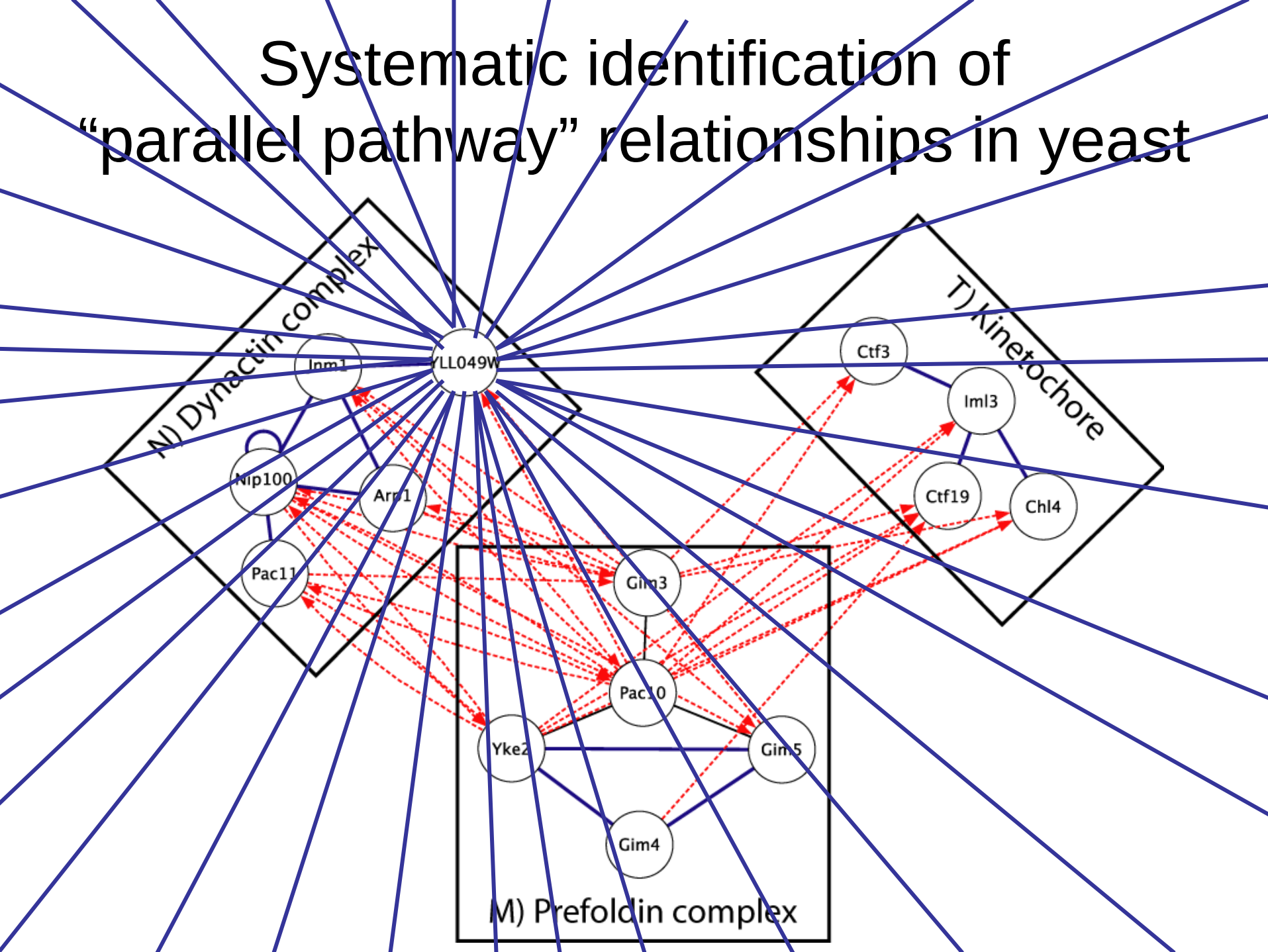
160 between-pathway models

101 within-pathway models

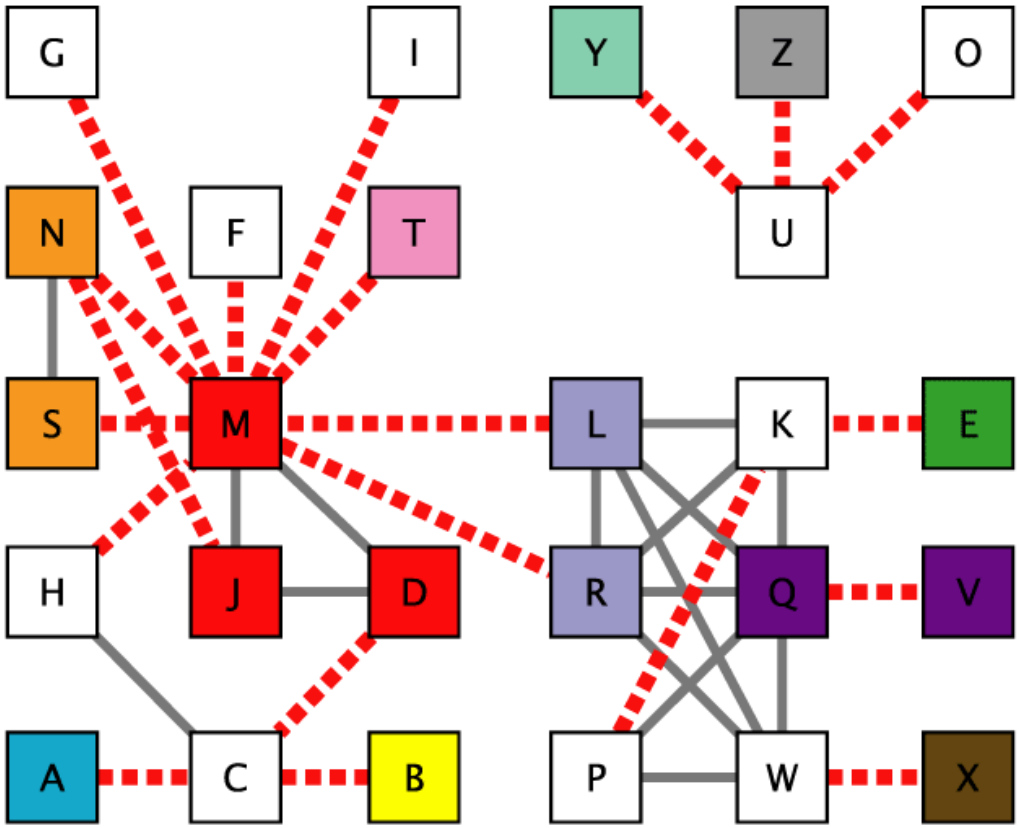
Num interactions:
1,102 genetic
933 physical

Kelley and Ideker *Nature Biotechnology (*2005)

Systematic identification of “parallel pathway” relationships in yeast



Global organization of genetic linkages between physical pathways (A-Z)



Bridging genetic interactions

Overlapping pathways

DNA catabolism
amino-terminal blocking
dynactin complex
glycoprotein metabolism
prefoldin complex
budding
cell cortex
regulation of biological process
retromer complex
chromosome
motor activity

www.cytoscape.org

Shannon et al. Genome Research (2003)

Funding: NIGMS and Unilever

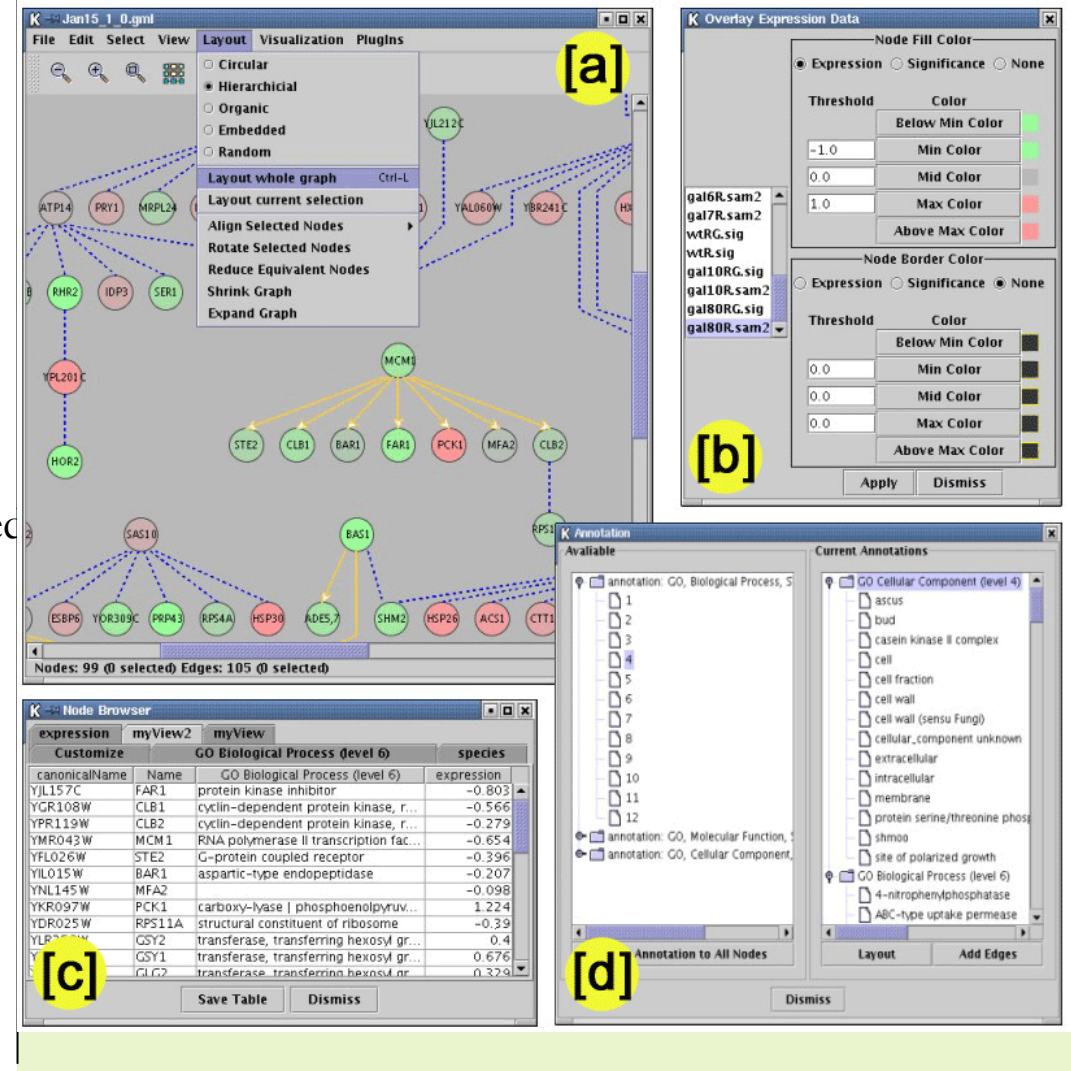
OPEN SOURCE Java-based platform for modeling large molecular interaction networks

CORE (layout & data integration)

- Layout of large interaction networks (including protein-protein, protein-DNA, genetic, and biochemical)
- Links to functional attributes (user defined GO, KEGG) and lower-level modeling environments (SBML/SBW)
- Generalized attribute-to-visual mapping

PLUG-INS (computation, extensions)

- Pathway/network analyses implemented through an extensible PlugIn architecture



JOINT PROJECT with the Inst. for Systems Biology (Hood), Inst. Pasteur (Schwikowski), Sloan-Kettering (Sander), U. Toronto (Bader), UCSF (Conklin) and Agilent (Adler/Kuchinsky)

Transcriptional response of *Saccharomyces cerevisiae* to DNA-damaging agents does not identify the genes that protect against these agents

Geoff W. Birrell*, James A. Brown*, H. Irene Wu*, Guri Giaever†, Angela M. Chu†, Ronald W. Davis†, and J. Martin Brown*‡

Departments of *Radiation Oncology and †Biochemistry, Stanford University School of Medicine, Stanford, CA 94305

Contributed by Ronald W. Davis, May 8, 2002

The recent genes in b determining to cytotoxic esis that ge are importa 4,627 diploi sential gen survival of y UV radiatio addition we type parental strain to the same DNA-damaging agents. We found no relationship between the genes necessary for survival to the DNA-damaging agents and those genes whose transcription is increased after exposure. These data show that few, if any, of the genes involved in repairing the DNA lesions produced in this study, including double-strand breaks, pyrimidine dimers, single-strand breaks, base damage, and DNA cross-links, are induced in response to toxic doses of the agents that produce these lesions. This finding suggests that the enzymes necessary for the repair of these lesions are at sufficient levels within the cell. The data also suggest that the nature of the lesions produced by DNA-damaging agents cannot easily be deduced from gene expression profiling.

Can this apparent paradox be explained by a physical model of the DNA damage response?

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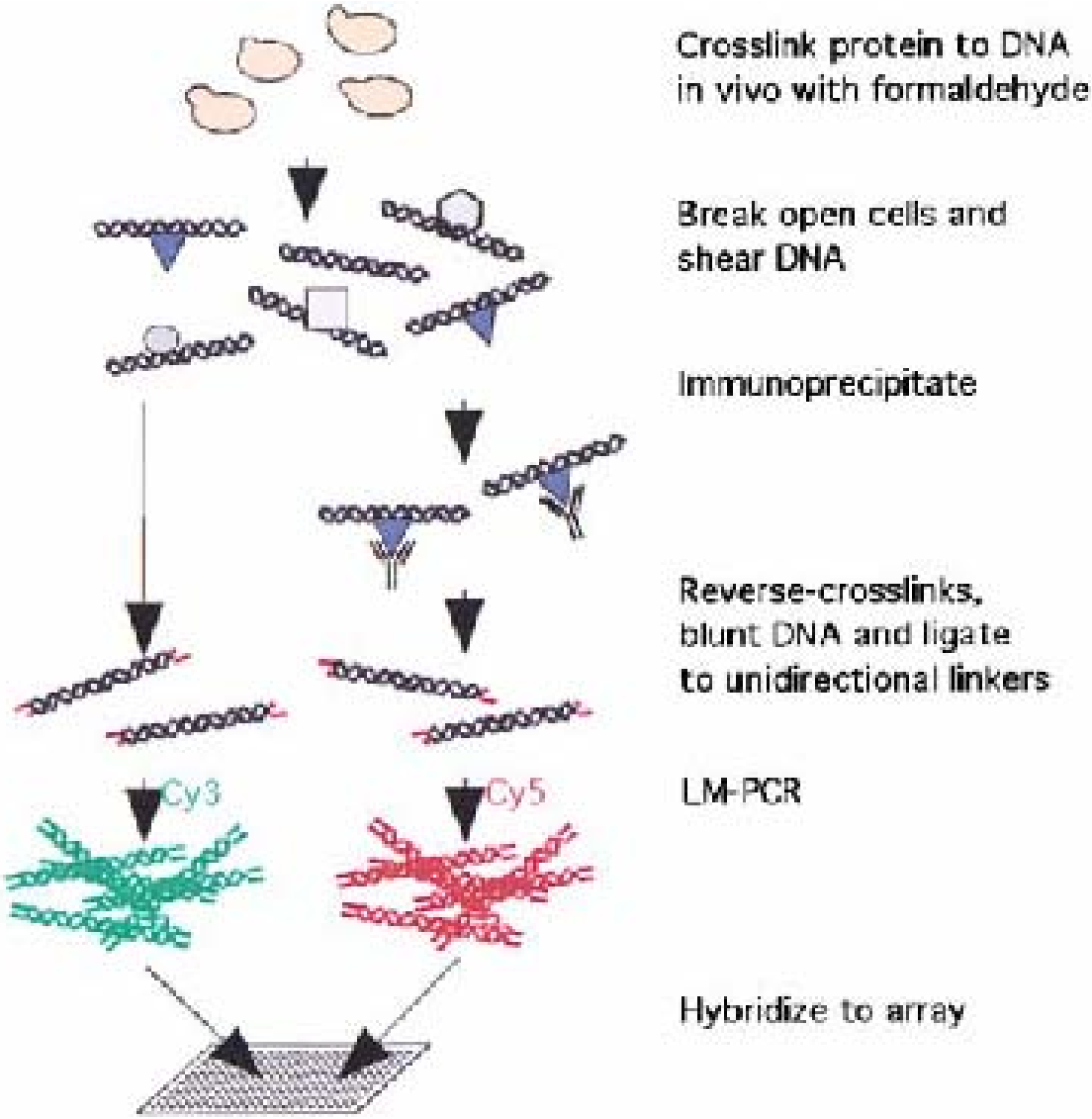
this hypothesis.

Deletion of the genes has been accomplished by an international consortium, the *Saccharomyces* Genome Deletion Project, that has replaced all of the ≈6,200 known open reading frames (ORFs) of yeast by using a PCR-mediated gene deletion strategy (20). In addition to a selectable marker, two molecular bar codes or "'tags," unique 20-base oligonucleotide sequences, are in the replacement cassette. These tags, after PCR amplification, can be detected by hybridization to the corresponding complementary sequence in a high-density oligonucleotide array, thus enabling the relative abundances of each tag, and hence the abundances of each deletion strain, to be determined (20). We have recently shown that this system can detect essentially all of

www.pnas.org/cgi/doi/10.1073/pnas.132275199

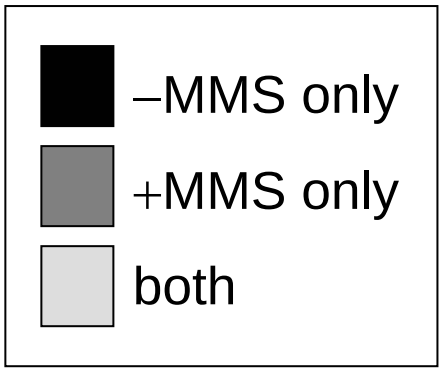
ChIP-chip measurement of protein→DNA interactions

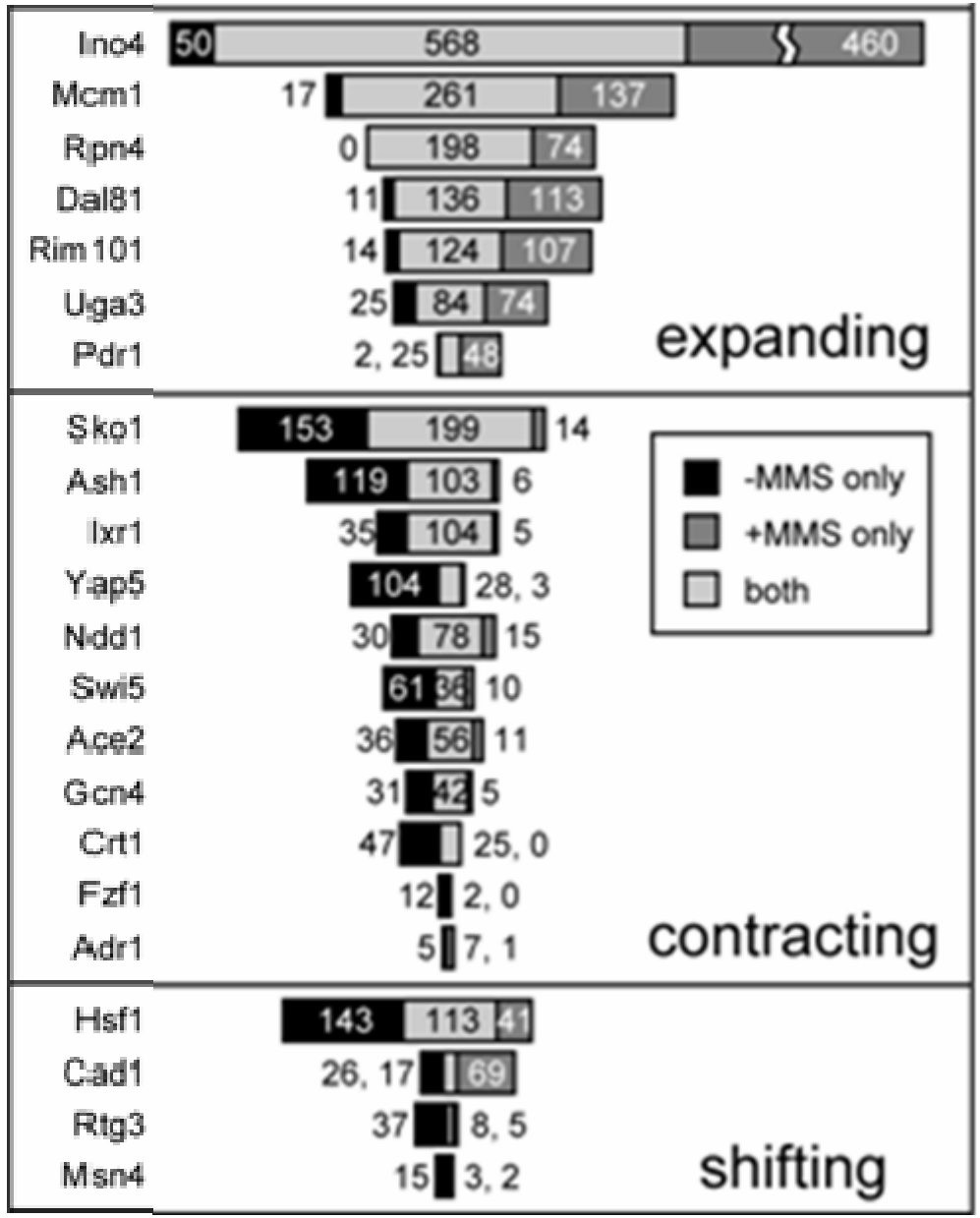


From Figure 1 of Simon et al. *Cell* 2001

A systems approach to mapping DNA damage networks

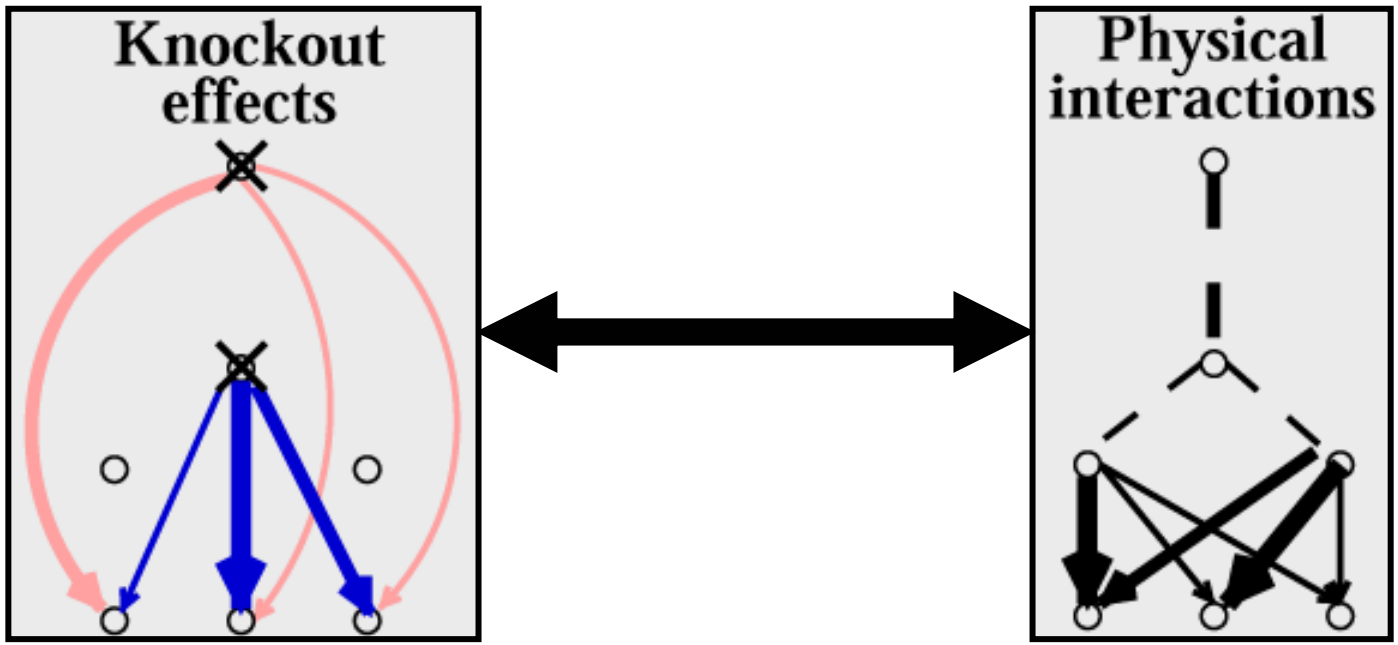
Numbers of promoters bound by each of 30 transcription factors (TFs) before and after exposure to methyl-methane sulfonate (MMS)





Workman, Mak, et al. *Science* 2006

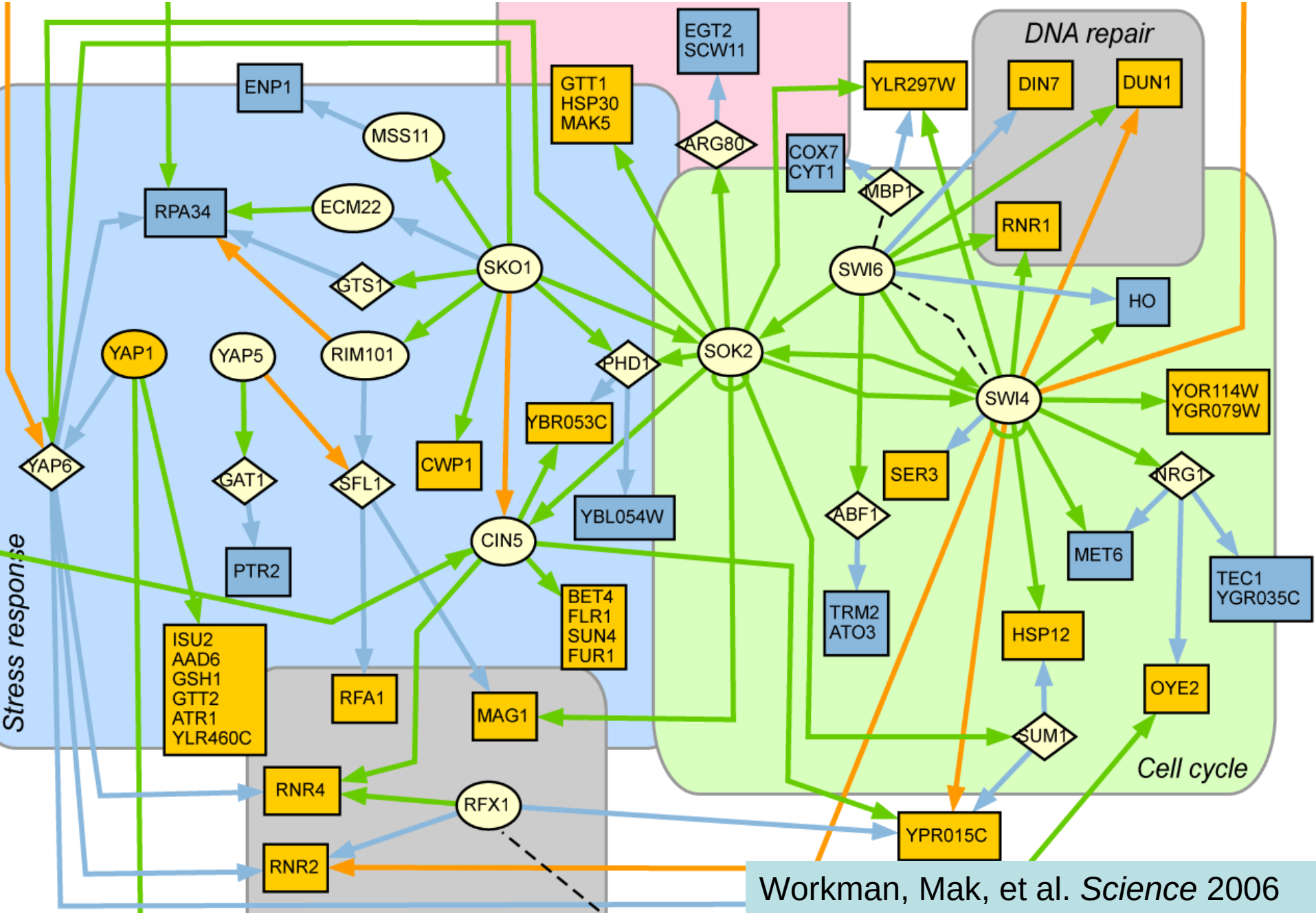
Validation of physical network by systematic gene knockout analysis



Knockout causes up-regulation
Knockout causes down-regulation
TF-promoter binding
Protein-protein binding

Yeang, Mak et al. *Genome Biology* 2005

Validation of binding with knockout data yields a large regulatory network



Workman, Mak, et al. *Science* 2006

Transcriptional response of *Saccharomyces cerevisiae* to DNA-damaging agents does not identify the genes that protect against these agents

Geoff W. Birrell*, James A. Brown*, H. Irene Wu*, Guri Giaever†, Angela M. Chu†, Ronald W. Davis†, and J. Martin Brown*‡

Departments of *Radiation Oncology and †Biochemistry, Stanford University School of Medicine, Stanford, CA 94305

Contributed by Ronald W. Davis, May 8, 2002

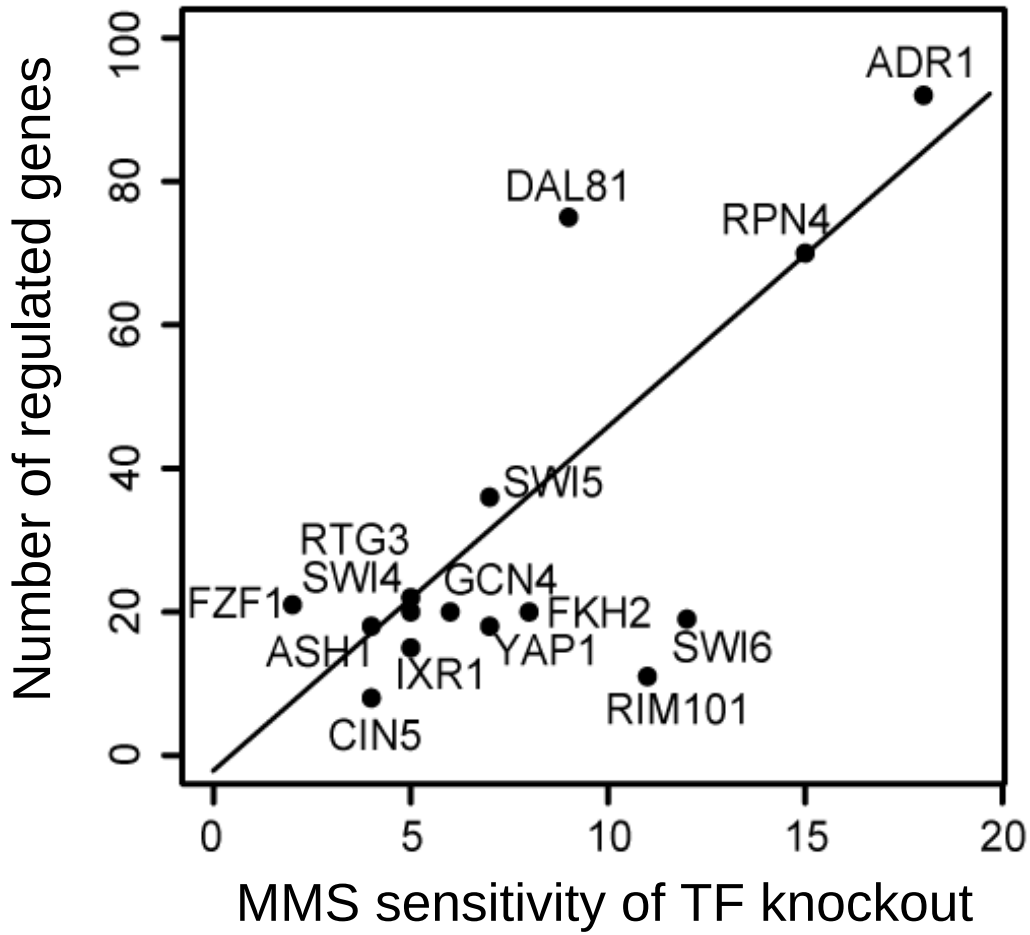
The recent completion of the deletion of all of the nonessential genes in budding yeast has provided a powerful new way of determining those genes that affect the sensitivity of this organism to cytotoxic agents. We have used this system to test the hypothesis that genes whose transcription is increased after DNA damage are important for the survival to that damage. We used a pool of 4,627 diploid strains each with homozygous deletion of a nonessential gene to identify those genes that are important for the survival of yeast to four DNA-damaging agents: ionizing radiation, UV radiation, and exposure to cisplatin or to hydrogen peroxide. In addition we measured the transcriptional response of the wild-type parental strain to the same DNA-damaging agents. We found no relationship between the genes necessary for survival to the DNA-damaging agents and those genes whose transcription is increased after exposure. These data show that few, if any, of the genes involved in repairing the DNA lesions produced in this study, including double-strand breaks, pyrimidine dimers, single-strand breaks, base damage, and DNA cross-links, are induced in response to toxic doses of the agents that produce these lesions. This finding suggests that the enzymes necessary for the repair of these lesions are at sufficient levels within the cell. The data also suggest that the nature of the lesions produced by DNA-damaging agents cannot easily be deduced from gene expression profiling.

conferring resistance to that agent, and hence provide information on its mechanism. Recent publications have, in fact, suggested that several of the genes induced by DNA-damaging agents are involved in the repair of DNA damage and hence in the protection of the cell against such treatments (17–19). However, the assumption that genes whose expression increases in response to a particular cytotoxic agent are those that protect against the damage caused by the agent has not been formally tested. Here we use a pool of strains of budding yeast, *S. cerevisiae*, with deletion of all nonessential genes to directly test this hypothesis.

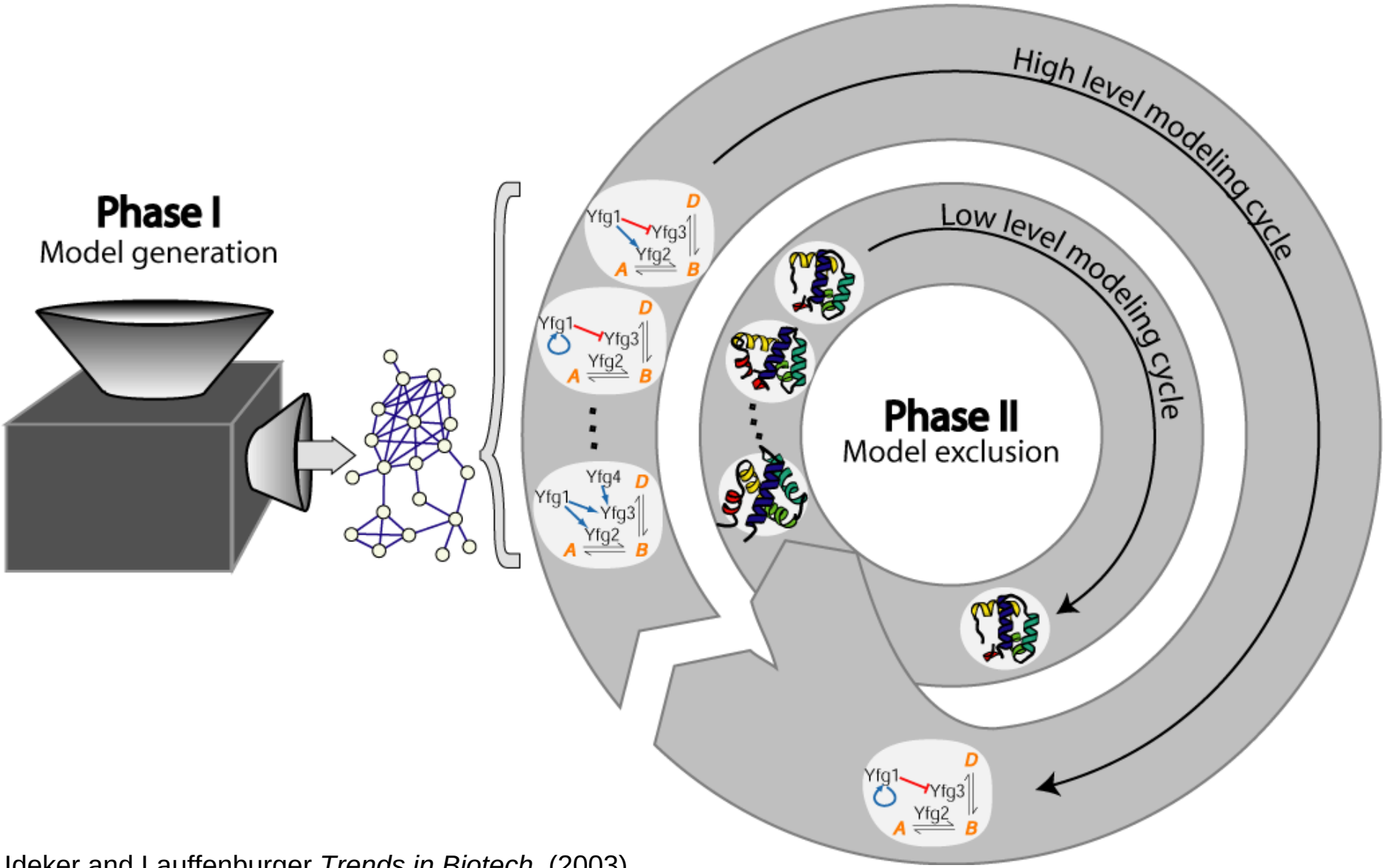
Deletion of the genes has been accomplished by an international consortium, the *Saccharomyces* Genome Deletion Project, that has replaced all of the ≈6,200 known open reading frames (ORFs) of yeast by using a PCR-mediated gene deletion strategy (20). In addition to a selectable marker, two molecular bar codes or "'tags," unique 20-base oligonucleotide sequences, are in the replacement cassette. These tags, after PCR amplification, can be detected by hybridization to the corresponding complementary sequence in a high-density oligonucleotide array, thus enabling the relative abundances of each tag, and hence the abundances of each deletion strain, to be determined (20). We have recently shown that this system can detect essentially all of

www.pnas.org/cgi/doi/10.1073/pnas.132275199

Sensitivity of the TF knockout phenotype correlates with its number of regulated targets



The vision:
First build the scaffold, then add the details



Ideker and Lauffenburger *Trends in Biotech.* (2003)

Network Comparison:
Sourav Bandyopadhyay,
Ryan Kelley,
Silpa Suthram

Collaborators: Roded Sharan (Tel Aviv), Richard Karp (Berkeley)

DNA Damage Networks:
Craig Mak
Chris Workman

Collaborators:
Leona Samson (MIT)
Tom Begley (U Albany)

Funding: Packard Fellowship; NIEHS, NCRR, NIGMS, NIAID, NSF, Unilever

Websites: www.pathblast.org; www.cytoscape.org