
SIAM San Diego
Trey Ideker
July 11 2008
Network Biology: Mapping pathways to understand and diagnose disease

Many kinds of interaction technologies

	PHYSICAL	**GENETIC**
ORDERED Cause and effect Signal transducing	Protein-gene (transcriptional, ChIP-Chip[22, 39]) Protein-RNA (RIP-chip[80]) Protein-protein (kinase-substrate arrays[21], *LUMIER*[81]) Protein-compound[82]	Epistatic orderings *a* < *b* OR *b* < *a* (EMAP[28, 83]) Knock-down expression profiles (RNAi[32], deletion mutants[36, 37]) Expression QTLs[41, 42]
UNORDERED Ambiguous directionality	Protein-protein (co-IP/MS/MS[18-20], Y2H[15, 84-86]) Gene-gene (co-regulon[87])	Synthetic lethality *ab* << *a*, *b, wt* (SGA[88], dSLAM[31, 71], EMAP[28, 83], chemogenomic profiling[89])

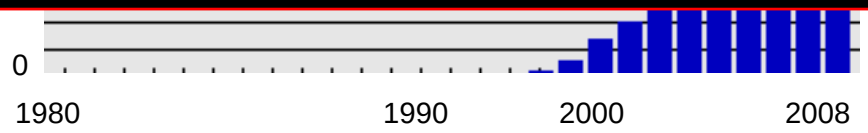
Beyer, Bandyopadhyay, and Ideker *Nat. Rev. Genetics* (2007)

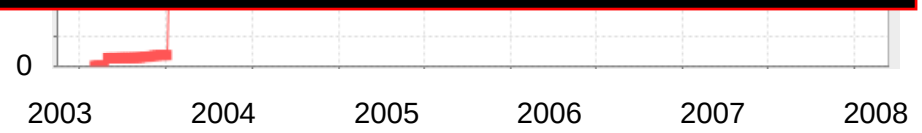
Like sequence, molecular interaction

Two overriding aims: g…

1) Assemble many interactions and types into unified models

2) Get rid of false and non-functional interactions





These aims lead to many subproblems

- ✓ Mapping transcriptional networks
- ✓ Networks to interpret genetic variations
- ✓ Networks to interpret combinatorial perturbations (e.g. synthetic lethals)
- ✓ Network evolution
- ✓ Network-based diagnosis

Assembly of physical and genetic interactions to map transcriptional circuits

(Chris Workman, Craig Mak with Leona Samson, Richard Kolodner)

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

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

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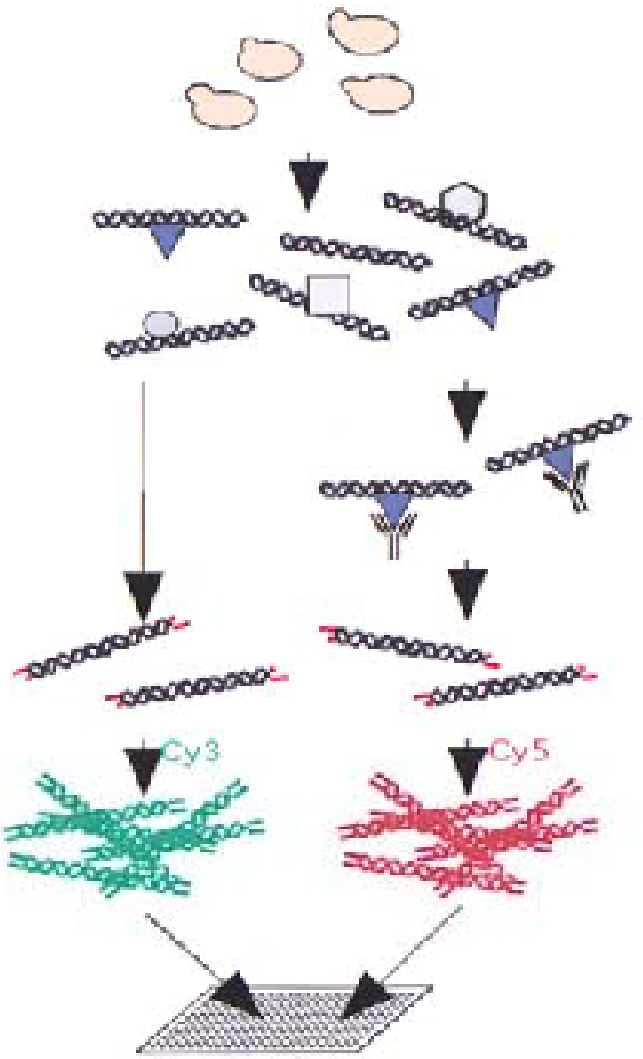
Deletion of the genes has been accomplished by an international consortium, the *Saccharomyces* Genome Deletion Project, that has replaced all of the ≈6,200 known open reading frames (ORFs) of yeast by using a PCR-mediated gene deletion strategy (20). In addition to a selectable marker, two molecular 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



Crosslink protein to DNA
in vivo with formaldehyde

Break open cells and
shear DNA

Immunoprecipitate

Reverse-crosslinks,
blunt DNA and ligate
to unidirectional linkers

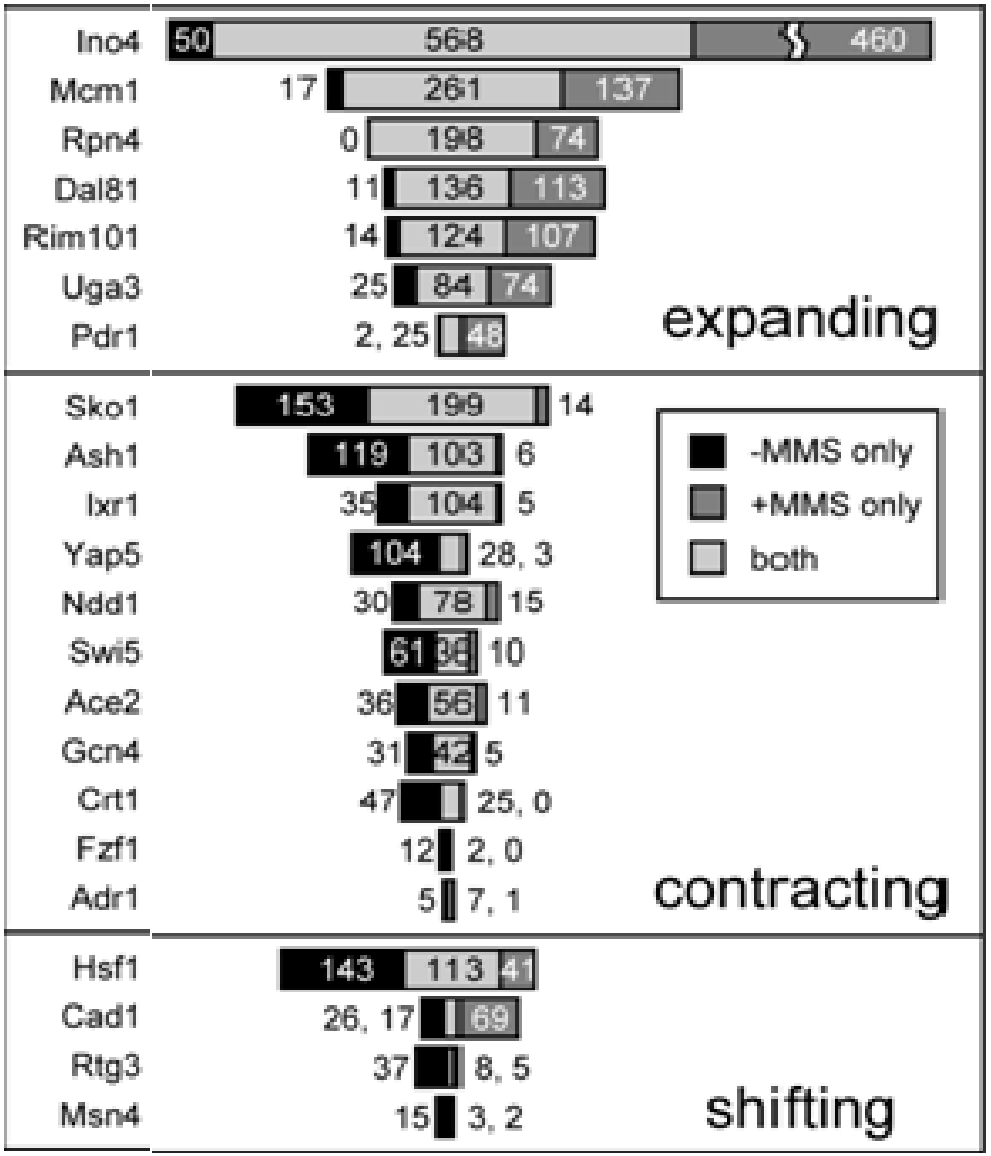
LM-PCR

Hybridize to array

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

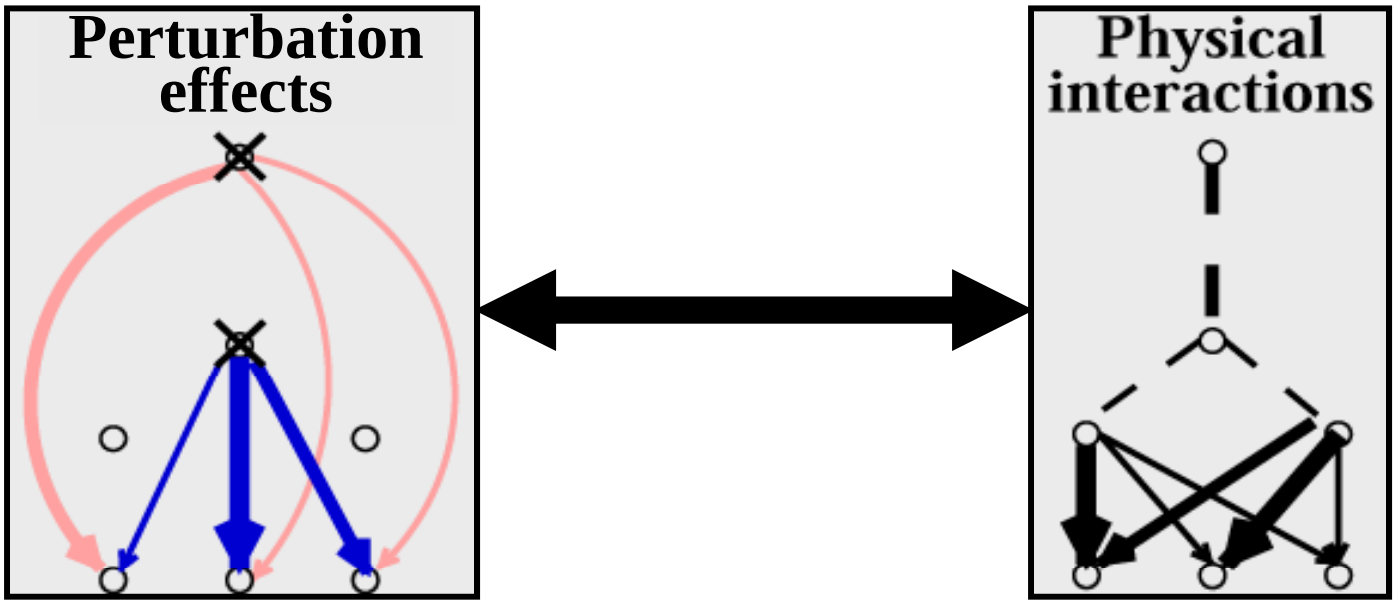
Mapping DNA Damage Response Networks

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

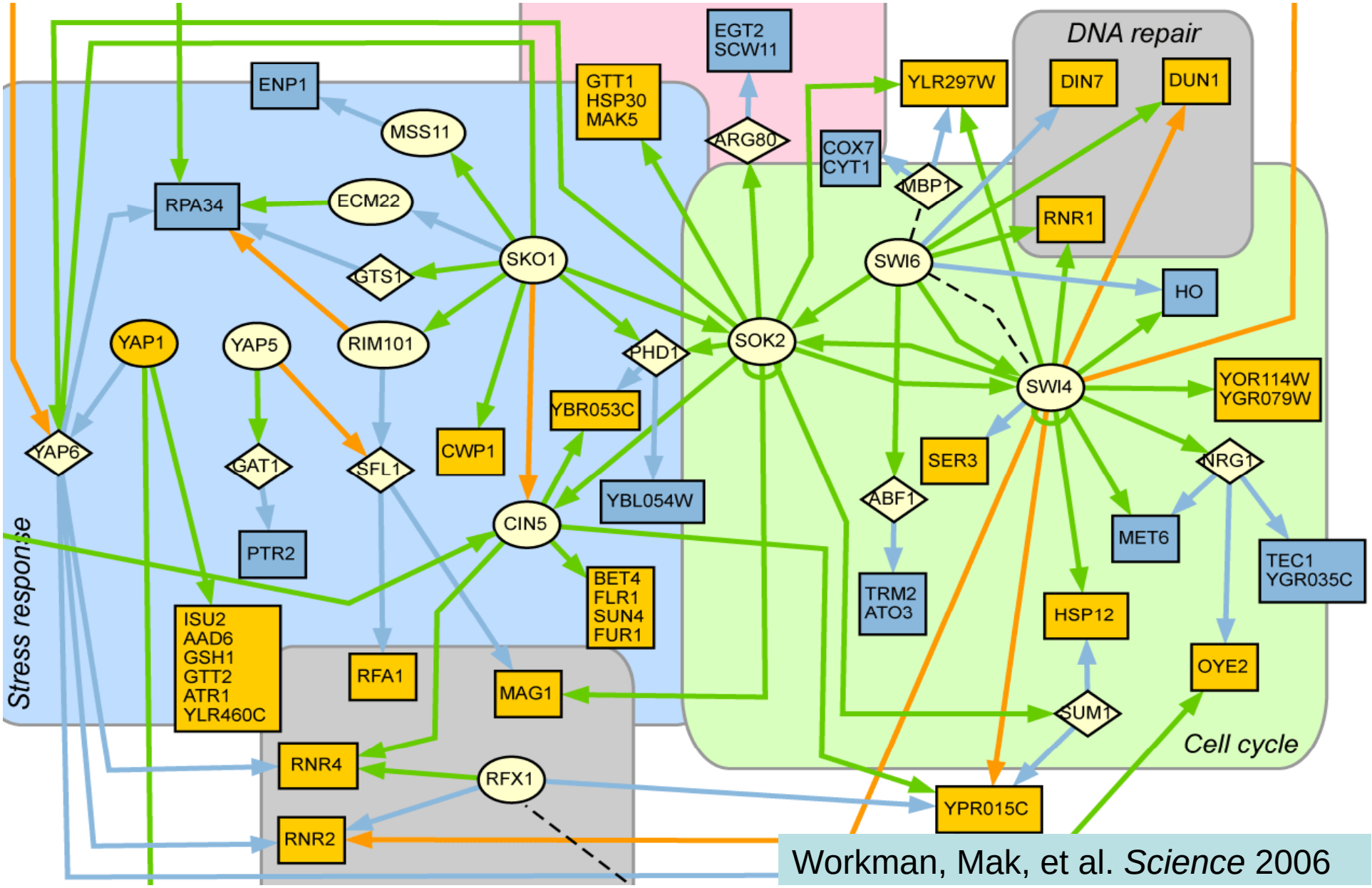
Integration of cause-and-effect interactions with physical networks



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

Yeang, Mak et al. *Genome Biology* 2005

Such methods can yield large regulatory networks



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

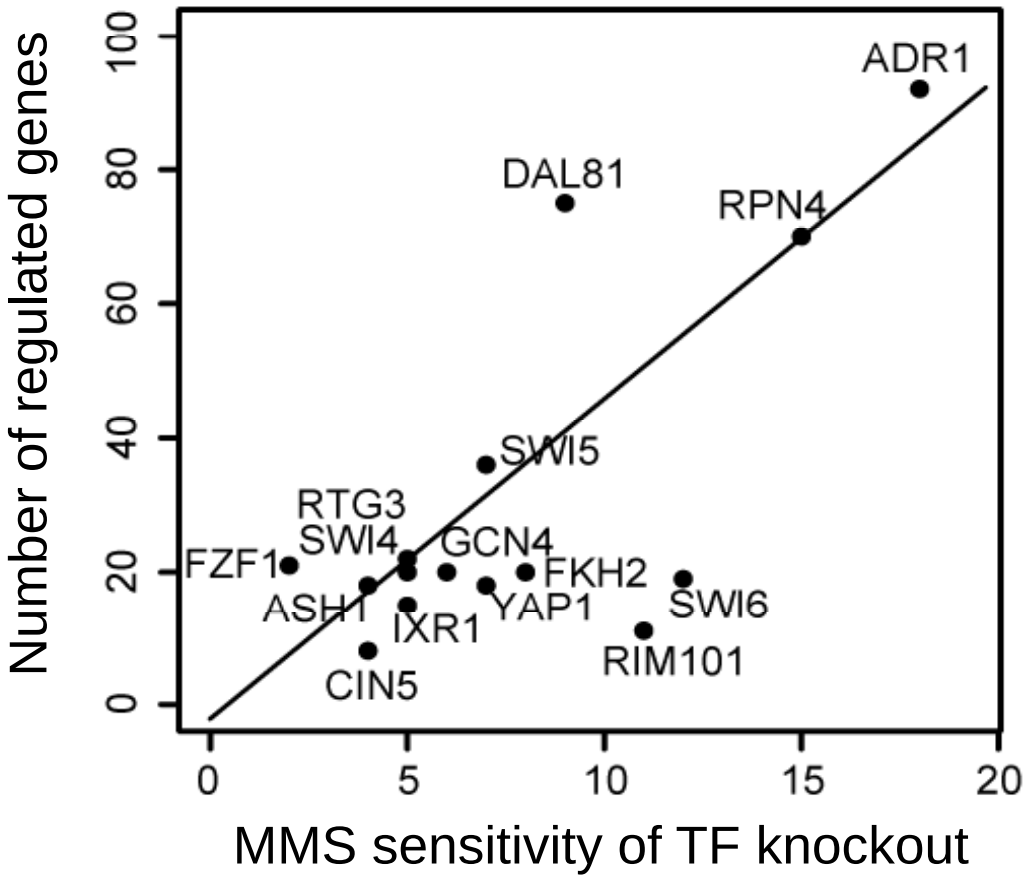
The recent completion of the deletion of all of the nonessential genes in budding yeast has provided a powerful new way of determining those genes that affect the sensitivity of this organism to cytotoxic agents. We have used this system to test the hypothesis that genes whose transcription is increased 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



Mapping Pathways in Synthetic Lethal Networks

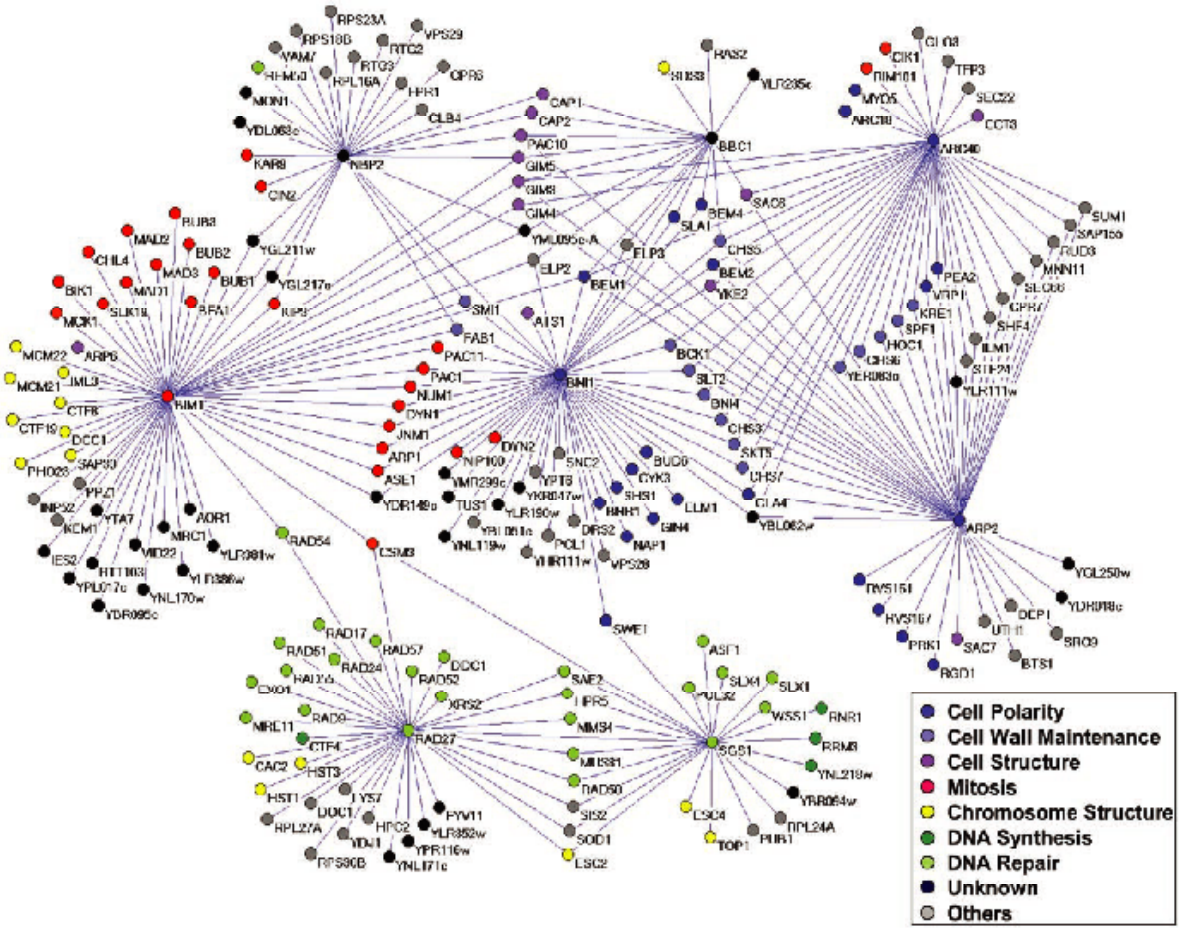
(Ryan Kelley, Sourav Bandyopadhyay
with Nevan Krogan)

Finding physical pathways to explain genetic interactions

Genetic Interactions:

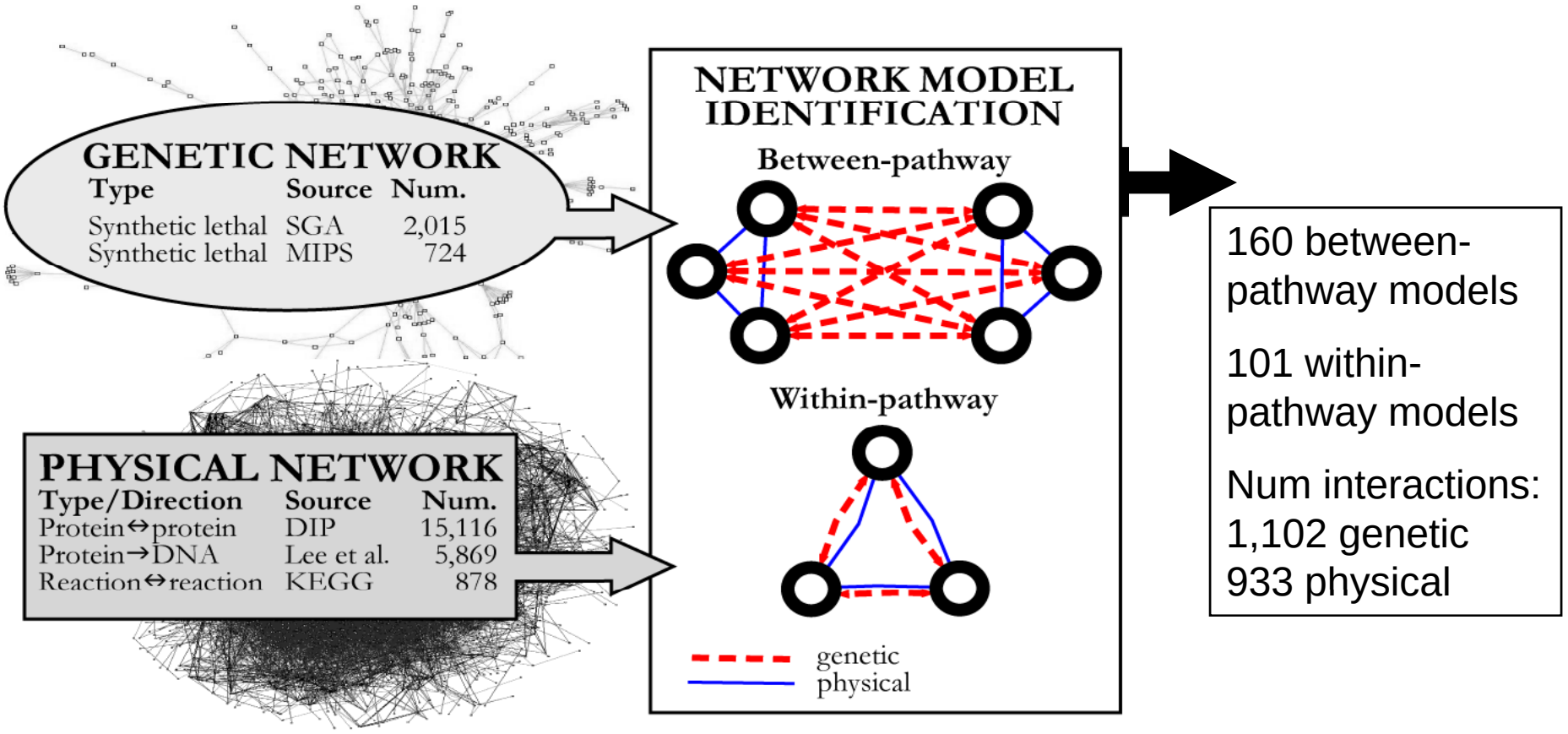
- Classical method used to map pathways in model species
- Highly analogous to multi-genic interaction in human disease and combination therapy
- Thousands are being uncovered through systematic studies

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



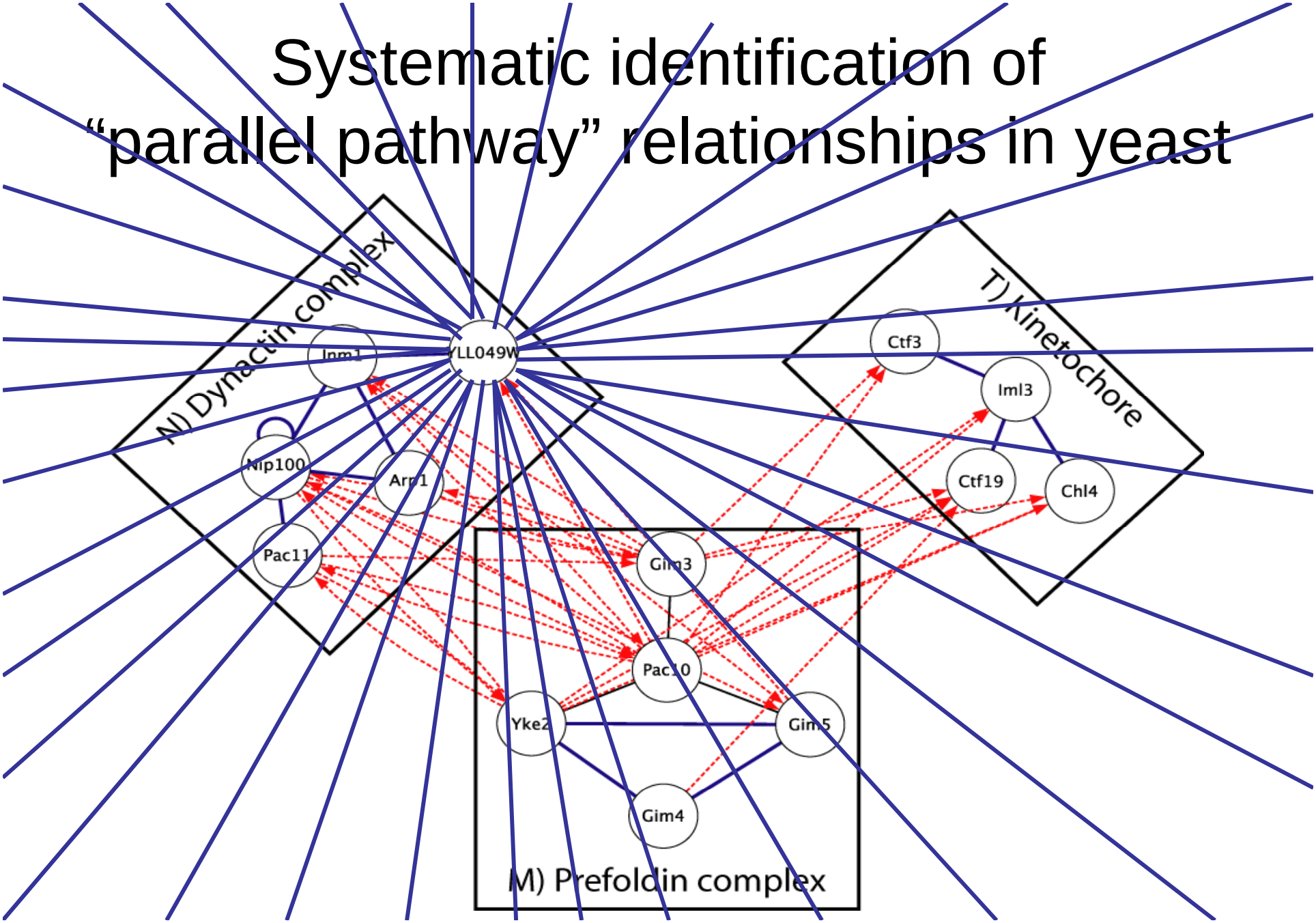
Adapted from Tong *et al.*, *Science* 2001

Integration of genetic and physical interactions

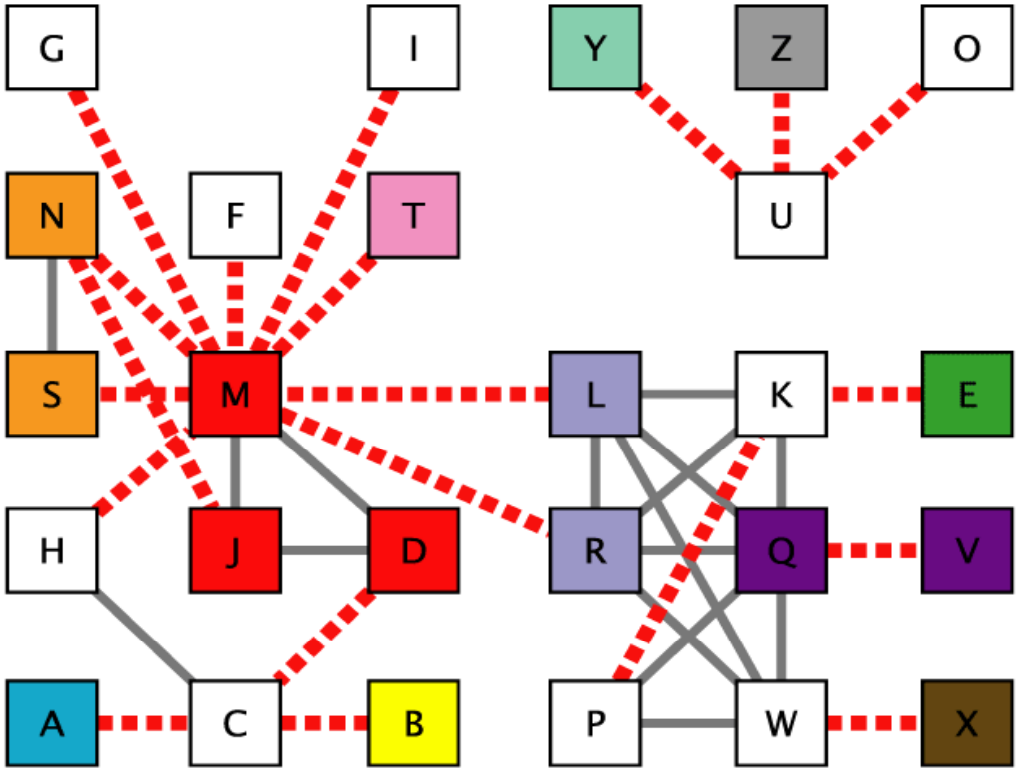


Kelley and Ideker *Nature Biotechnology (*2005)

Systematic identification of "parallel pathway" relationships in yeast



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



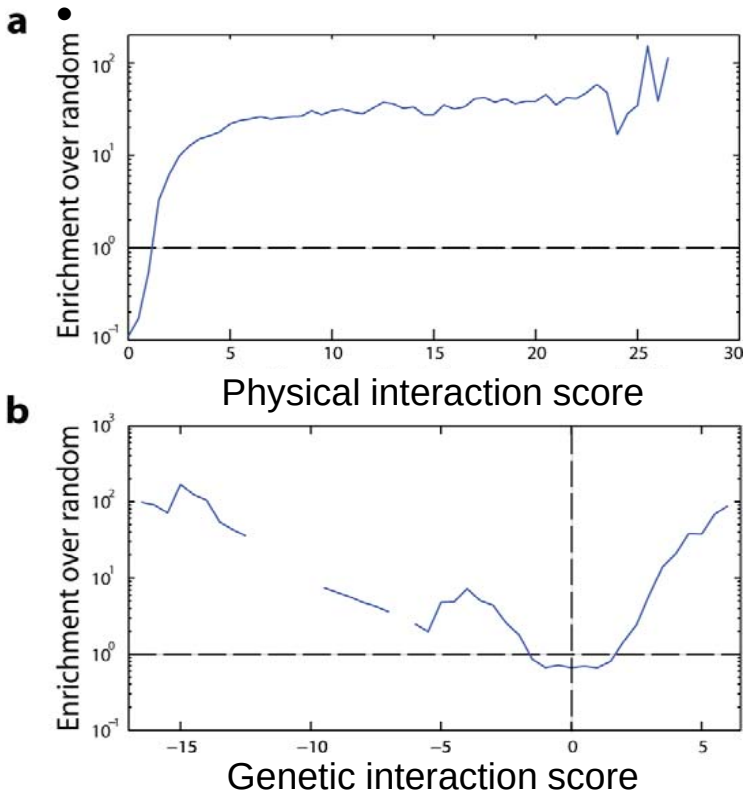
Bridging genetic interactions

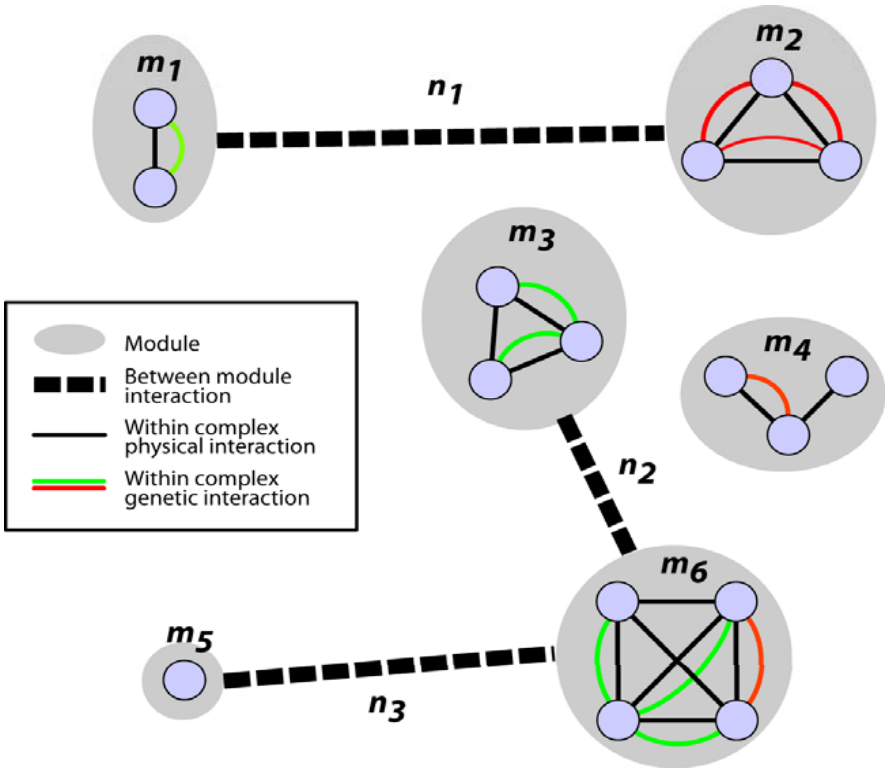
Overlapping pathways

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

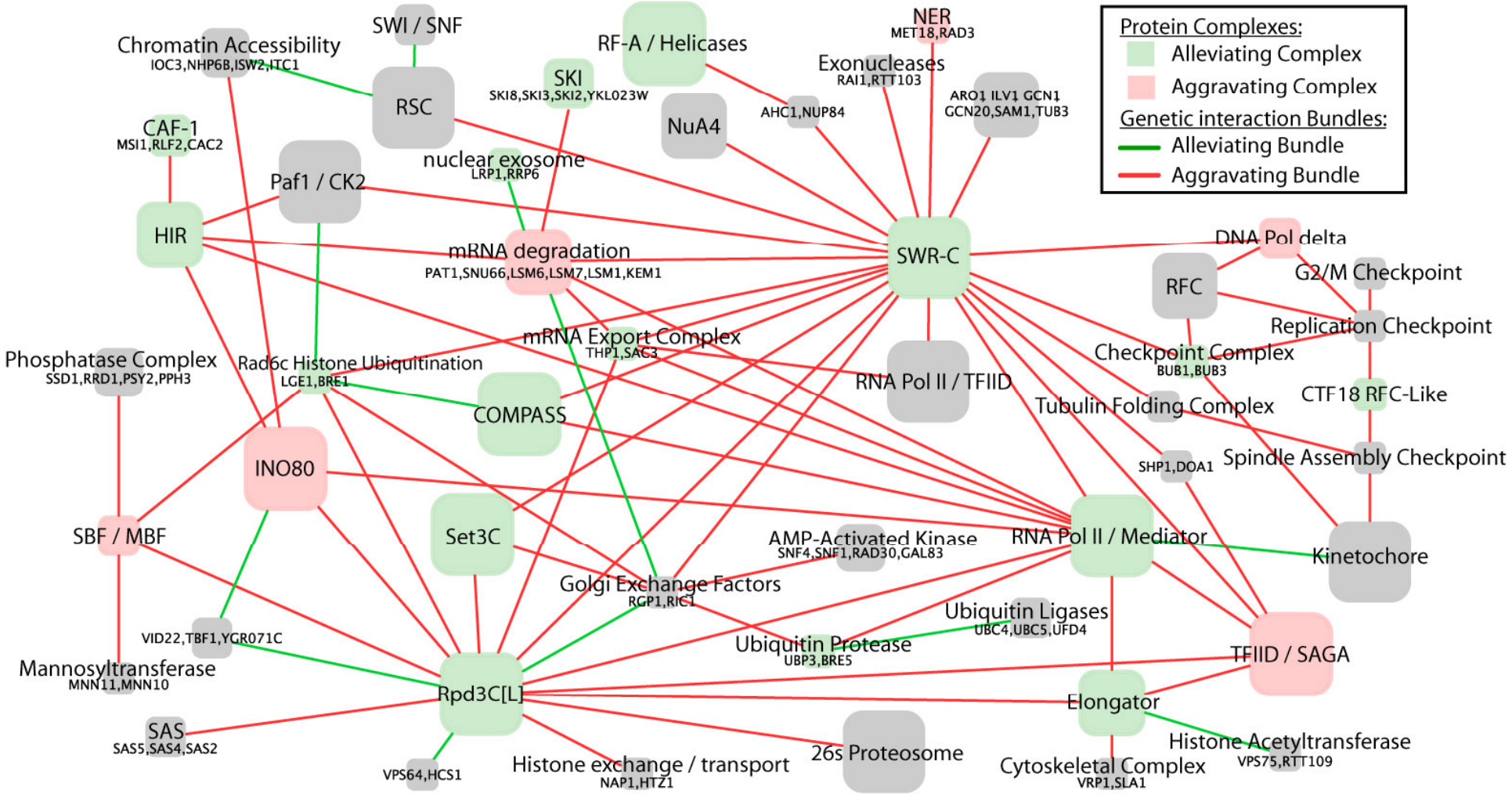
Towards a generative module map

- Use generative model of cell which considers *k* modules simultaneously along with their inter-module functional relationships.
- Consider both positive and negative quantitative genetic interactions (alleviating and aggravating)





Functional maps of protein complexes



with Nevan Krogan

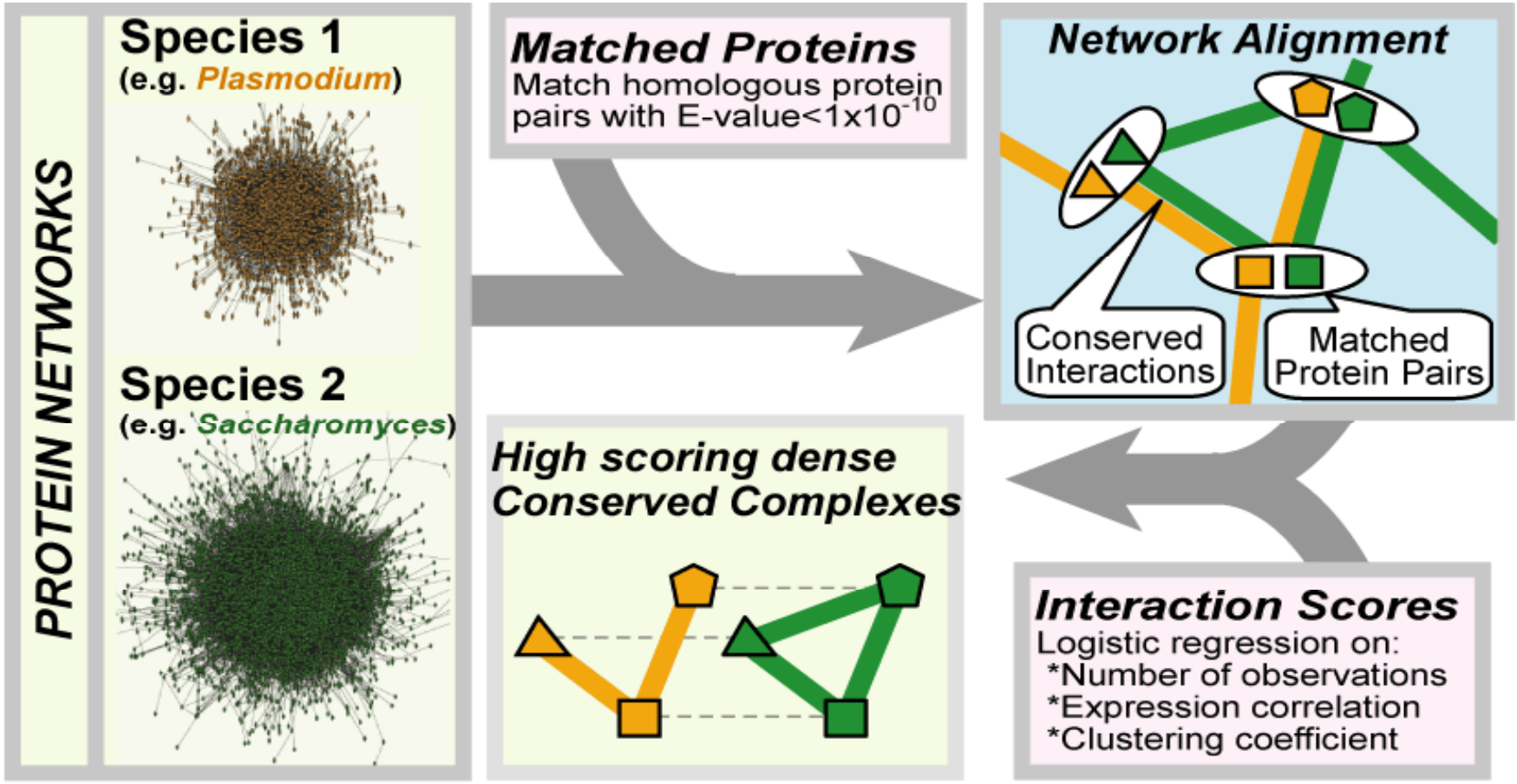
Using protein networks to understand molecular evolution

(with Roded Sharan, Richard Karp, and others)

Cross-comparison of networks:

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

(2) Conserved regions across different species

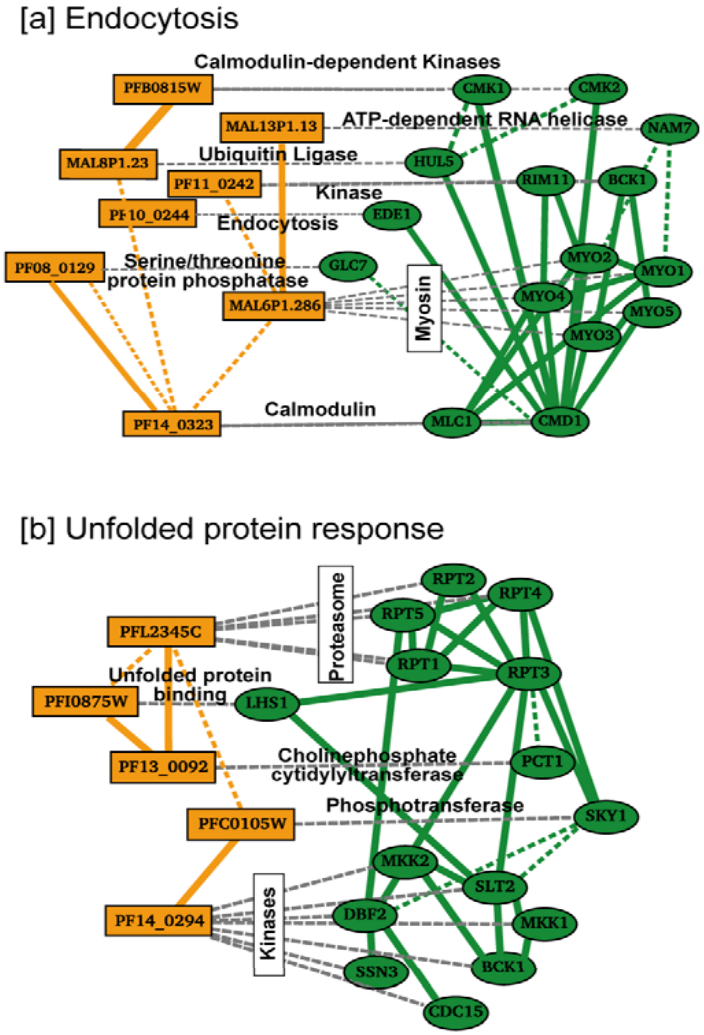


Kelley et al. *PNAS* 2003
Ideker & Sharan *Gen Res* 2008

Suthram et al. *Nature* 2005
Sharan & Ideker *Nat. Biotech.* 2006

Sharan et al. *RECOMB* 2004
Scott et al. *RECOMB* 2005

Plasmodium: a network apart?

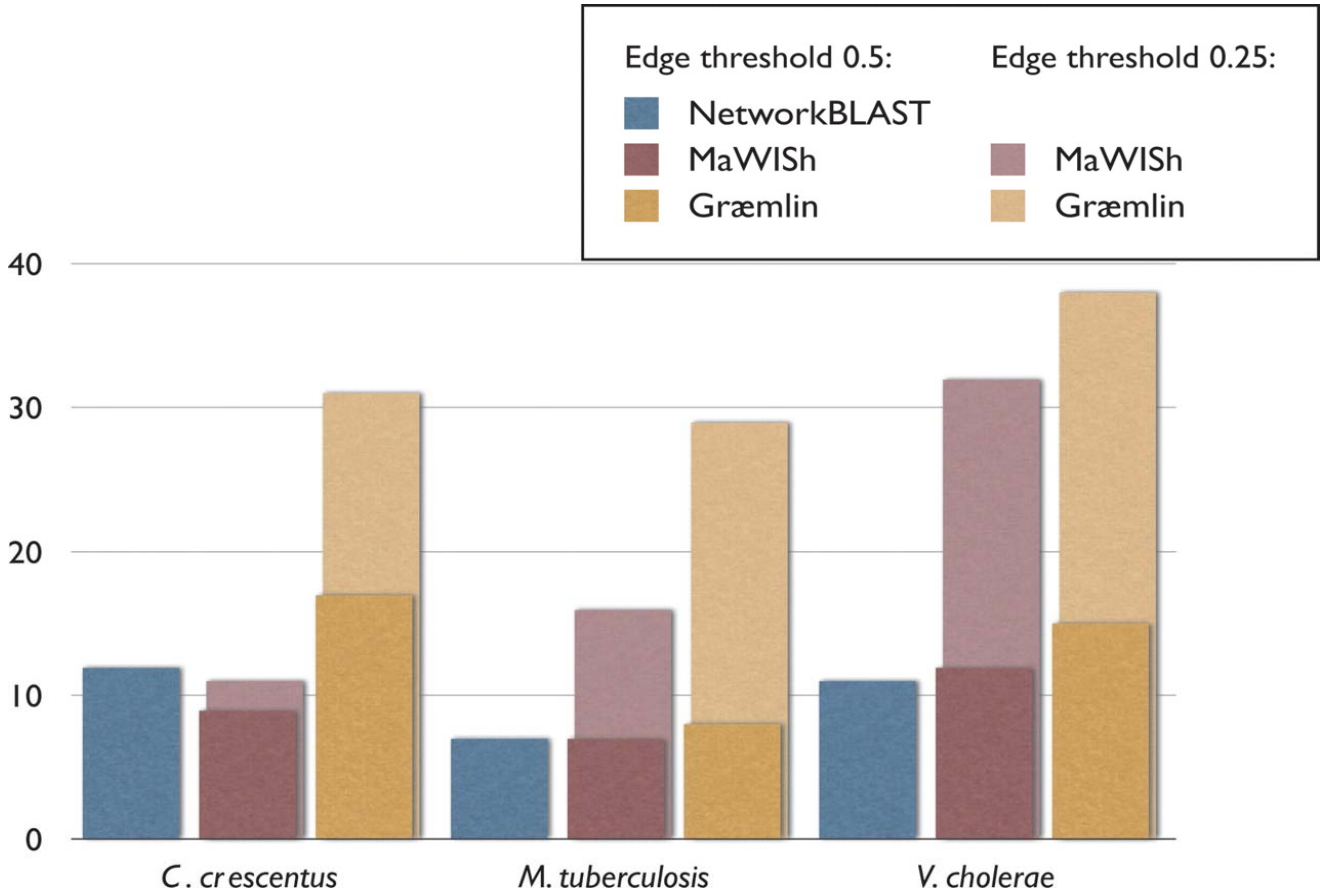


Conserved *Plasmodium* / *Saccharomyces* protein complexes

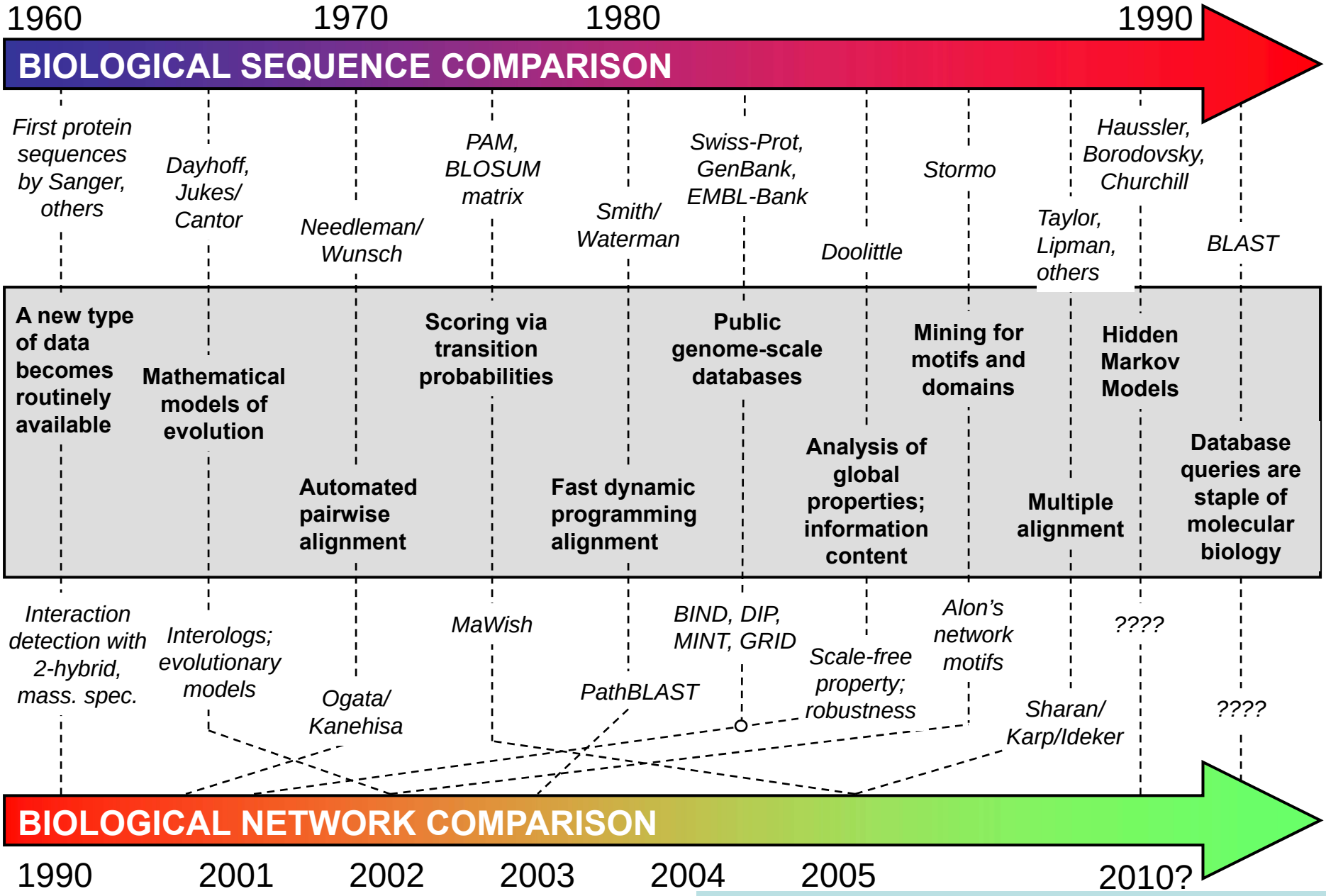
Plasmodium-specific protein complexes

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

Pairwise alignment of the *E. coli* protein network versus the indicated species; Sensitivity comparison of different methods



Flannick et al. *Genome Research* (2006) [Batzoglou Lab]

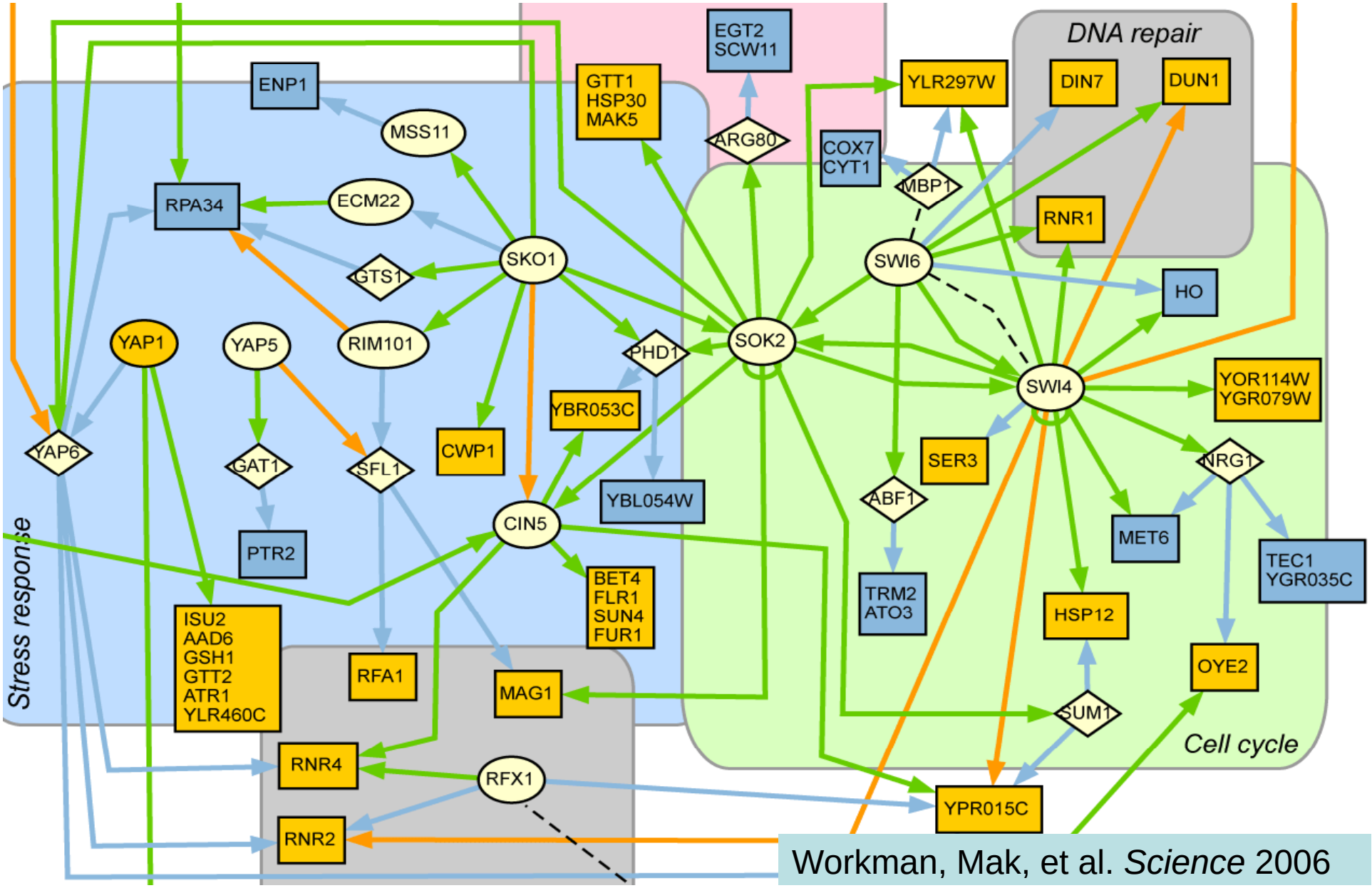


Sharan and Ideker *Nat. Biotech* (2006)

Using protein networks for disease classification

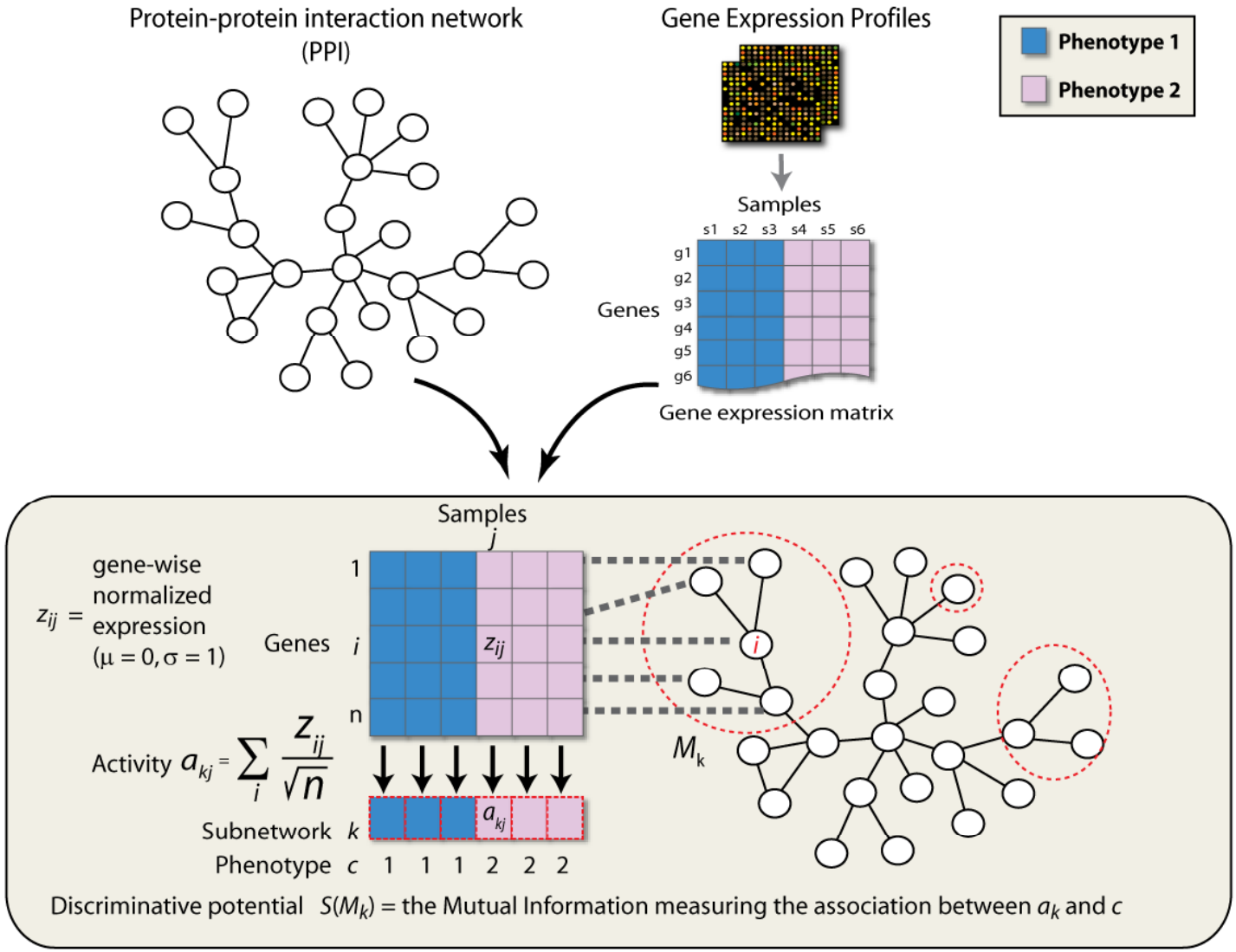
(Han Yu Chuang)

Such methods can yield large regulatory networks

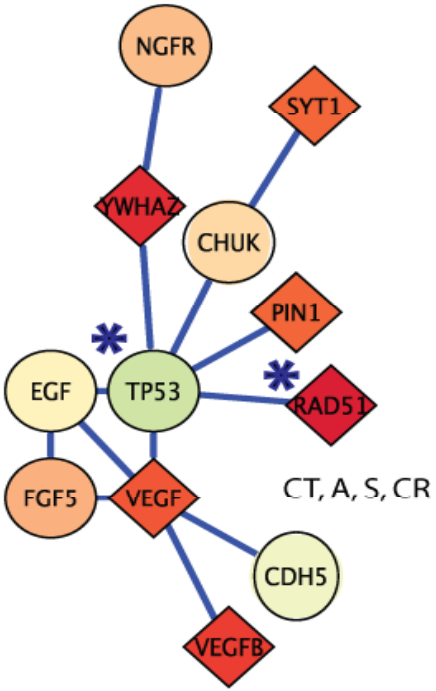


Workman, Mak, et al. *Science* 2006

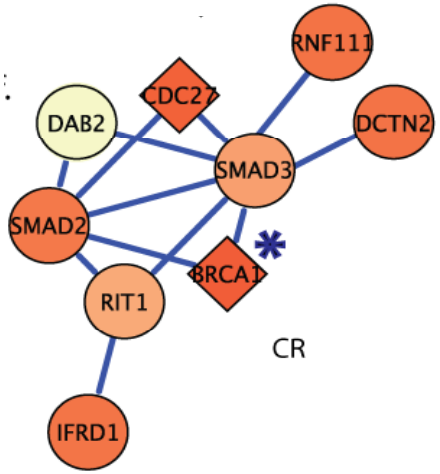
Using protein networks to diagnose breast cancer metastasis



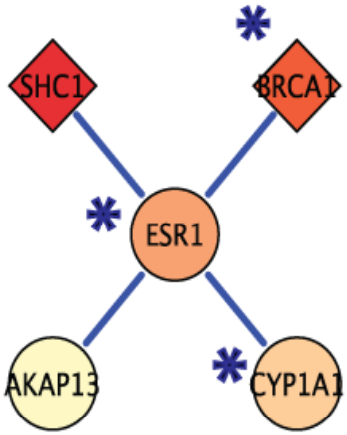
Examples of “informative subnetworks”



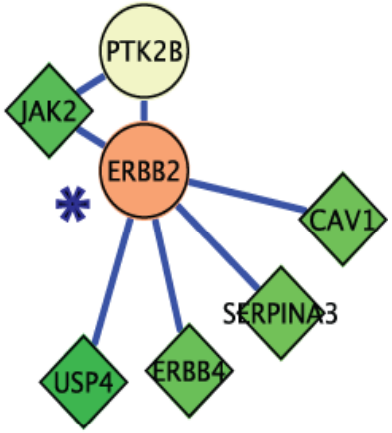
CT, A, S, CR



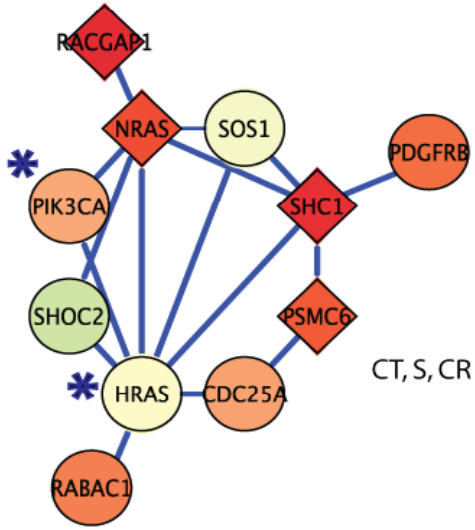
CR



CR

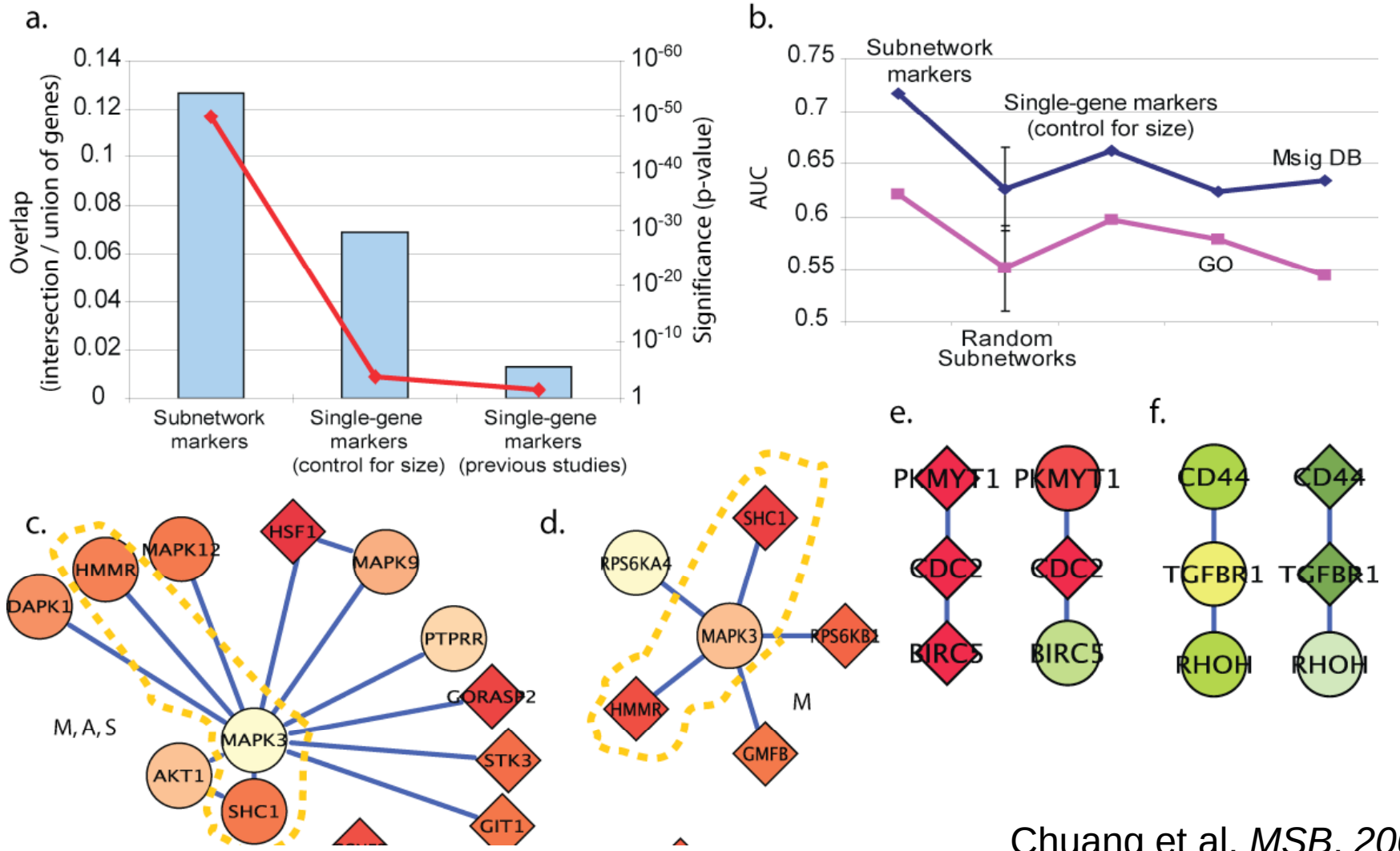


M, S, CR



CT, S, CR

Network markers are more reproducible and increase classification accuracy of breast cancer metastasis



Chuang et al. *MSB*, *2007*

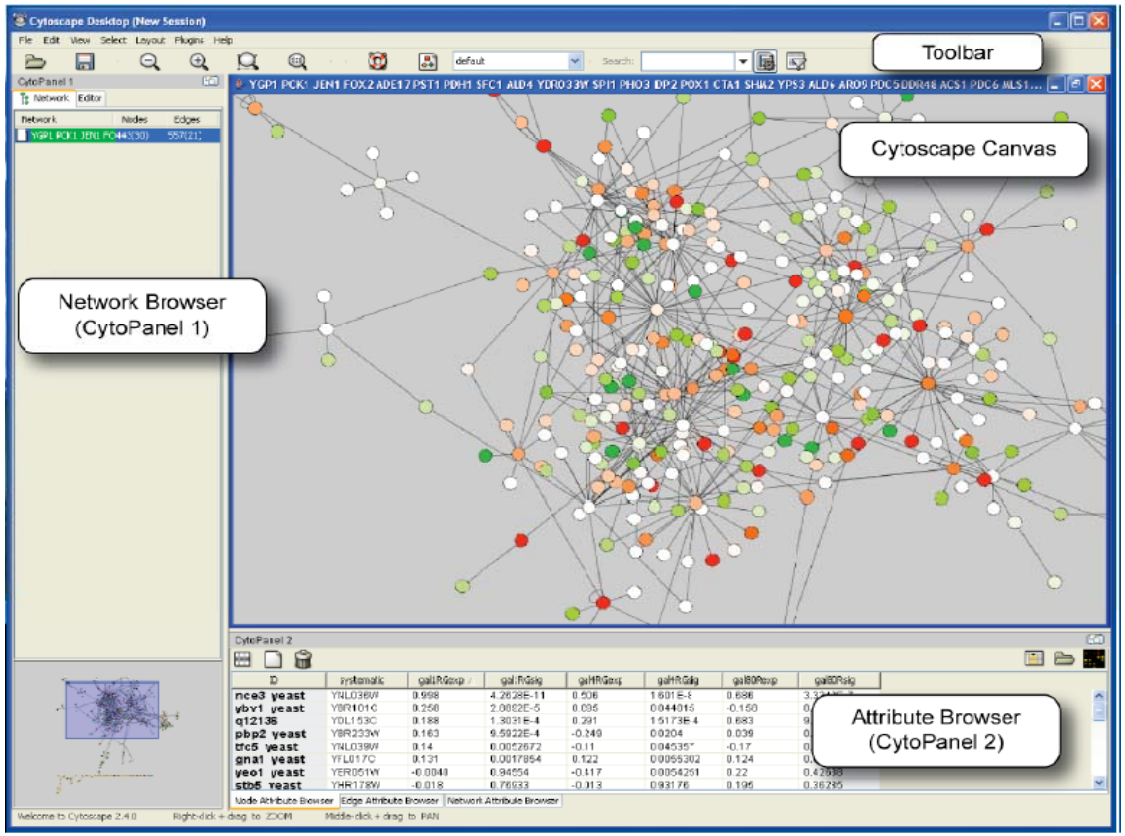
www.cytoscape.org

OPEN SOURCE Java platform for integration of systems biology data

•Layout and query of interaction networks (physical and genetic)

•Visual and programmatic integration of molecular state data (attributes)

•The ultimate goal is to provide the tools to facilitate all aspects of pathway assembly and annotation.



RECENT NEWS

•Version 2.5 released Summer 2007; Scalability+efficiency now equivalent to best commercial packages

•The Cytoscape Consortium is a 501(c)3 non-for-profit in the State of California

•The Cytoscape ® Registered Trademark awarded

JOINTLY CODED with Agilent, ISB, Pasteur, Sloan-Kettering, UCSF, Unilever, U Toronto

DNA Damage Networks

Chris Workman
Craig Mak
Leona Samson (MIT)
Tom Begley (U Albany)

Network Evolution:

Silpa Suthram
Roded Sharan (Tel Aviv)
Richard Karp (Berkeley)

Genetic Interactions:

Ryan Kelley,
Sourav Bandyopadhyay,
Nev Krogan (UCSF)

Interpretation of eQTLs:

Silpa Suthram
Andreas Beyer
Yonina Eldar (Technion)
Richard Karp (Berkeley)

Cancer Diagnosis:

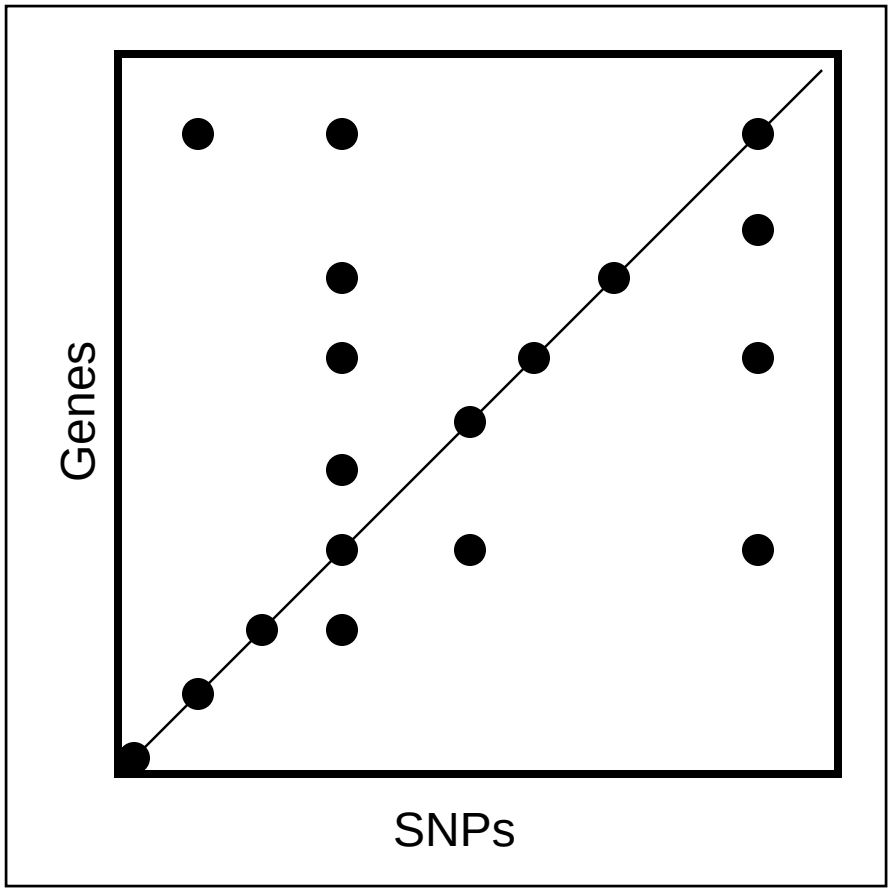
Han Yu Chuang,
Steve Briggs,
Tom Kipps,
Eunjun Lee (KAIST),
Doheon Lee (KAIST)

Funding: NIEHS, NIGMS, NSF, Packard, Agilent, Unilever

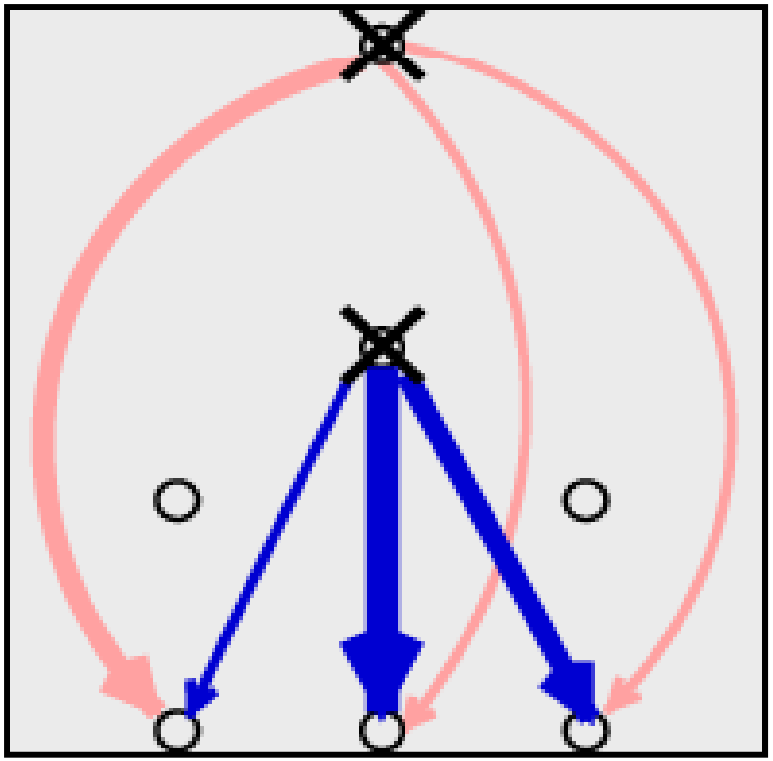
Websites: www.pathblast.org; www.cytoscape.org

Networks perturbed by individual genetic variations

(Silpa Suthram)


Genes
SNPs

Cause and effect interactions



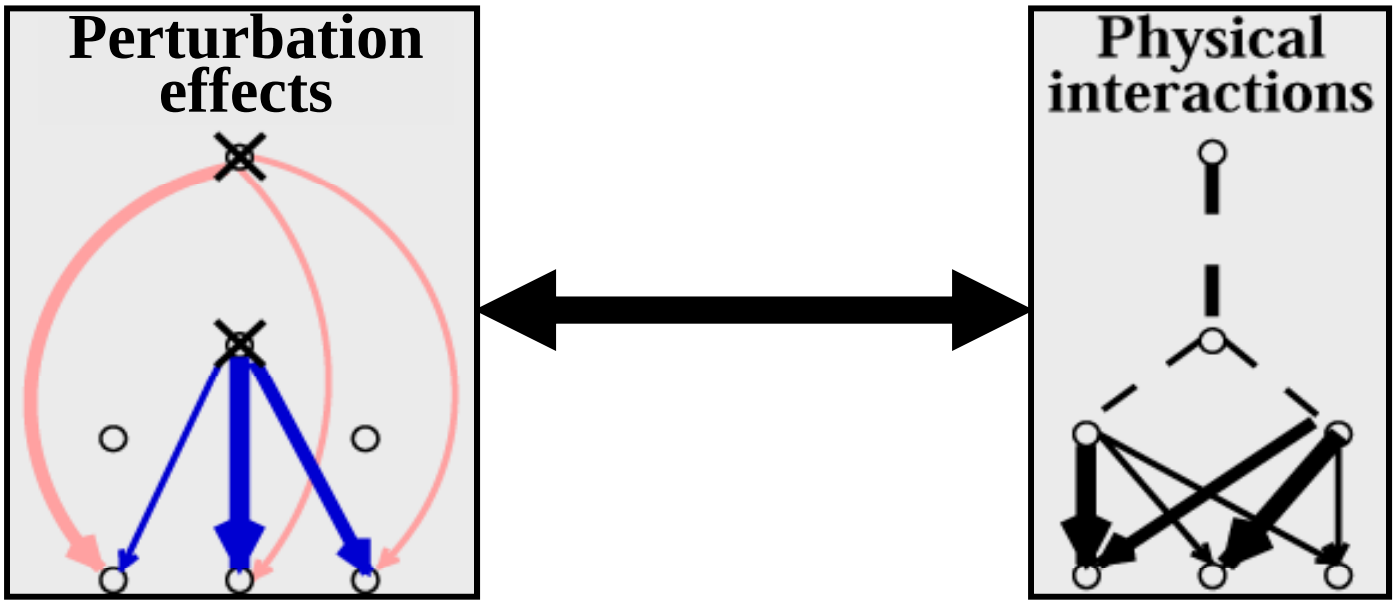
Knock-down expression profiles
(RNAi, deletion mutants)

OR

Expression QTLs

Knockout causes up-regulation
Knockout causes down-regulation

Integration of cause-and-effect interactions with physical networks



Perturbation causes up-regulation
Perturbation causes down-regulation
TF-promoter binding
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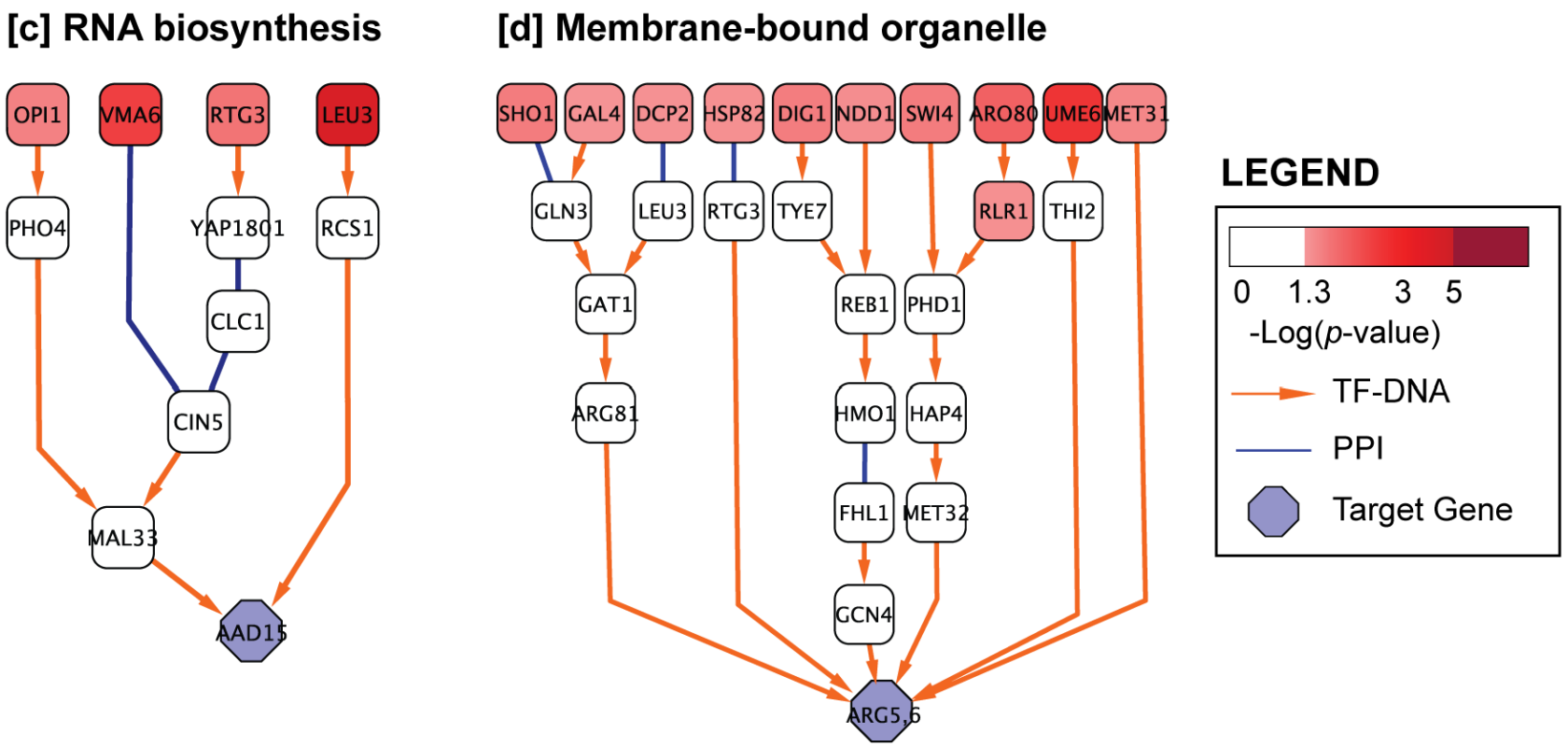
Yeang, Mak et al. *Genome Biology* 2005

Examples



Silpa Suthram

Suthram et al. *Nature/EMBO MSB* 2008