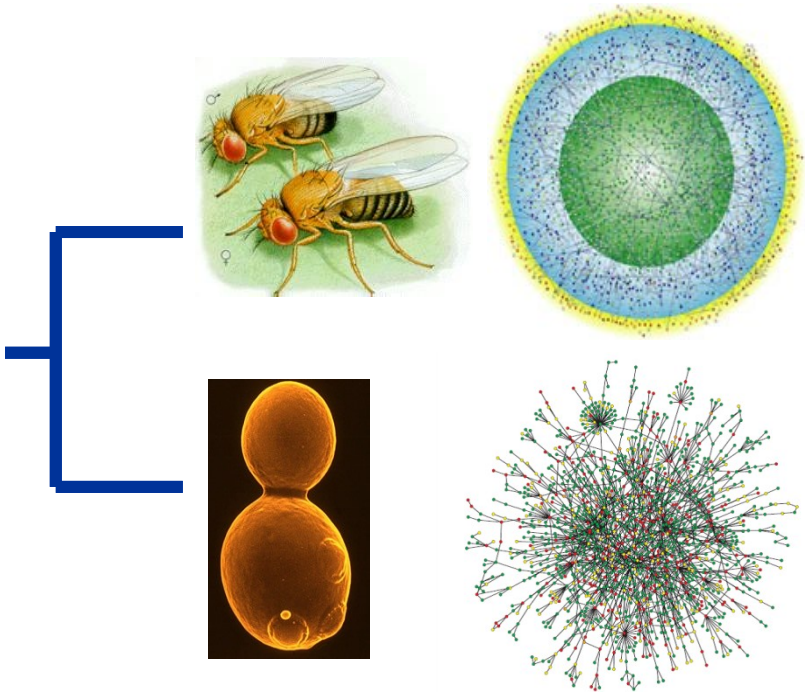
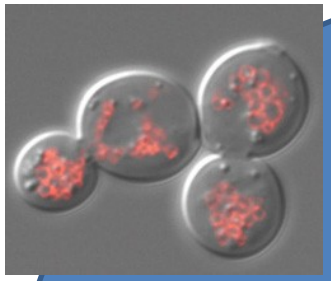
Comparative Interactomics

comparative genomics of high throughput data between species and evolution of function

- Function prediction,
  - for what aspects of function from model organism to e.g. human is orthology equals function “true”
- Evolution of function
- Some studies suggest interactions evolve quite rapidly between species, e,g, only 10% overlap fly-yeast (Suthram et al. Nature 2005)
- What happens to the function of duplications

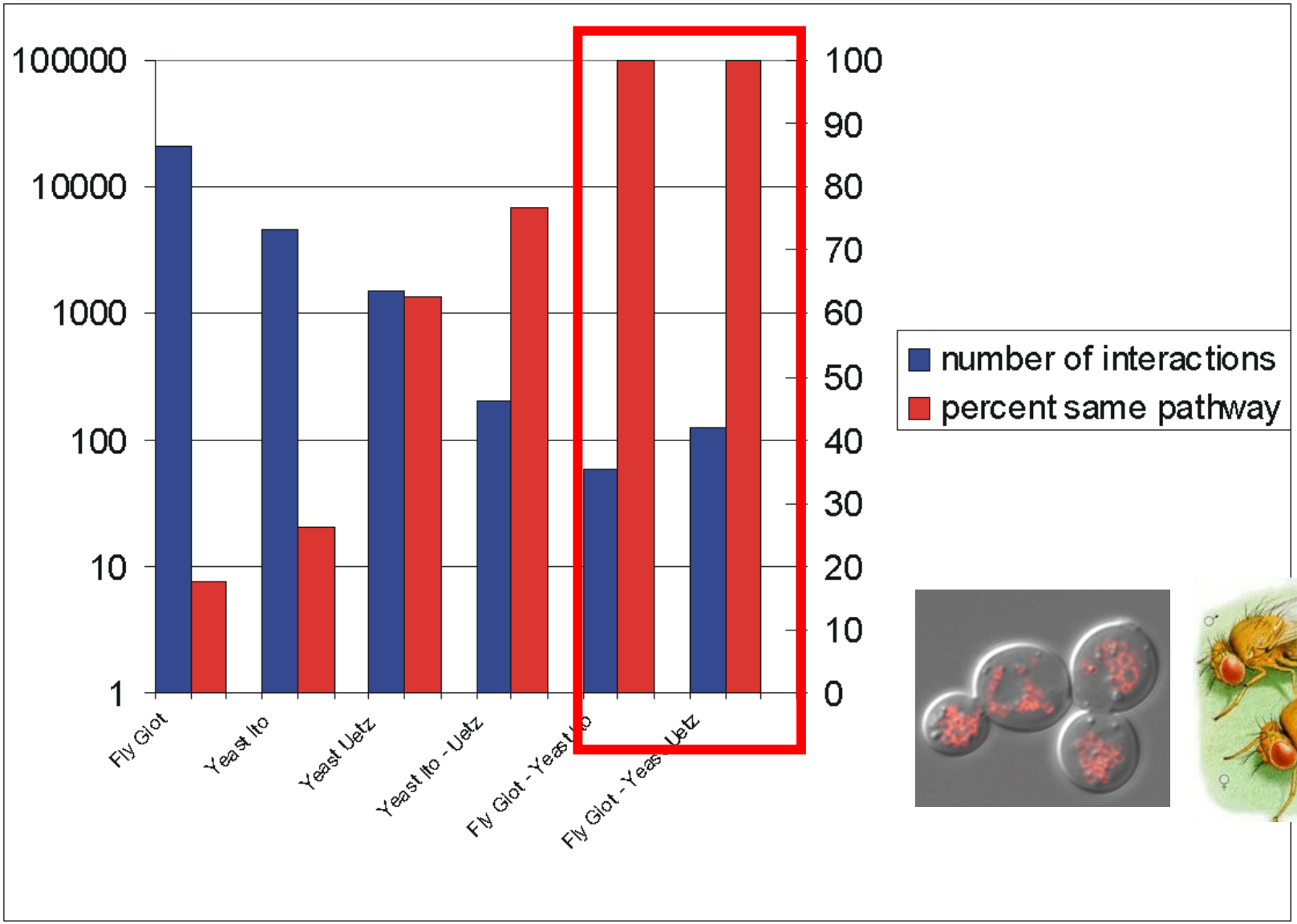


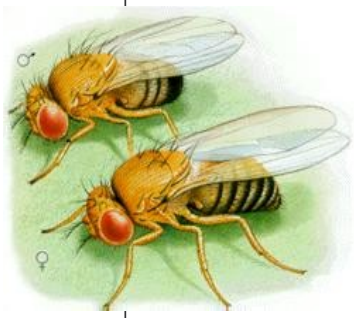
Integration between species / conservation



orthologs

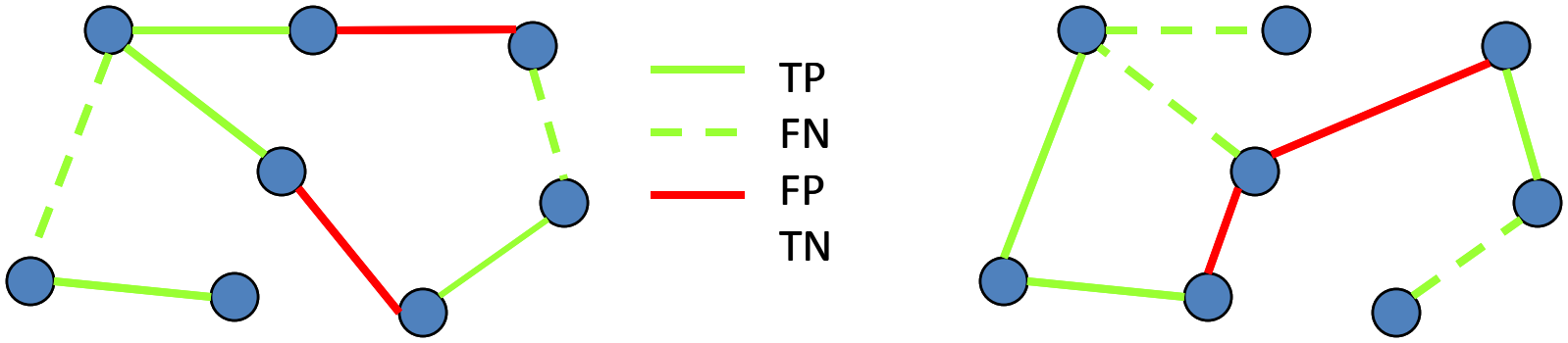
Accuracy of Y2H and how to improve it BUT coverage: real divergence?





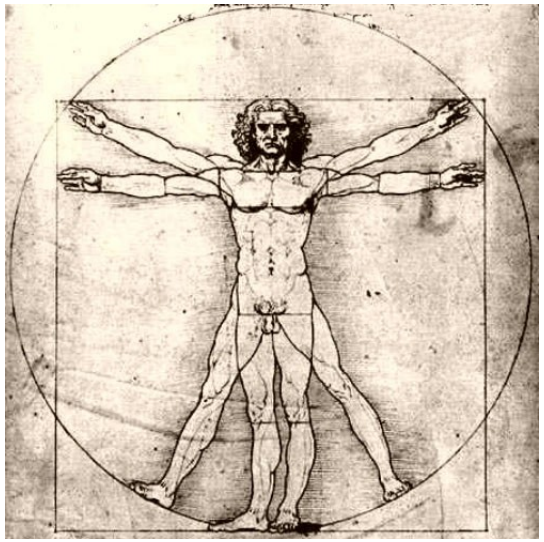
B

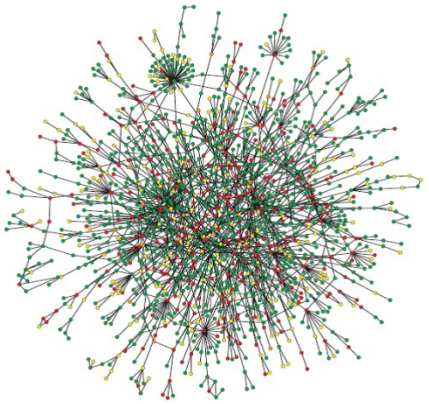
false positives (FP) and false negatives (FN), noise / incomplete knowledge, are stacked against detecting conservation



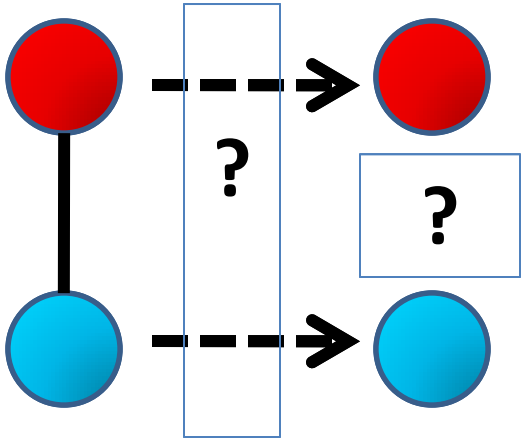
- Genes falsely selected as interacting in species A lower the conservation level, while genes falsely *not* selected (i.e. FN) do not
- Genes falsely selected to be *not* interacting in species B lower the conservation level (FN). Detecting absence?
  - E.g. strict co-expression threshold leads to many false negatives

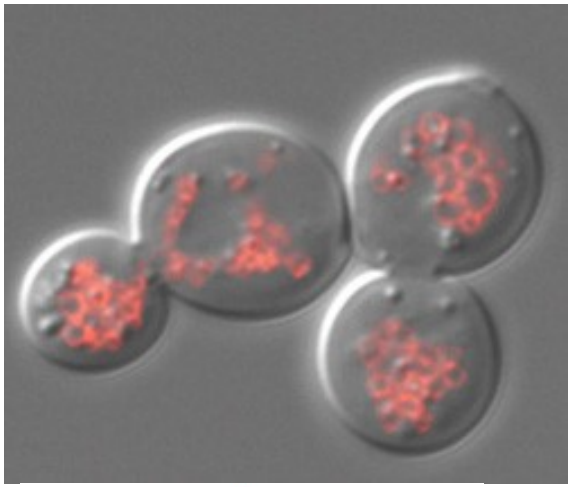
How to perform comparative genomics of interactions (networks/interactome)

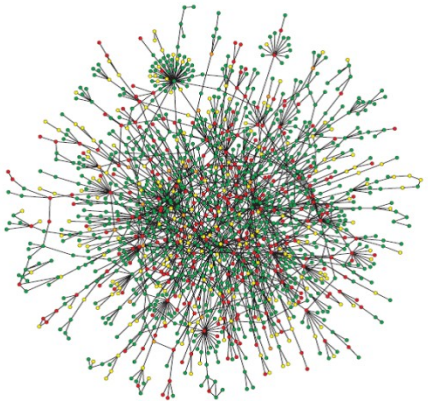




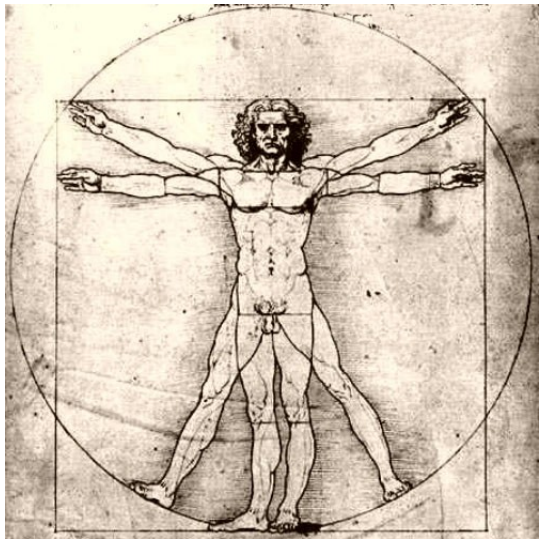
orthology

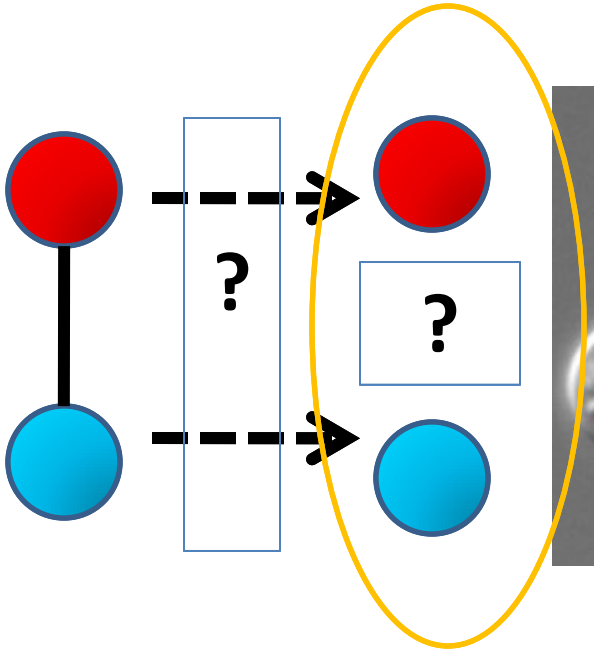


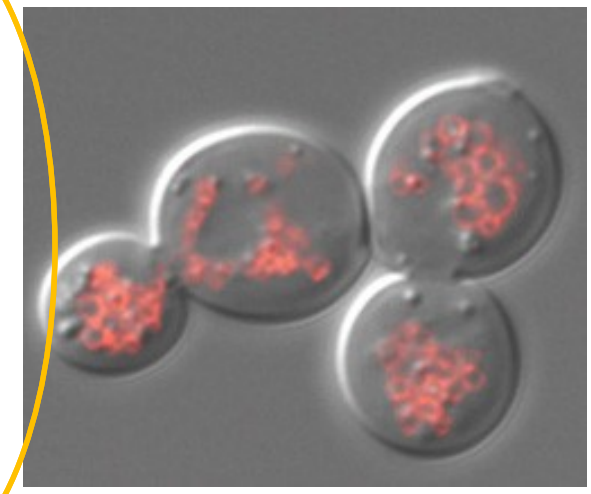




Reliability and coverage of data (false positives, false negatives)







If two proteins are part of the same complex in human how often are they also part of the same complex in yeast

Interactions?

- - stable interactions such as in complexes like ribosomes and proteosomes or between subunits of an enzyme, etc.
- - labile interactions such as between kinases to their substrates, phophatase to their substrates

- Because of quality of expert curation (to use as source or reference) and most prolific HTP data (complex purification) complexes

Absence of interaction … ?

Conservation =

$$\frac{\text{number of interactions conserved}}{(\text{number of interactions conserved} + \text{number of interactions NOT conserved})}$$

TAP-MS data from krogan, and gavin unprecedented coverage so that failure to report co-purification might really mean absence of co-complex membership

Vol 440|30 March 2006|doi:10.1038/nature04532 nature

ARTICLES

Proteome survey reveals modularity of the yeast cell machinery

Anne-Claude Gavin[1]*†, Patrick Aloy[2]*, Paola Grandi[1], Roland Krause[1,3], Markus Boesche[1], Martina Marzioch[1], Christina Rau[1], Lars Juhl Jensen[2], Sonja Bastuck[1], Birgit Dümpelfeld[1], Angela Edelmann[1], Marie-Anne Heurtier[1], Verena Hoffman[1], Christian Hoefert[1], Karin Klein[1], Manuela Hudak[1], Anne-Marie Michon[1], Malgorzata Schelder[1], Markus Schirle[1], Marita Remor[1], Tatjana Rudi[1], Sean Hooper[2], Andreas Bauer[1], Tewis Bouwmeester[1], Georg Casari[1], Gerard Drewes[1], Gitte Neubauer[1], Jens M. Rick[1], Bernhard Kuster[1], Peer Bork[2], Robert B. Russell[2] & Giulio Superti-Furga[1,4]

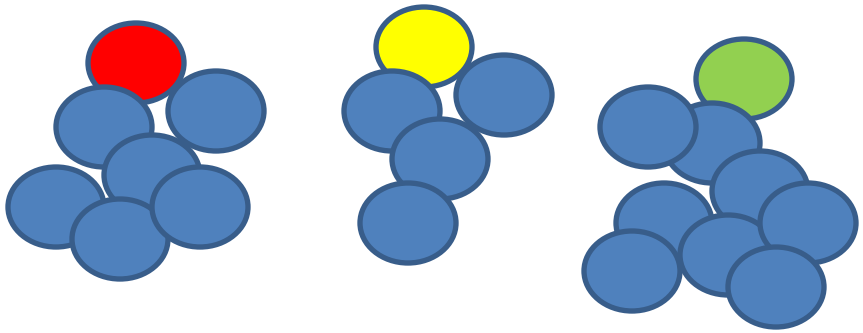
Vol 440|30 March 2006|doi:10.1038/nature04670 nature

ARTICLES

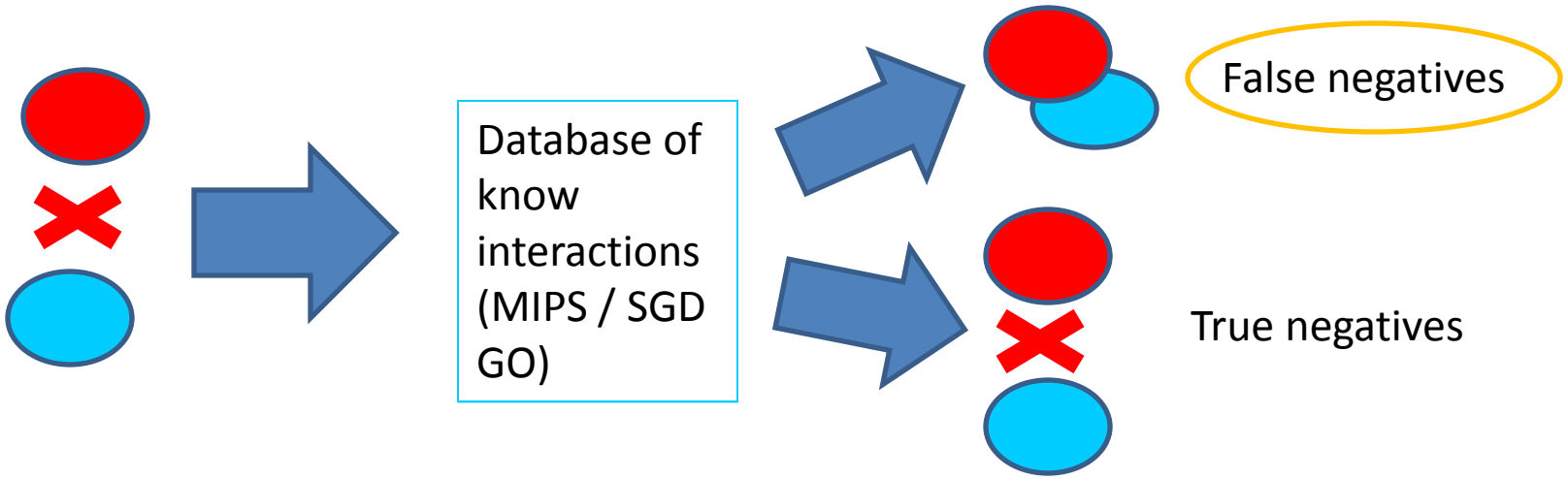
Global landscape of protein complexes in the yeast *Saccharomyces cerevisiae*

Nevan J. Krogan[1,2]*†, Gerard Cagney[1,3]*, Haiyuan Yu[4], Gouqing Zhong[1], Xinghua Guo[1], Alexandr Ignatchenko[1], Joyce Li[1], Shuye Pu[5], Nira Datta[1], Aaron P. Tikuisis[1], Thanuja Punna[1], José M. Peregrín-Alvarez[5], Michael Shales[1], Xin Zhang[1], Michael Davey[1], Mark D. Robinson[1], Alberto Paccanaro[4], James E. Bray[1], Anthony Sheung[1], Bryan Beattie[6], Dawn P. Richards[6], Veronica Canadien[6], Atanas Lalev[1], Frank Mena[6], Peter Wong[1], Andrei Starostine[1], Myra M. Canete[1], James Vlasblom[5], Samuel Wu[5], Chris Orsi[5], Sean R. Collins[7], Shamanta Chandran[1], Robin Haw[1], Jennifer J. Rilstone[1], Kiran Gandi[1], Natalie J. Thompson[1], Gabe Musso[1], Peter St Onge[1], Shaun Ghanny[1], Mandy H. Y. Lam[1,2], Gareth Butland[1], Amin M. Altaf-Ul[8], Shigehiko Kanaya[8], Ali Shilatifard[9], Erin O'Shea[10], Jonathan S. Weissman[7], C. James Ingles[1,2], Timothy R. Hughes[1,2], John Parkinson[5], Mark Gerstein[4], Shoshana J. Wodak[5], Andrew Emili[1,2] & Jack F. Greenblatt[1,2]

Estimating absence of interactions from HTP data
-> yeast; what do we call an absence of interaction data



Two proteins that have been successfully purified and identified as bate or prey, but never together



The **false negative rate** (FNR) is the proportion of positive instances that were erroneously reported as negative.

Proten pairs known to be part of the same protein complex

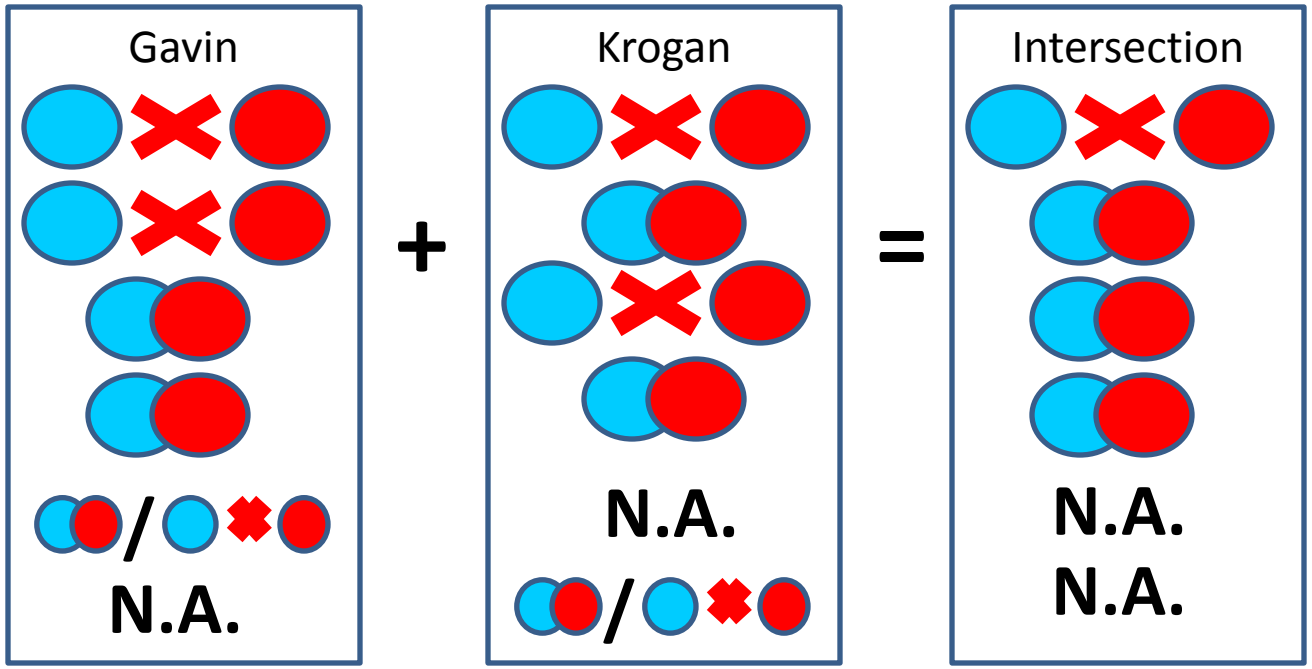
Datasets	FNR	#FN	#TP
Gavin et al.	0.23	1226	4083
Krogan et al.	0.32	2209	4644

Positive instances: co-complex relation in MIPS *and* SGD-GO. Similarly negative instances,: two proteins known to be involved in complexes in MIPS and SGD-GO but in either ref never together

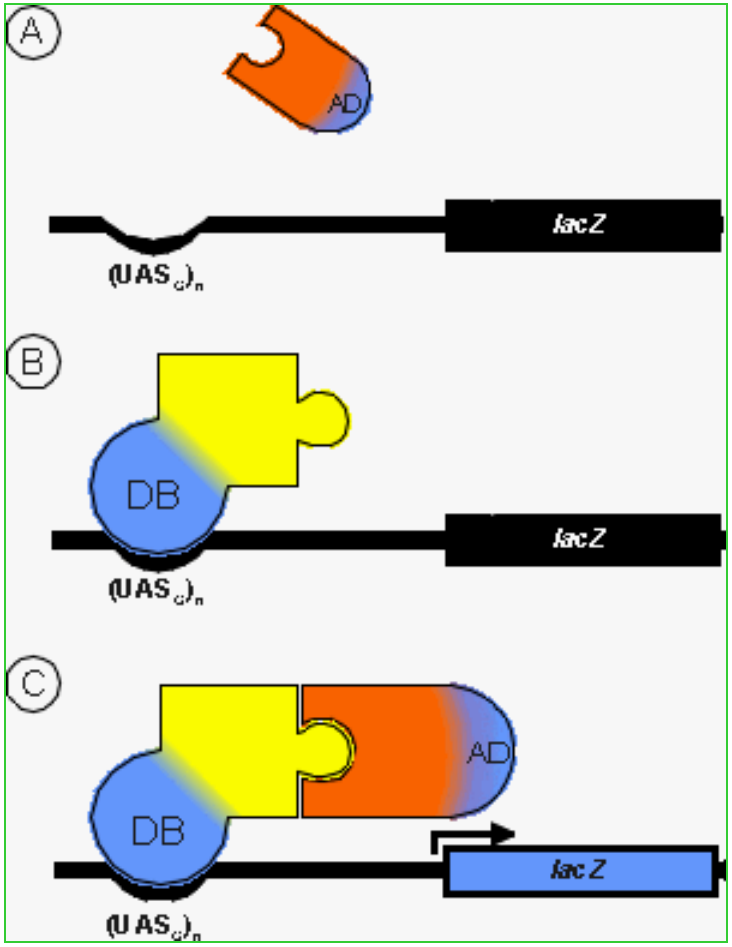
The **false negative rate** (FNR) is the proportion of positive instances that were erroneously reported as negative.

Proten pairs known to be part of the same protein complex

Datasets	FNR	#FN	#TP
Gavin et al.	0.23	1226	4083
Krogan et al.	0.32	2209	4644
Intersection	0.11	517	4396



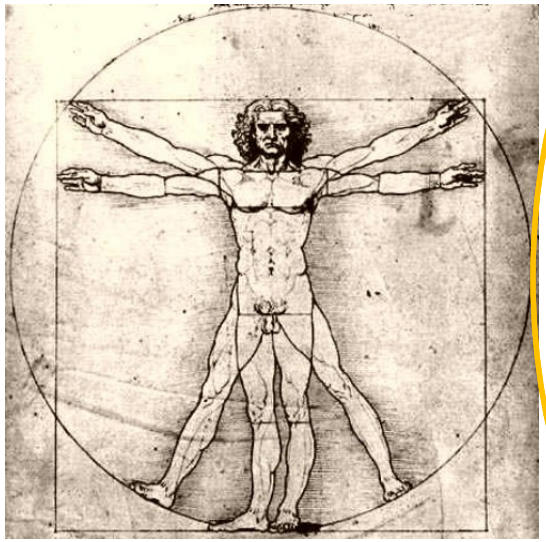
… but Y2H != TAP-MS

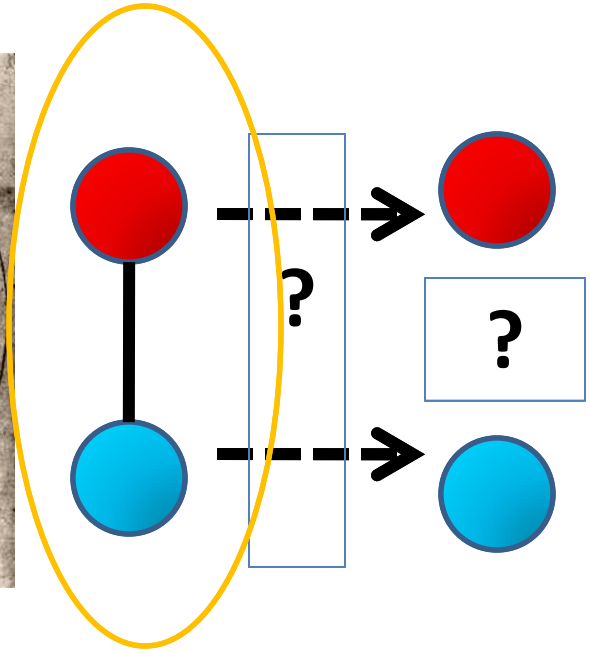


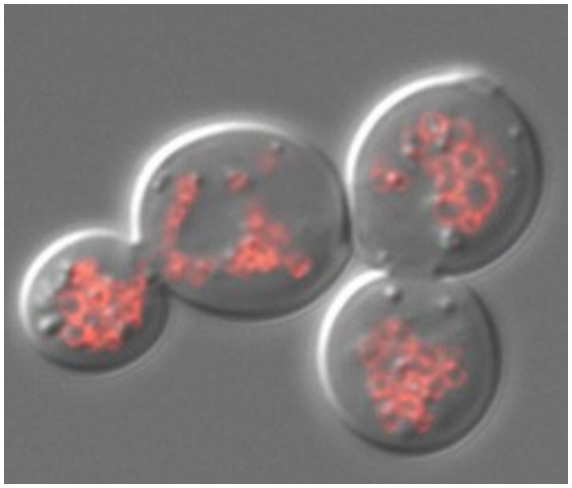
How do we know which bait prey pairs (hybridizations) have been "properly" tested?

Only count as not interactions pairs where both proteins have been successful as bait and prey

Datasets	FNR	#FN	#TP
Gavin et al.	0.23	1226	4083
Krogan et al.	0.32	2209	4644
Intersection	0.11	517	4396
Uetz et al.	0.66	91	46
Ito et al.	0.92	822	76
Uetz et al. strict	0.1	5	46







In human less htp and less curation = less coverage (reason for assymetrry)

- High quality, non comprehensive literature curation: reactome direct complex: 5960 co-complex pairs
- Some 2h but even worse than yeast 2h
- new HTP data:

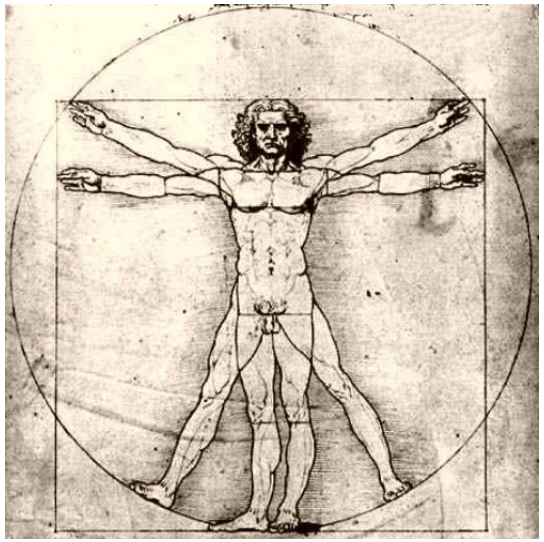
Molecular Systems Biology 3; Article number 89; doi:10.1038/msb4100134
Citation: *Molecular Systems Biology* 3: 89

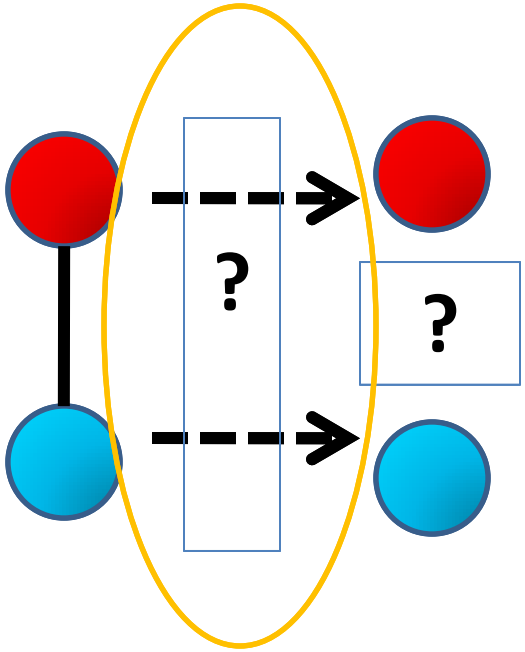
www.molecularsystemsbiology.com

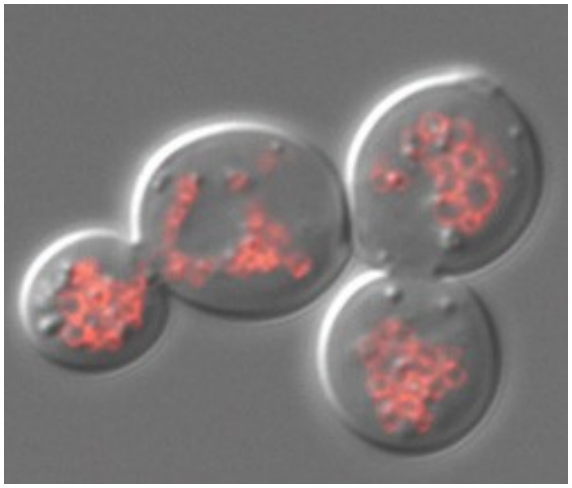
molecular systems biology

Large-scale mapping of human protein–protein interactions by mass spectrometry

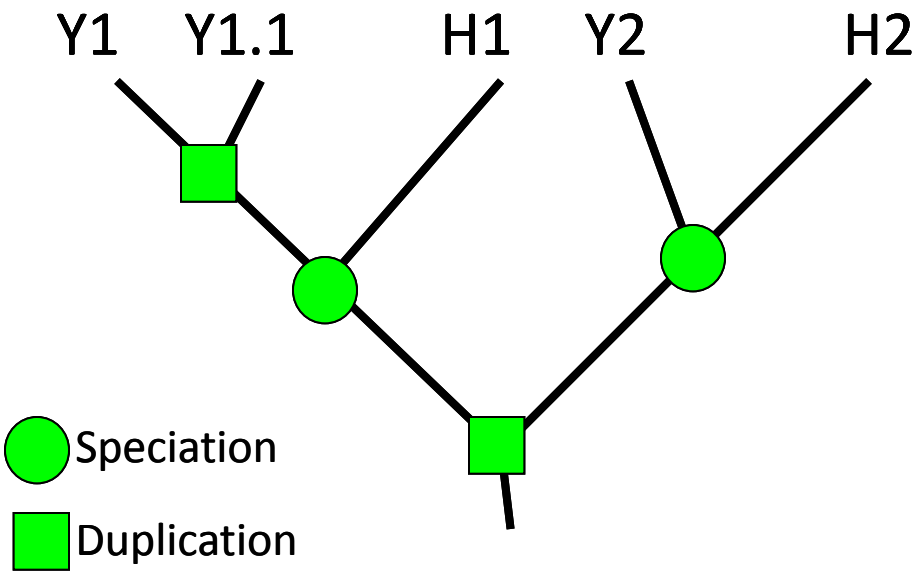
Rob M Ewing[1,2], Peter Chu[1,5], Fred Elisma[3], Hongyan Li[1,6], Paul Taylor[1,7], Shane Climie[1,8], Linda McBroom-Cerajewski[1,9], Mark D Robinson[1,10], Liam O'Connor[1,11], Michael Li[1,12], Rod Taylor[1], Moyez Dharsee[1,2], Yuen Ho[1,13], Adrian Heilbut[1,14], Lynda Moore[1,15], Shudong Zhang[1], Olga Ornatsky[1,16], Yury V Bukhman[1,17], Martin Ethier[3], Yinglun Sheng[3], Julian Vasilescu[3], Mohamed Abu-Farha[3], Jean-Philippe Lambert[3], Henry S Duewel[1,18], Ian I Stewart[1,2], Bonnie Kuehl[1,19], Kelly Hogue[1,20], Karen Colwill[1,21], Katharine Gladwish[1], Brenda Muskat[1,22], Robert Kinach[1,16], Sally-Lin Adams[1,23], Michael F Moran[1,7], Gregg B Morin[1,15], Thodoros Topaloglou[1,4] and Daniel Figeys[1,3,*]

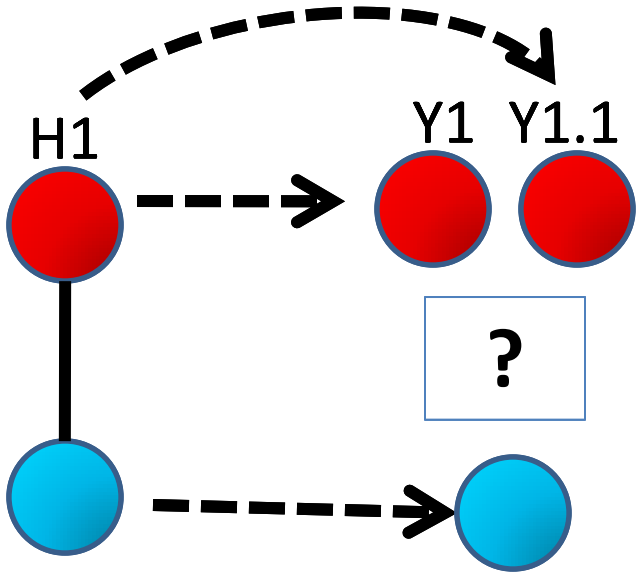






Orthology: complication

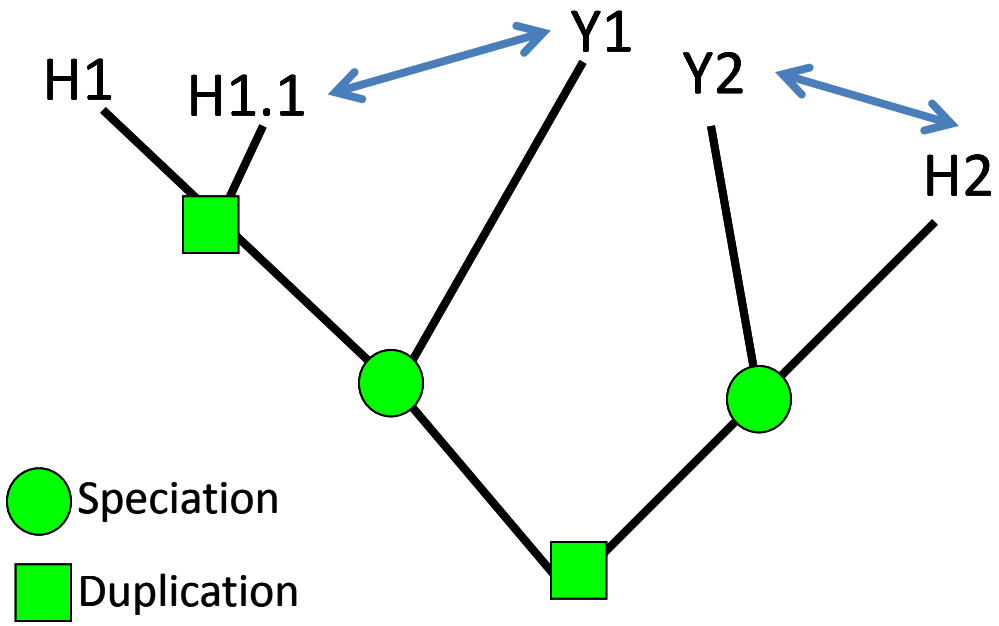




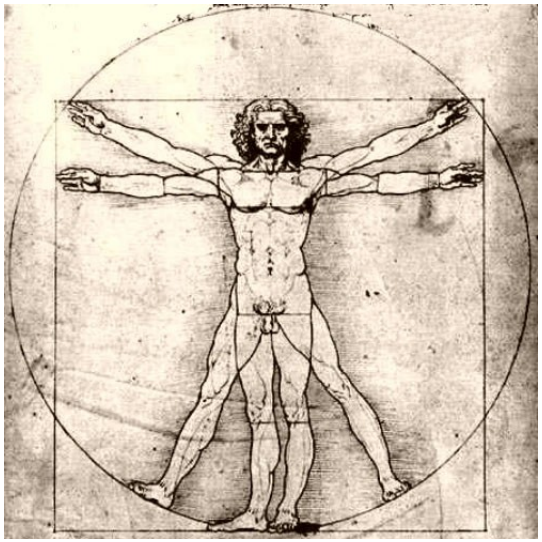
H1 and H1.1 are “Inparalogs”

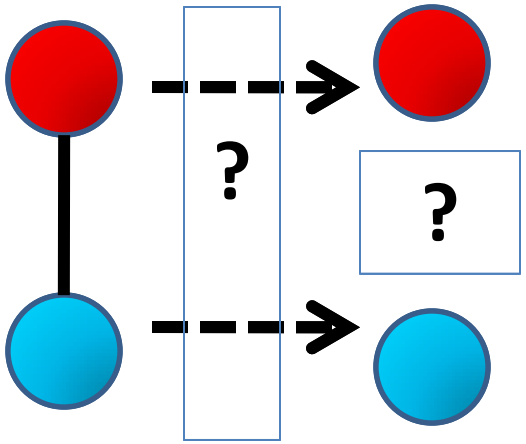
H1 and H1.1 are “Co-orthologous” to Y1

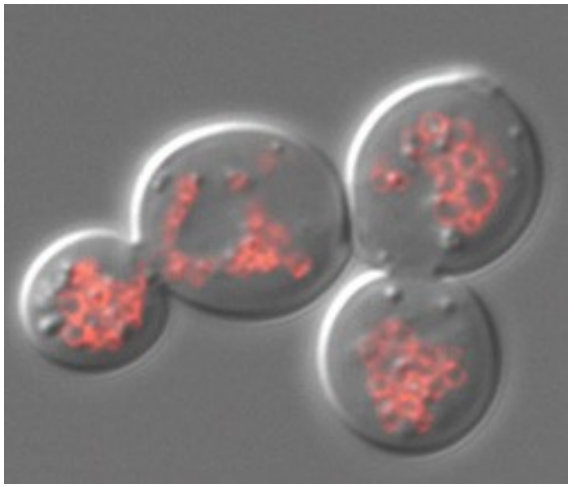
BBH only (inparanoid's main ortholog)

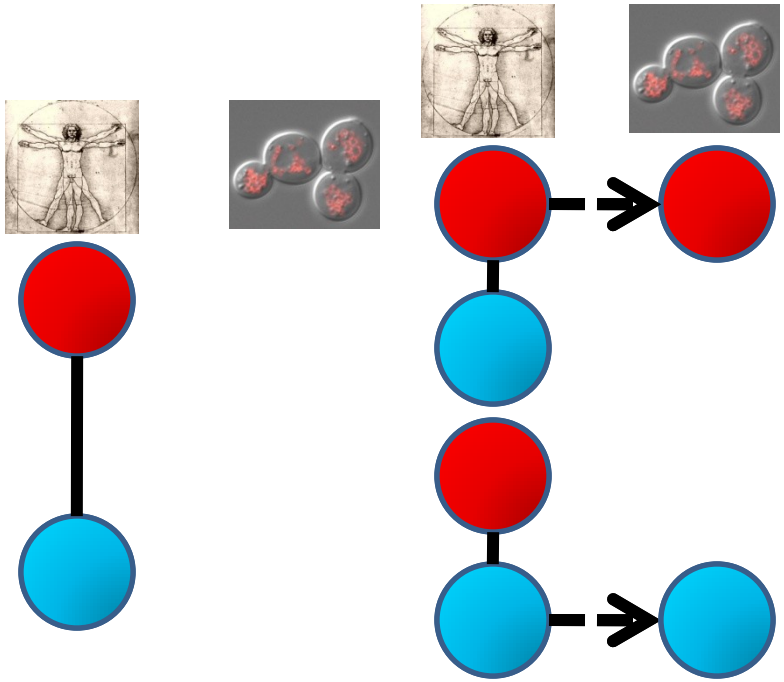


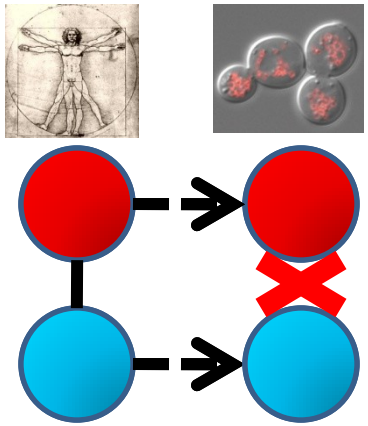
What can happen to an interaction in evolution

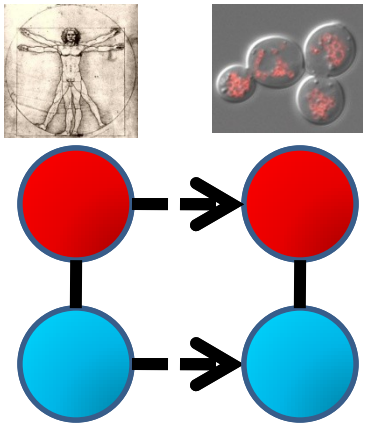




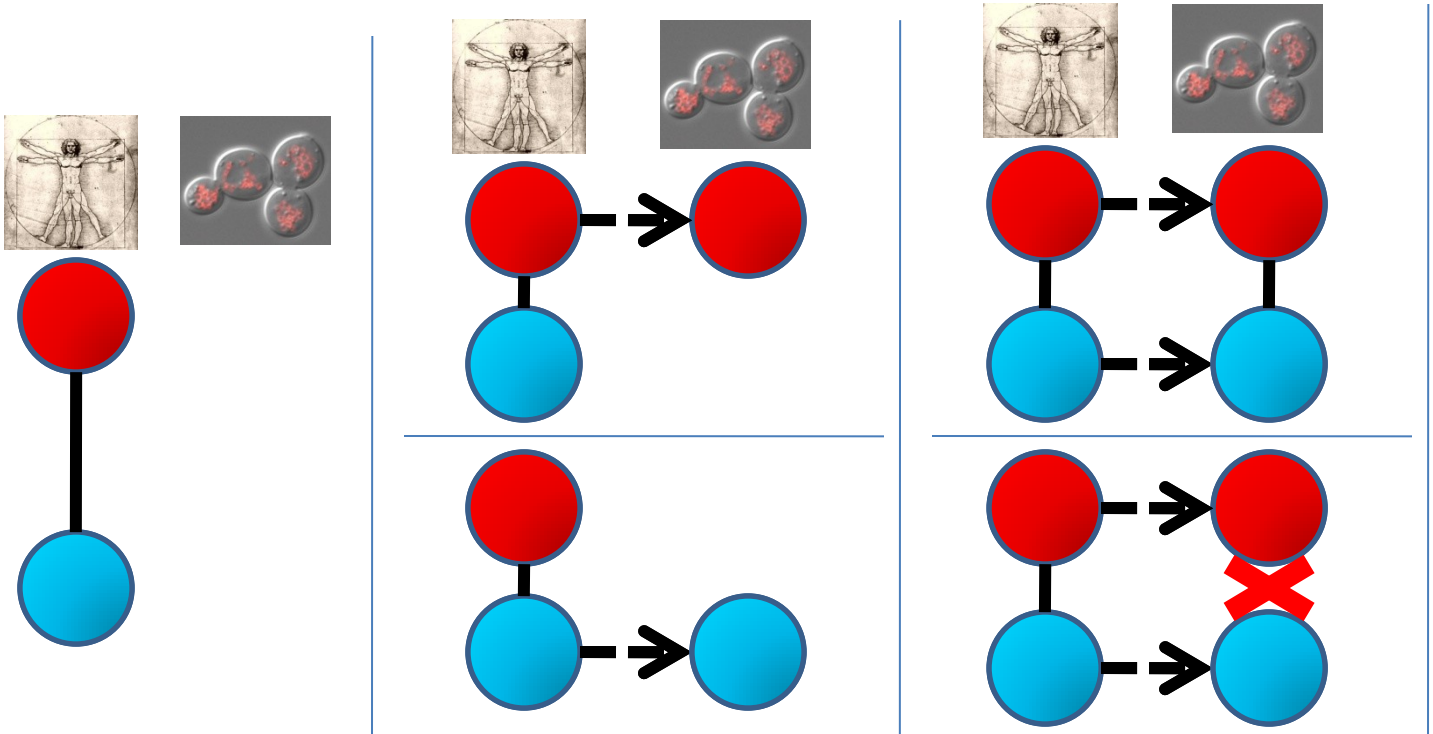






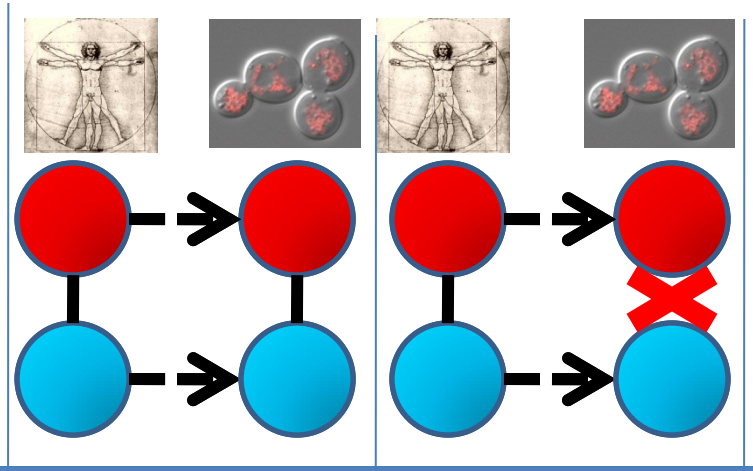


Many interactions are not “conserved” because the genes themselves are not conserved



BestHit	2276	1417	2267
InParanoid	1916	1448	2596
Ensembl	2216	1828	1916

If both genes are conserved the interactions also tends to be conserved

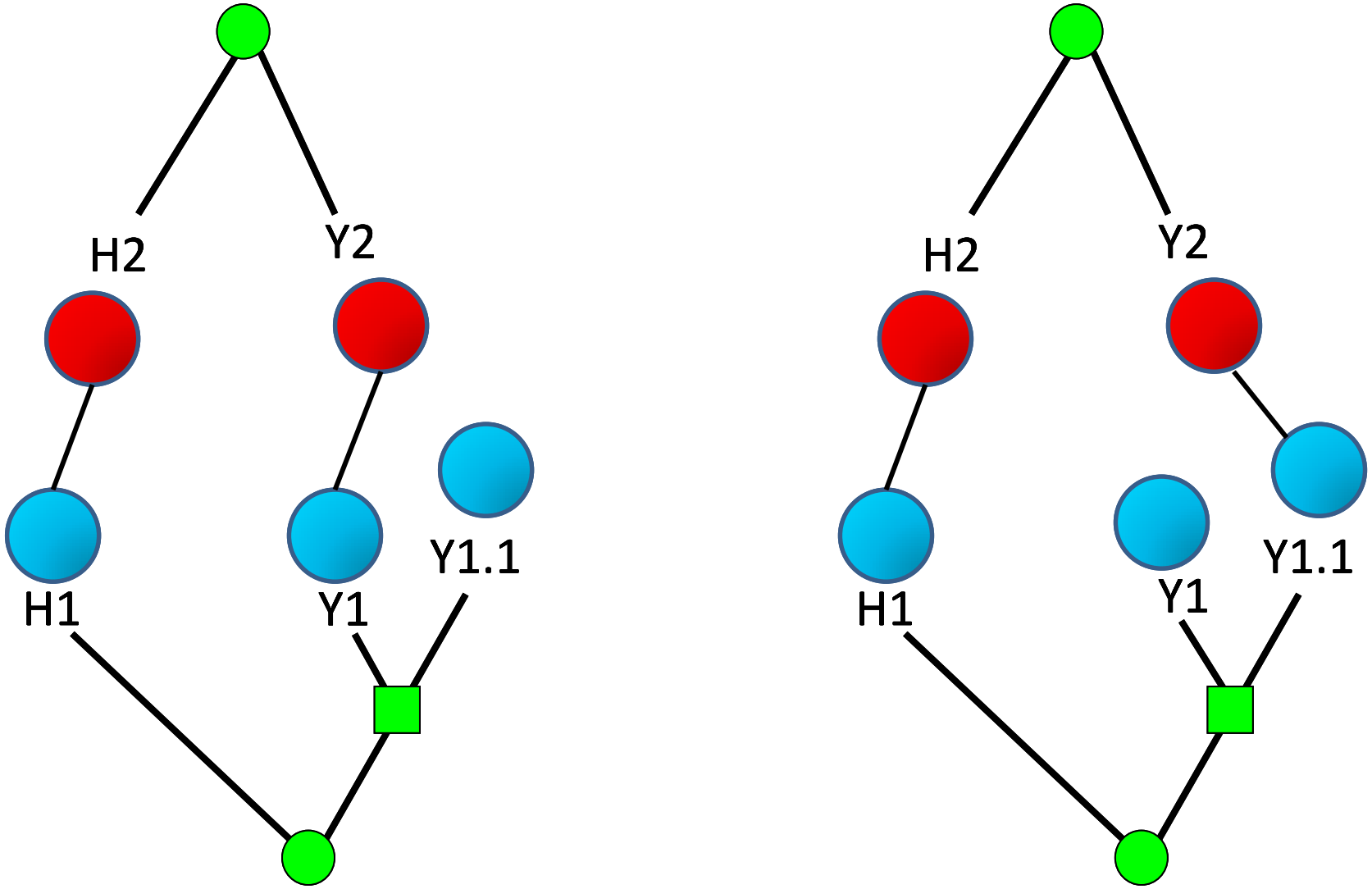


Dataset	int	Non-int	Conservation	Coverage
Gavin	1305	226	85.2%	68.1%
Krogan	1547	328	82.5%	80.7%
Intersection	1392	75	94.9%	72.7%
Uetz	21	63	25.0%	1.1%
UetzInt	21	4	84.0%	1.1%

Human HTP data (Ewing, IP-HTMS)

Ewing cut-off	int	non-int	conservation
0	117	245	32.32
0.3	78	59	56.93
0.5	20	3	86.96

Yeast data set = intersection



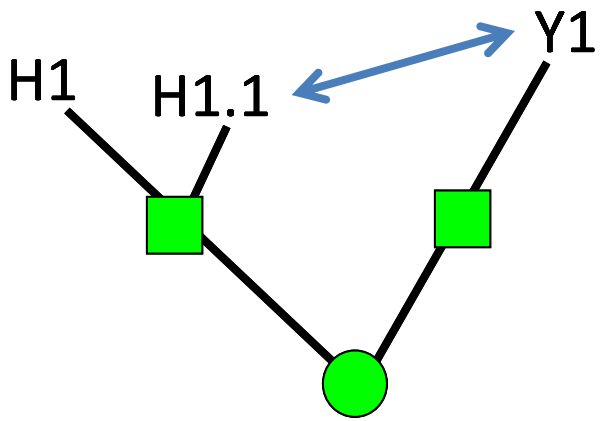
• Some conserved interactions are missed when taking the sequence-wise most similar ortholog cf. Notebaart2005 / Ideker 2006

Different results of orthologies

Dataset	Orthology	int	Non-int	Conservation	Coverage
Intersection	BBH	1429	141	91.0%	63.0%
Intersection	Ensembl	1392	75	94.9%	72.7%
Intersection	InParanoid	1761	84	95.4%	67.8%

Inparanoid / ensembl similar conservation percentages despite different absolute values, But BBH

… inparalogs



Non-conserved interactions …

- Curation errors in reactome
- potential false negatives in HTP data as literature in yeast says the two do interact.
- Our high level of conservation is underestimation?
- few cases of genuine evo divergence … (e.g. new paralog in human involved in a new complex, human PCBP1 & yeast XAB2)
- flexibility resides in duplications cf. inparalogs

Cell

Resource

A Protein Complex Network of *Drosophila melanogaster*

K.G. Guruharsha,[1,4] Jean-François Rual,[1,4] Bo Zhai,[1,4] Julian Mintseris,[1,4] Pujita Vaidya,[1] Namita Vaidya,[1] Chapman Beekman,[1] Christina Wong,[1] David Y. Rhee,[1] Odise Cenaj,[1] Emily McKillip,[1] Saumini Shah,[1] Mark Stapleton,[2] Kenneth H. Wan,[2] Charles Yu,[2] Bayan Parsa,[2] Joseph W. Carlson,[2] Xiao Chen,[2] Bhaveen Kapadia,[2] K. VijayRaghavan,[3] Steven P. Gygi,[1] Susan E. Celniker,[2] Robert A. Obar,[1,*] and Spyros Artavanis-Tsakonas[1,*]

- "Our data support models of protein network evolution that are driven by the acquisition or loss of protein complex members rather than rewiring of existing components (van Dam and Snel, 2008 and Yamada and Bork, 2009)."

Summarizing conclusions

- Most interactions are not conserved because of acquisition / loss subunits but if two proteins *are* present they tend to interact
- Despite issues, >> 10% previously implied
- Function prediction from model organism to man is justified w.r.t. co-complex membership
- Differences between species reside perhaps more in genome evolution
- Genome and network evolution are tightly connected and should not be studied independently (e.g. the simple distinction between loss/gain of interaction with existing protein vs loss/gain of interactor.)

Another aspect of function: subcellular localization

Research

Open Access

Expansion of the human mitochondrial proteome by intra- and inter-compartmental protein duplication

Radek Szklarczyk and Martijn A Huynen

1-to-1 human-yeast orthologs have conserved ancestral subcellular localization.

Gene duplication relaxes this constraint

- Quite some **intra**-mitochondrial duplications
- And **inter**-compartmental duplications create novel mitochondrial localization of the protein encoded by one of the daughter genes

1-to-1 human-yeast orthologs have conserved ancestral subcellular localization

- Use high quality data in localization: experimental identification, bioinformatics analysis, and literature curation

- “Of 143 one-to-one orthologous pairs localized to mitochondria in either of the two species, we find that 124 proteins (87%) are found in this organelle in both species and only 19 proteins localize to mitochondria in one species, but not the other”

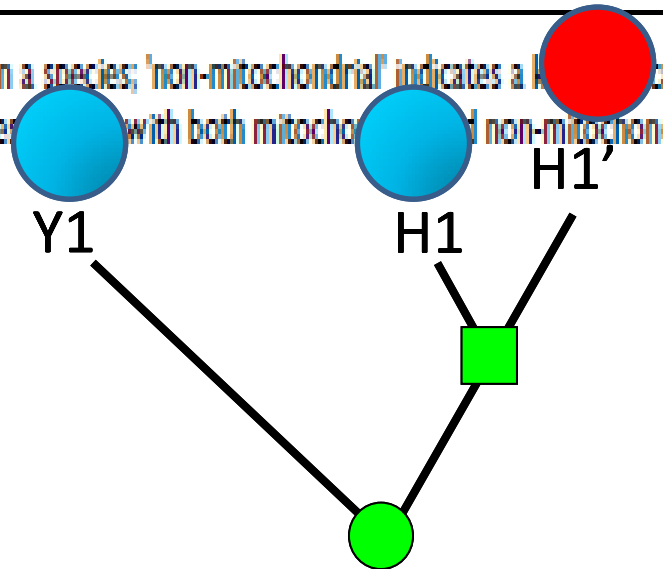
intra-mitochondrial duplications are most frequent & gain of mitochondrial localization after gene duplication

Table I

Duplications in gene families with products localized to the mitochondria

Human localization of gene family	Yeast localization of gene family	Number of families	Number of human proteins
Mitochondrial	Mitochondrial	53	118
Mitochondrial and non-mitochondrial	Non-mitochondrial	26	101
Other	Other	25	55

'Mitochondrial' denotes mitochondrial localization for all genes from this family in a species; 'non-mitochondrial' indicates a l[illegible]calization to another subcellular compartment; 'mitochondrial and non-mitochondrial' indicate[illegible]with both mitocho[illegible]d non-mitochondrial paralogs. See also Table S4 in Additional data file 1 for other duplication classes.



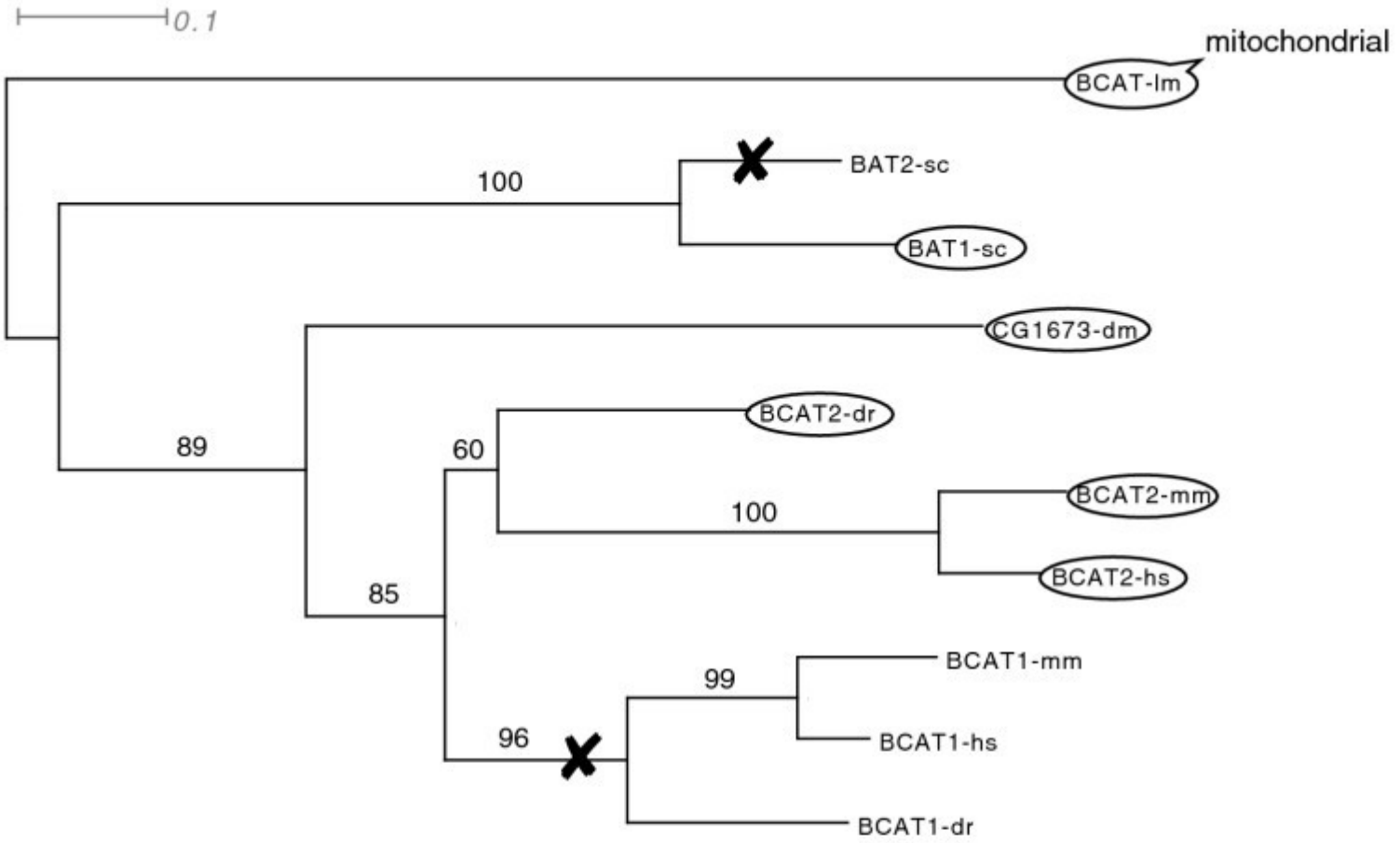
“Parallel evolution”

Table 3

Independent duplications and parallel relocalizations in the human and yeast lineages have happened multiple times during evolution

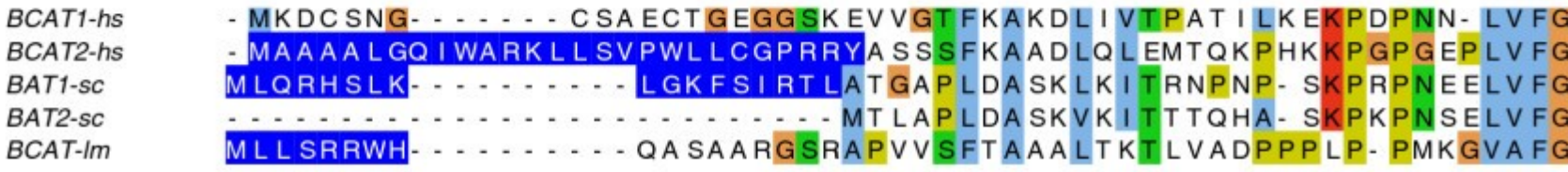
	Human		Yeast	
Family	Mitochondrial	Non-mitochondrial	Mitochondrial	Non-mitochondrial
Thioredoxins	TXN, TXN2	TXNDC2	TRX3	TRX1, TRX2
Glutaredoxins	GLRX2	GLRX, GLRXL	GRX2	GRX1 (nucleus)
Isocitrate dehydrogenases [NADP]	IDH2	IDH1	IDP1	IDP2, IDP3 (peroxisome)
Branched-chain-amino-acid aminotransferases	BCAT2	BCAT1	BAT1	BAT2
Serine hydroxymethyltransferases	SHMT2	SHMT1	SHM1	SHM2

(a)



"Parallel evolution through rapid parallel loss"

(b)



OPEN ACCESS Freely available online PLoS COMPUTATIONAL BIOLOGY

Measuring the Evolutionary Rewiring of Biological Networks

Chong Shou[1], Nitin Bhardwaj[2], Hugo Y. K. Lam[1], Koon-Kiu Yan[2], Philip M. Kim[3], Michael Snyder[4], Mark B. Gerstein[1,2,5]*

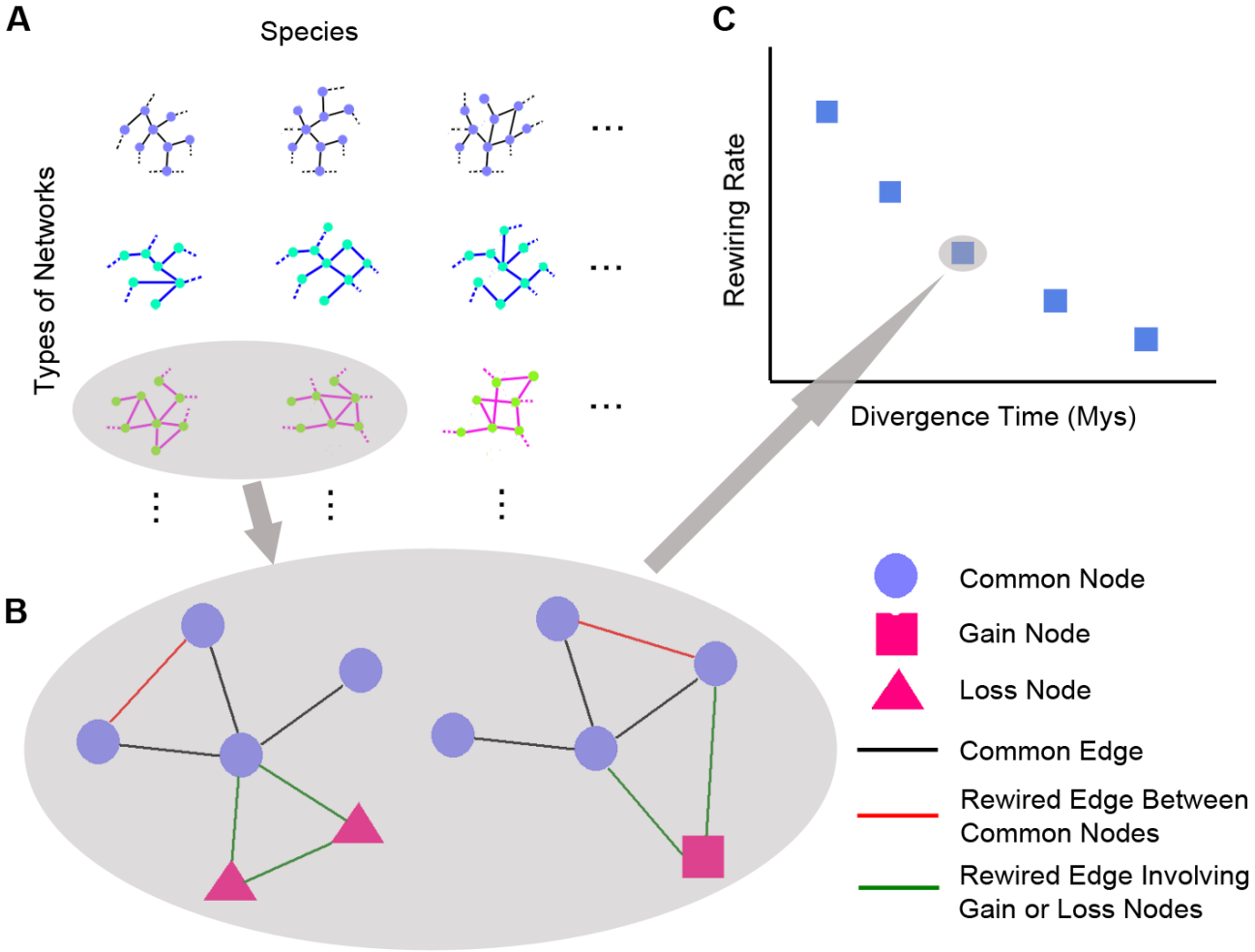
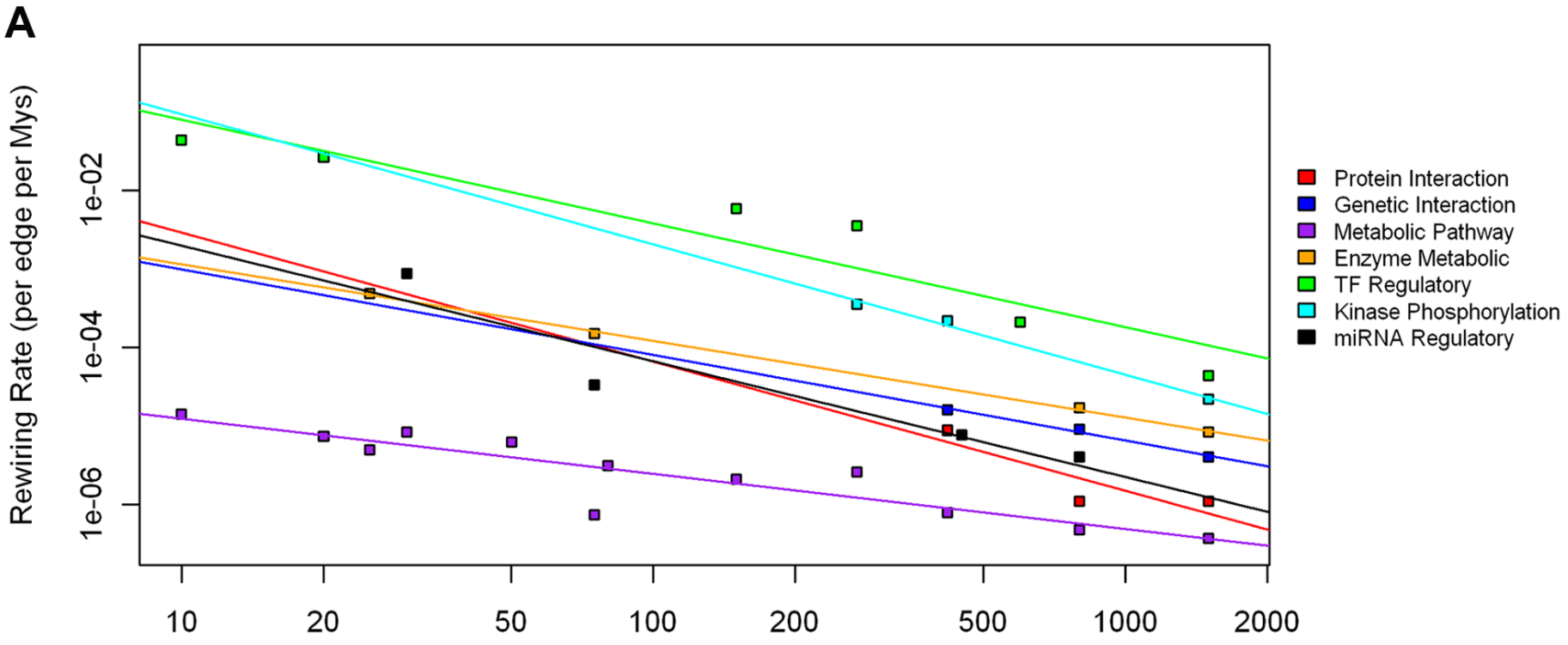


Table S3.

Network Type		
TF	*S. cerevisiae*, *S. bayanus*	*D. melanogaster*, *S. cerevisiae*
Edge change from Edge Gain	26	80
Edge change from Edge Loss	53	80
Edge change from Node Gain	60	12733
Edge change from Node Loss	306	76543

!

Other interactions / HTP data



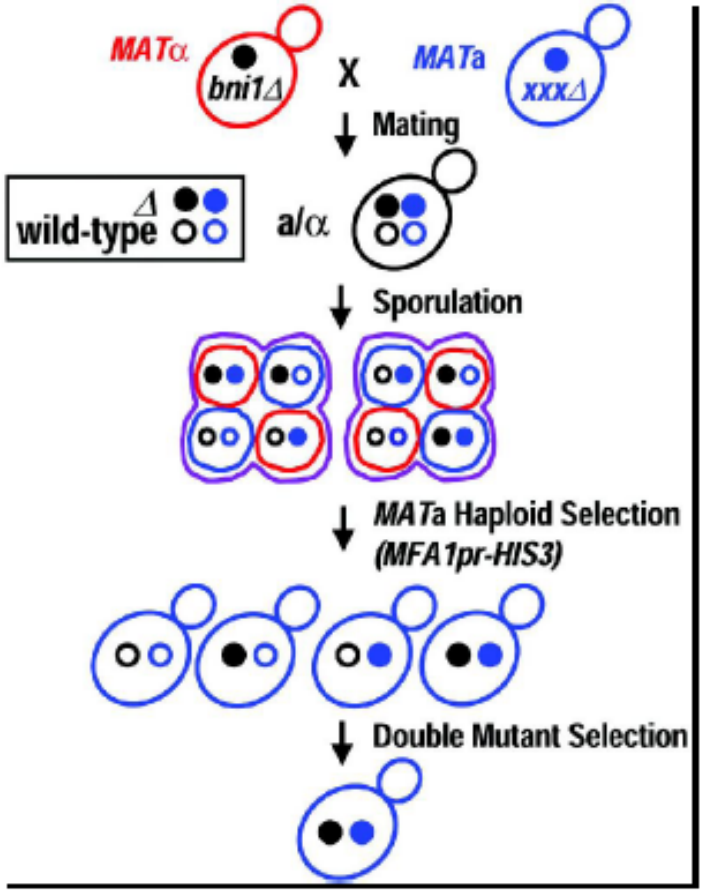
3.

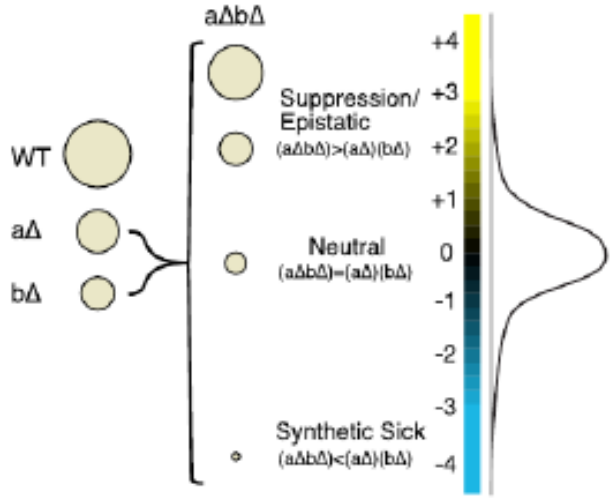
Measuring the evolutionary rewiring of biological networks.

Shou C, Bhardwaj N, Lam HY, Yan KK, Kim PM, Snyder M, **Gerstein** MB.

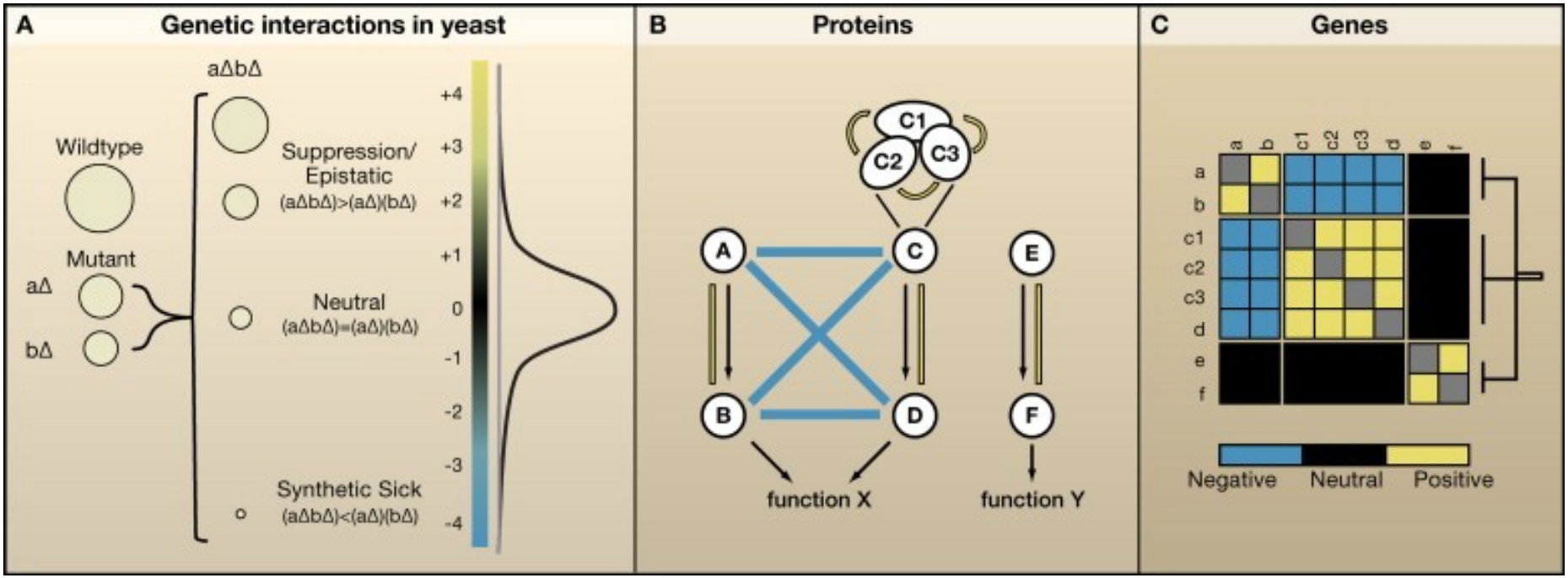
PLoS Comput Biol. 2011 Jan 6;7(1):e1001050.

Genetic interactions





Tong et al. 2001 Science
Schuldliner et al. 2005 Cell



Negative / syntetic lethal / aggravating
Positive / buffering / alleviating

Cell

Functional Repurposing Revealed by Comparing *S. pombe* and *S. cerevisiae* Genetic Interactions

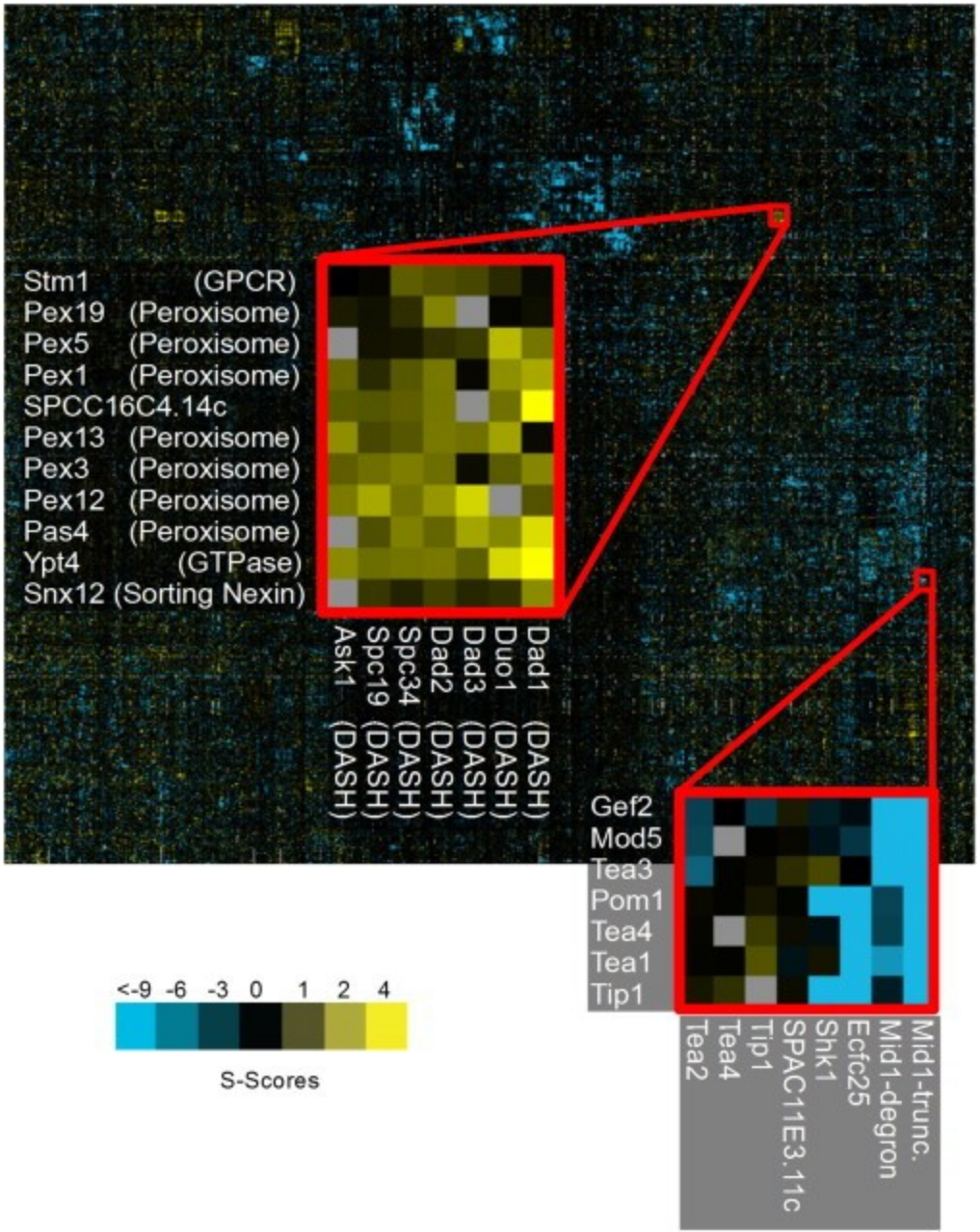
Adam Frost,[1,*] Marc G. Elgort,[1] Onn Brandman,[2,3,4] Clinton Ives,[2,3,4] Sean R. Collins,[7] Lakshmi Miller-Vedam,[2,3,4] Jimena Weibezahn,[2,3,4] Marco Y. Hein,[5] Ina Poser,[6] Matthias Mann,[5] Anthony A. Hyman,[6] and Jonathan S. Weissman[2,3,4]

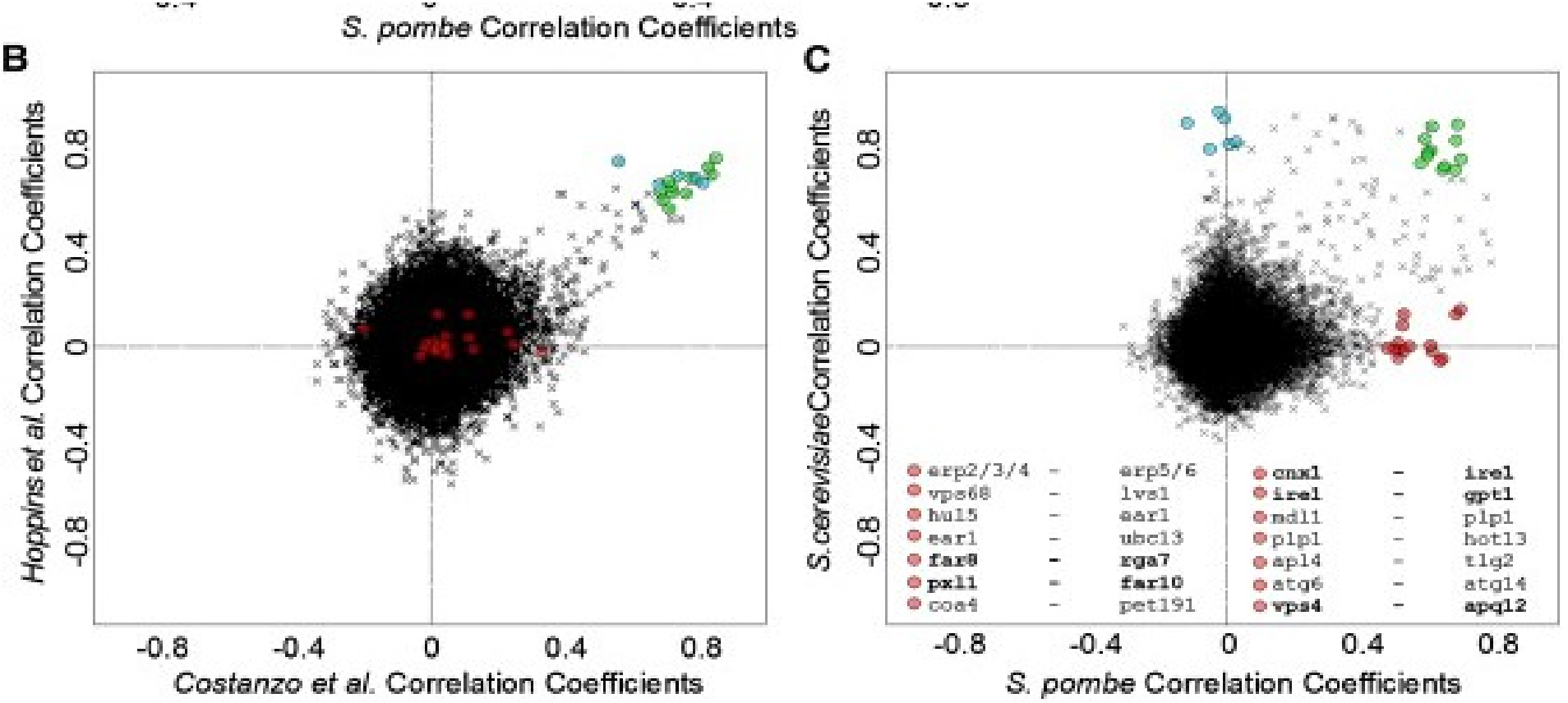
"generate 774,309 double mutants "

But …

"Our *Sp* map identified > 700 high-confidence gene-to-gene correlations indicative of genes with related functions"

Genetic interaction correlations

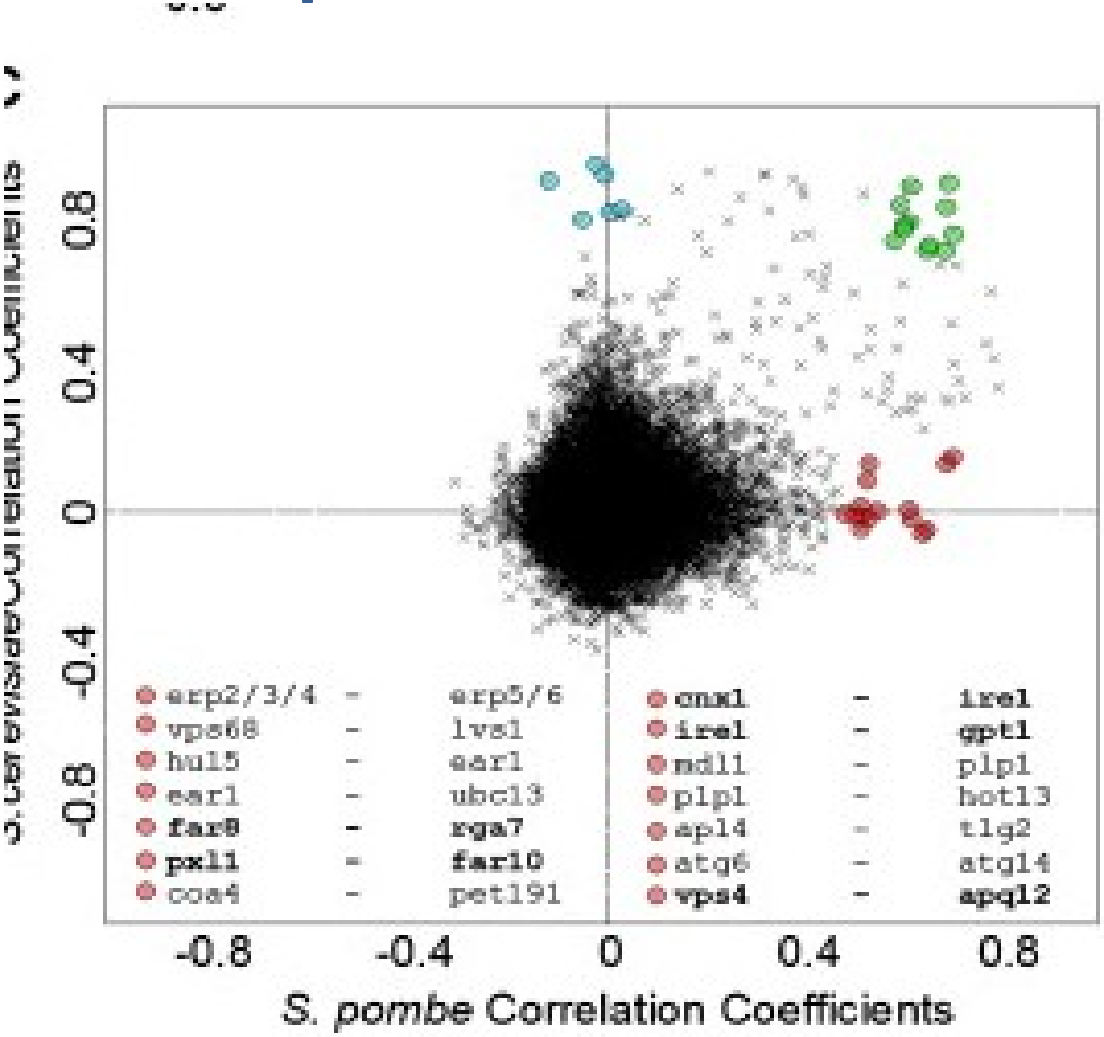


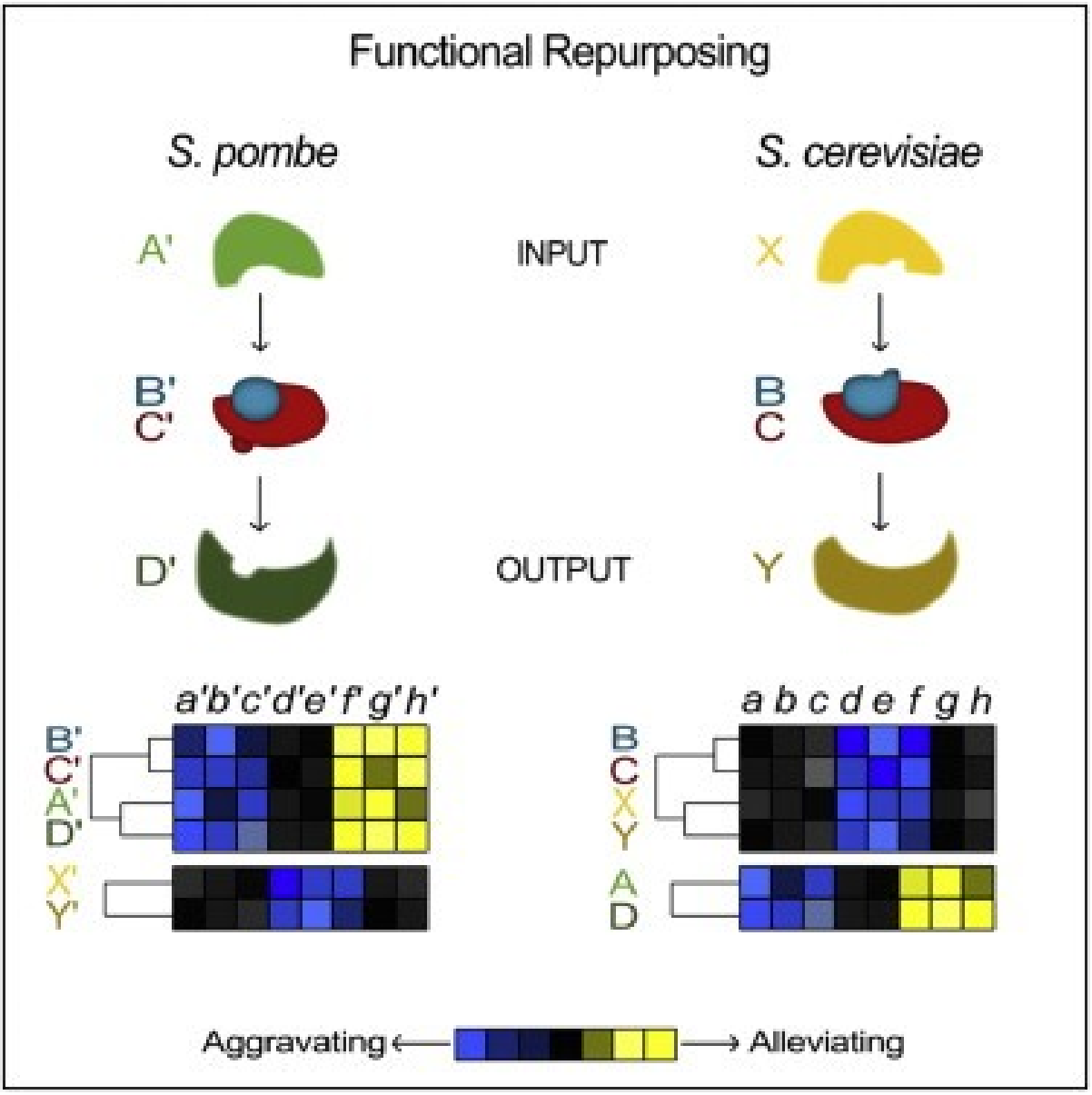


We present a genetic interaction map of pairwise measures including ~40% of nonessential *S. pombe* genes. By comparing interaction maps for fission and budding yeast, we confirmed widespread conservation of genetic relationships **within** and **between** complexes and pathways.

Duplication as cause of divergence in genetic relationships

- in *Sp* only GOLD-domain proteins of COP-II coat components (SPAC17A5.08 and SPBC16E9.09). In *Sc*, there three homologs of SPAC17A5.08 (*ERP2*, *ERP3*, and *ERP4*) and two homologs of SPBC16E9.09 (*ERP5* and *ERP6*). SPAC17A5.08 and SPBC16E9.09 share virtually all of the same interactions in *Sp*, whereas none of the pairwise comparisons of *ERP2/3/4* versus *ERP5/6* profiles shared significant overlap in *Sc*

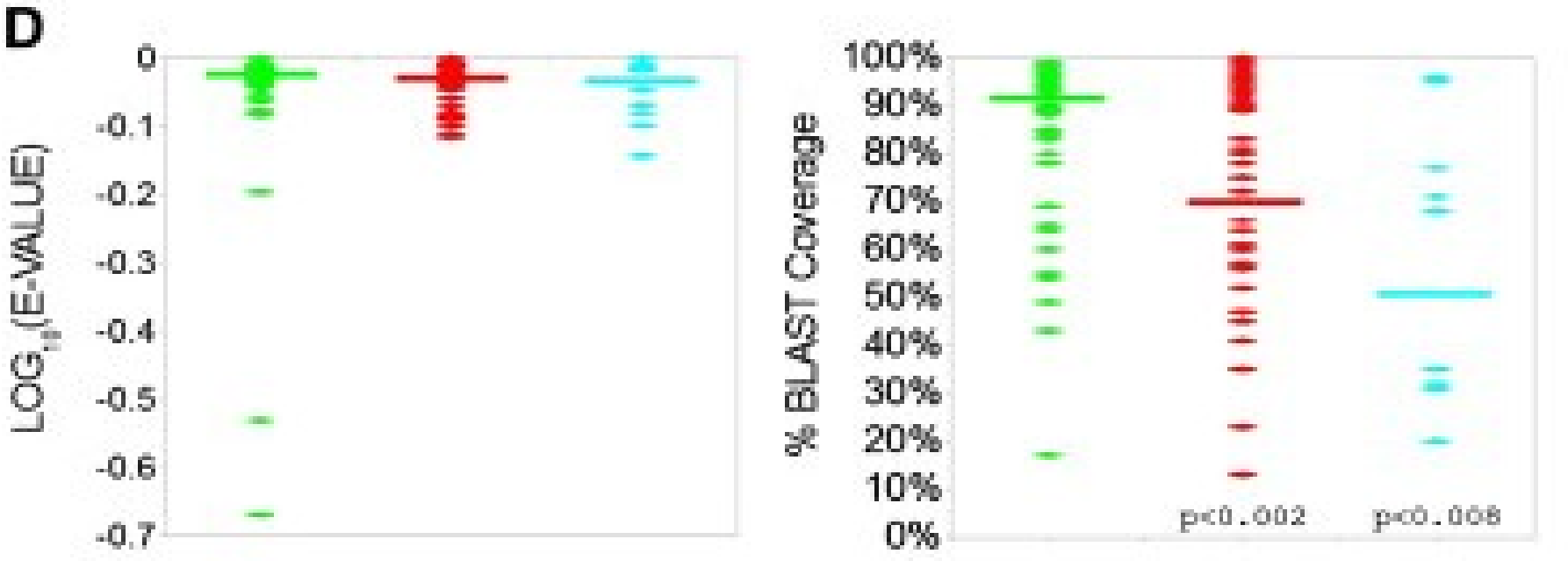




an important subset of orthologous complexes that have undergone functional "repurposing": the evolution of divergent functions and partnerships

Example ESCRT

- the *e*ndosomal *s*orting *c*omplex *r*equired for *t*ransport (ESCRT) genes in endosomal maturation
- Also a role in cytokinesis in pombe (and animals) but not in cerevisiae
- Extensive experimental validation
- ? Loss of function in yeast
- ? Different behavior for intra complex vs inter-complex interactions in evolution?



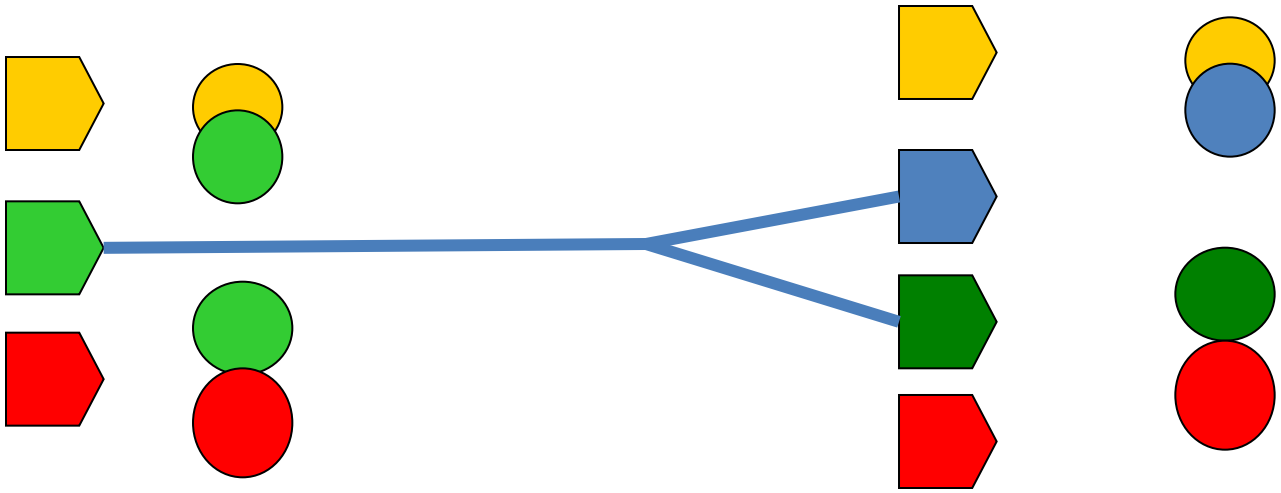
Lower amino acid similarity did not correlate with repurposing (Figure 2D, left), but lower percentage coverage (i.e., additional motifs or domains present in only one of the orthologs) did correlate with apparent repurposing

Fate after gene duplication

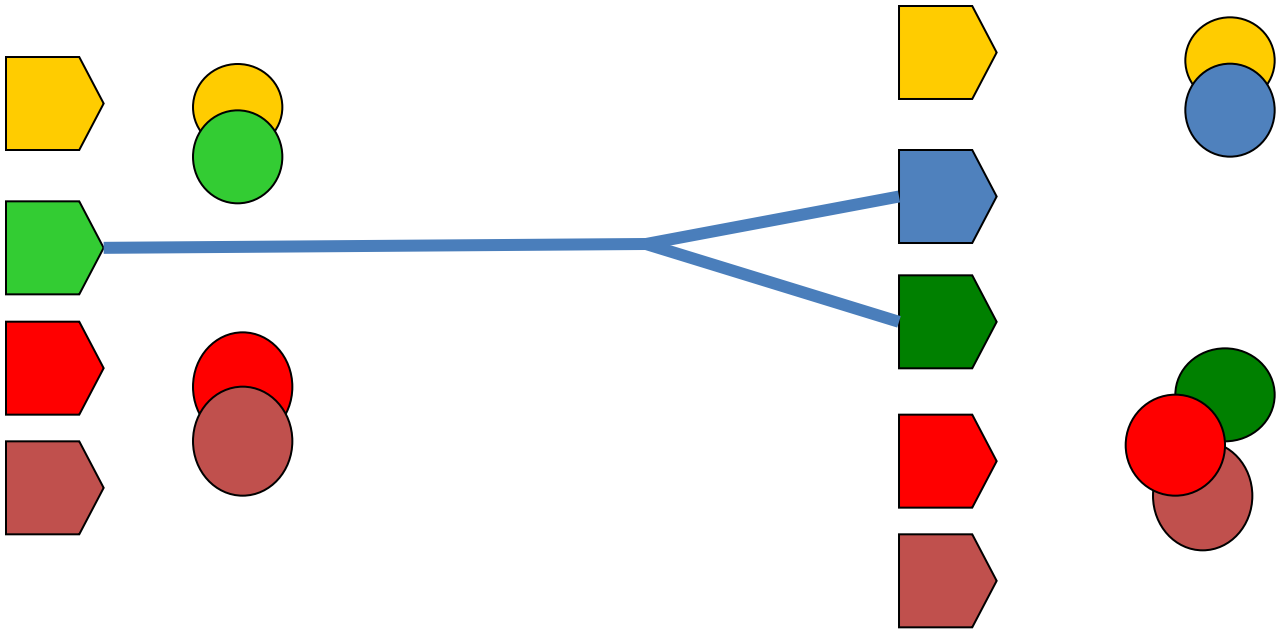
- Most duplications are thought to be deleterious (like most mutations). Hence theories (A) on why they stay (are neutral/selected) on short time scale vs (B) how they evolve and are “used” on longer time scale. We focus on B
- Dosage
- Redundancy
- Subfunctionalization
- Neofunctionalization
- (pseudogenization)

The evolution of gene duplications: classifying and distinguishing between models.
Innan H, Kondrashov F.
Nat Rev Genet. **2010** Feb;11(2):97-108

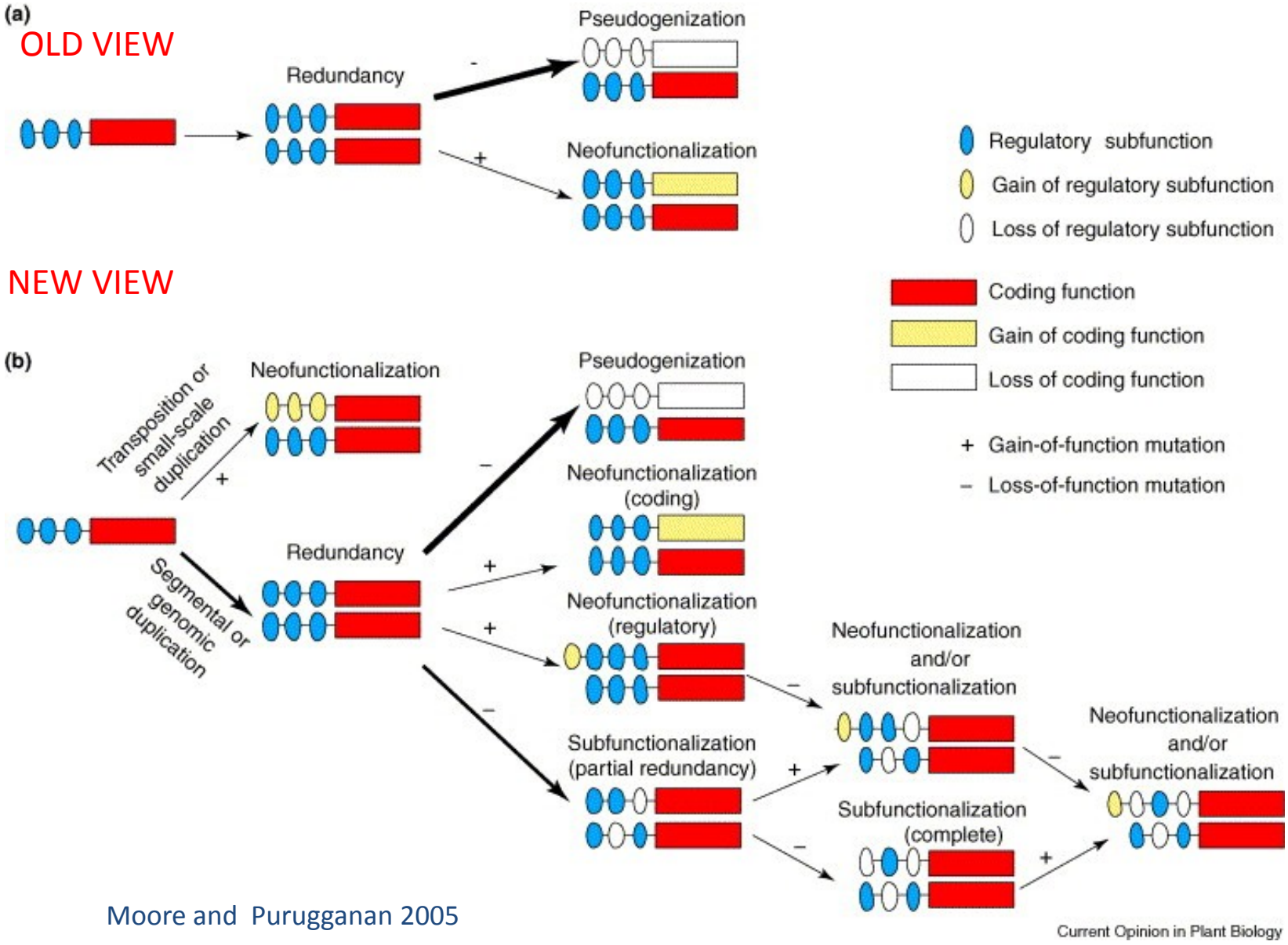
subfunctionalization: example in terms of protein complexes (=GO cellular component)



neofunctionalization: example in terms of protein complexes (=GO cellular component)

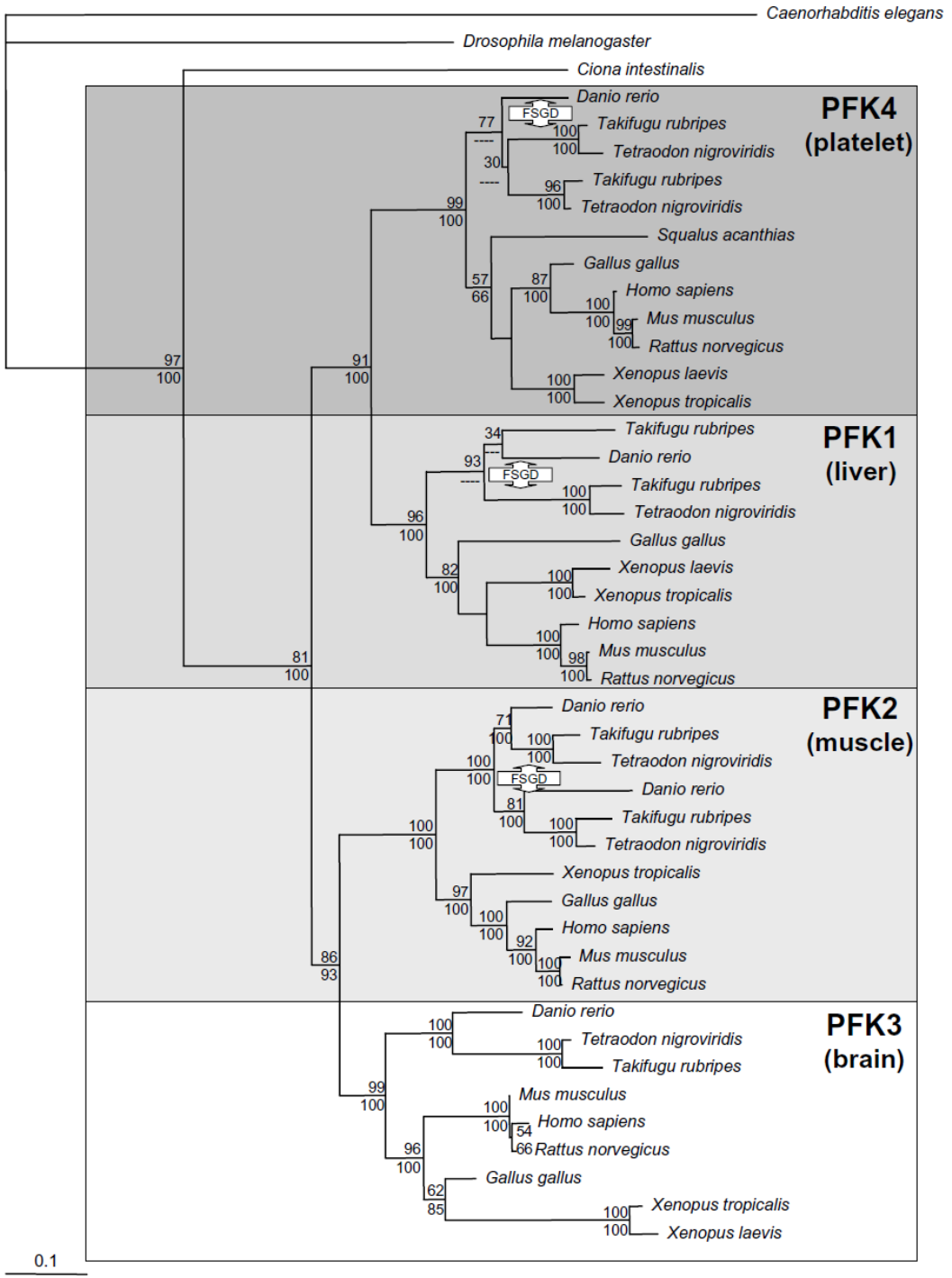


Sub vs neo in regulatory context



Moore and Purugganan 2005

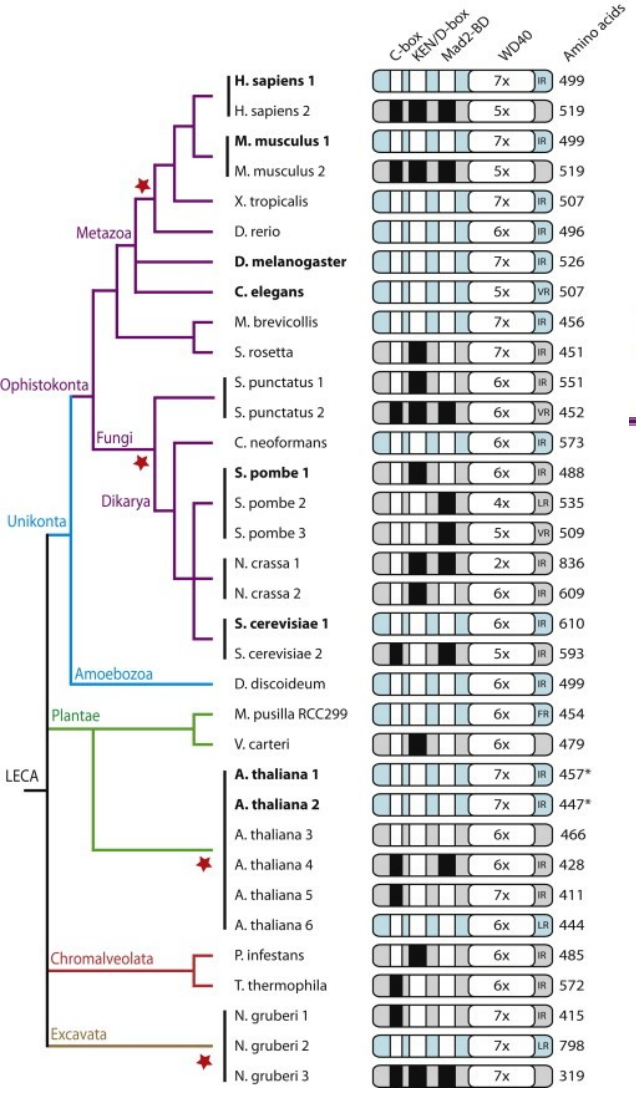
b

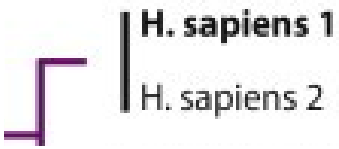


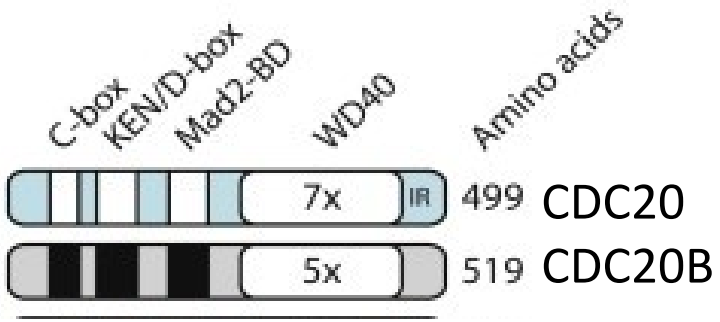
[Three rounds (1R/2R/3R) of genome duplications evolution of the glycolytic pathway in vertebrates]

Steinke D, **Hoegg** S, **Brinkmann** H, Meyer A.
BMC Biol. 2006 Jun 6;4:16.

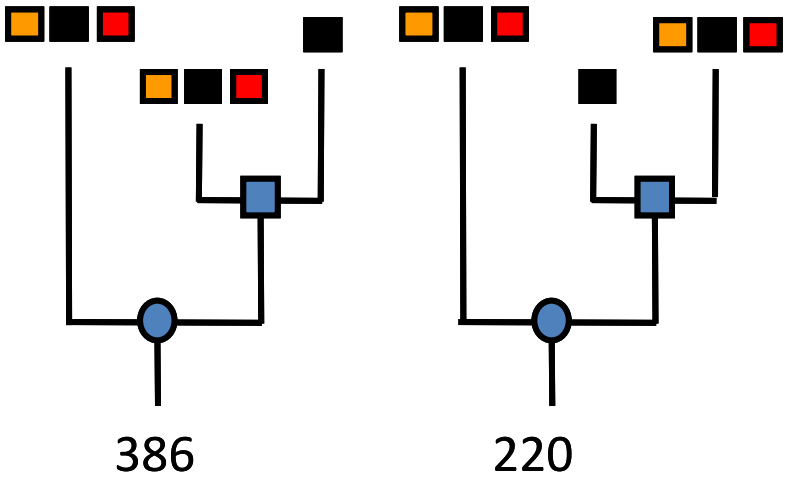
Pseudogenization vs neofunctionalization vs “marginalization”, eg. CDC20B

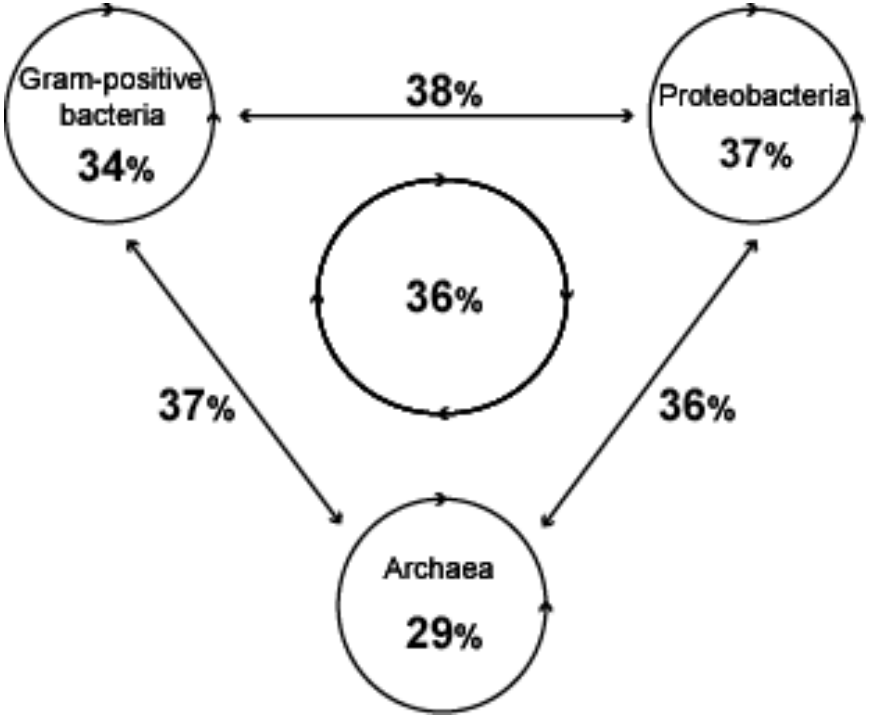




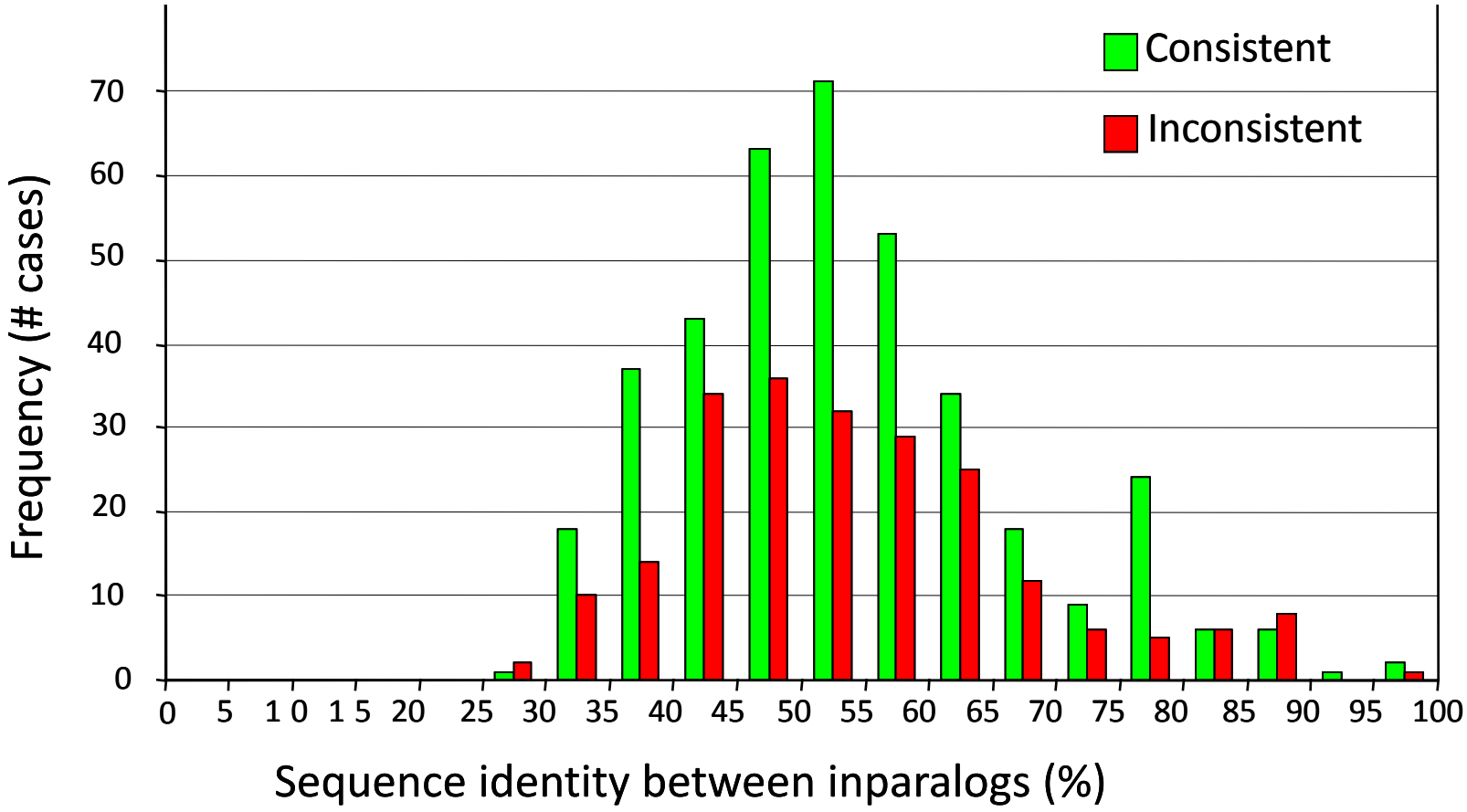


Does retaining the ancestral “role” correlate with speed of sequence evolution: yes but a substantial minority is inconsistent



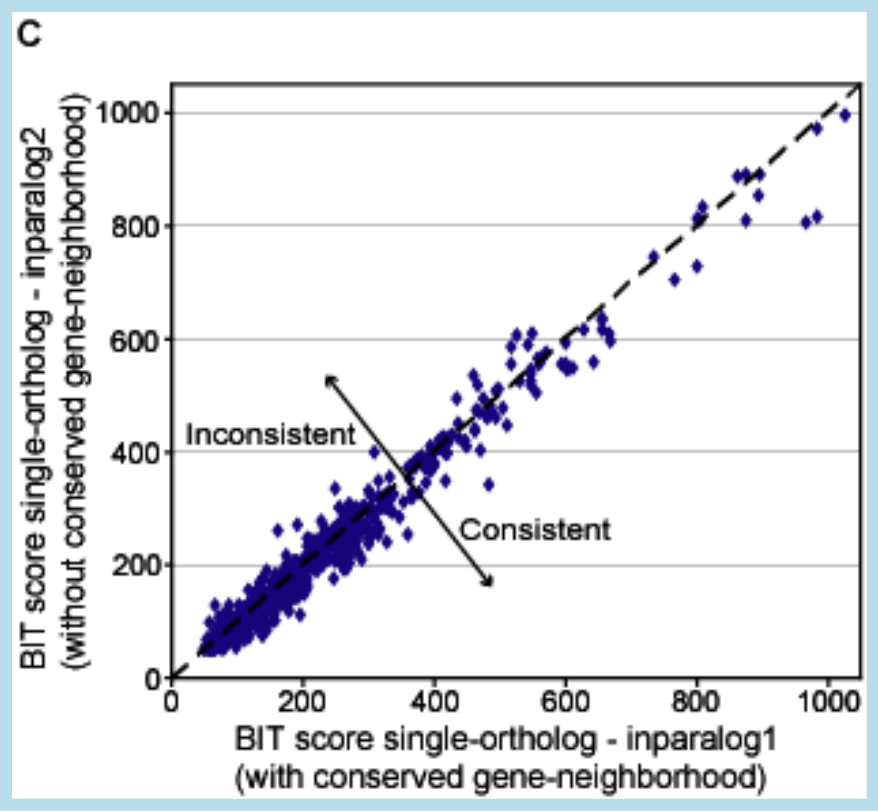


Why inconsistencies?



Not because of chance due to lack of divergence time

Why do observe inconsistencies?



Similar sequence divergence of inparalogs relative to their single-ortholog, molecular function similar?

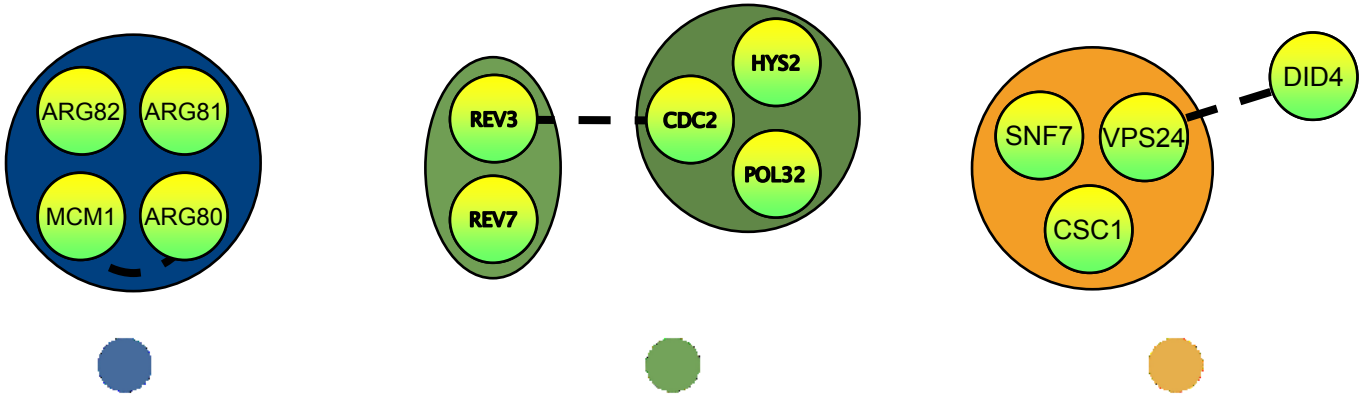
Any inconsistencies are then a chance outcome: both duplicates have diverged, but at (roughly) the same evolutionary speed (most amino acids substitutions are only been subject to purifying selection and not to adaptive selection)

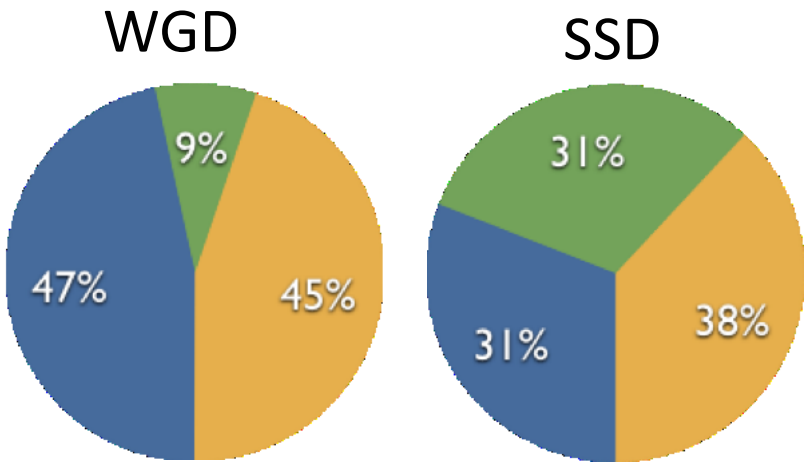
Fate of Duplicate Genes in Protein Complexes

Paralogs

- WGD + SSD, ~40% of yeast genes
- SSD
  - mostly ancient (older than WGD)
  - 500 pairs
- Complexes:

	GO curated	HTP computational
Modules	232	536
Proteins	1473	2177

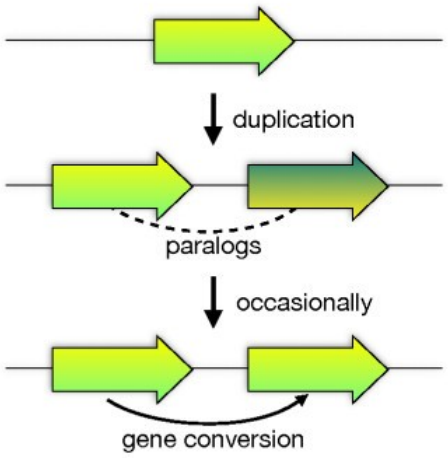




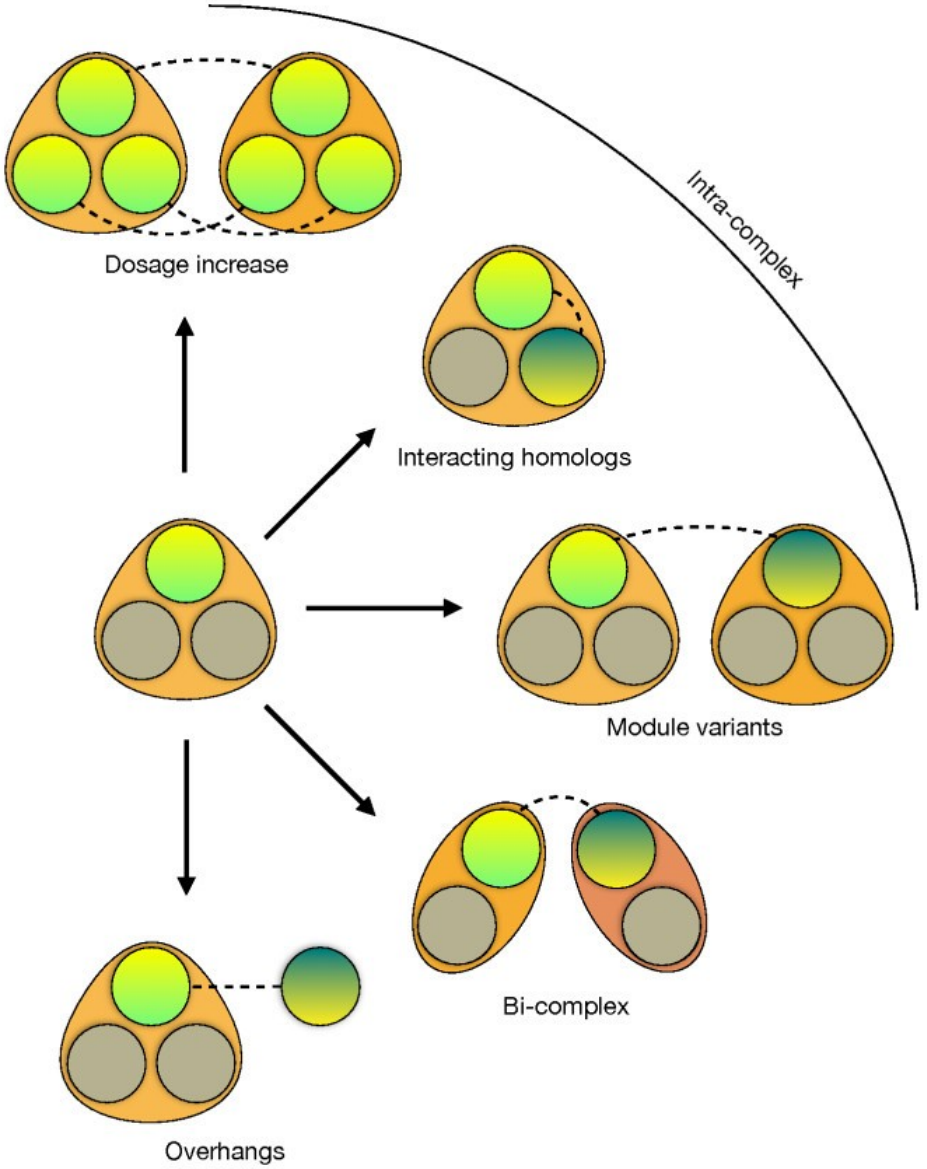
Intra-complex 216 46 ($P < 10^{-3}$)

Bi-complex 62

Overhangs 58

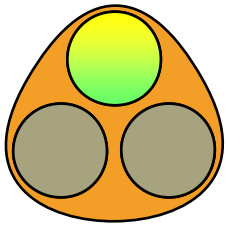

duplication
paralogs
occasionally
gene conversion

a


Intra-complex
Dosage increase
Interacting homologs
Module variants
Bi-complex
Overhangs

b

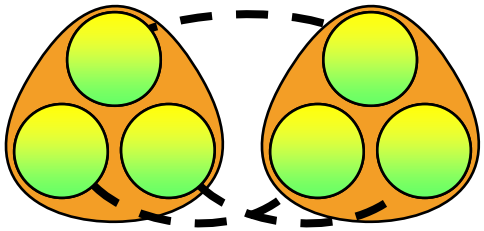
Intra-complex

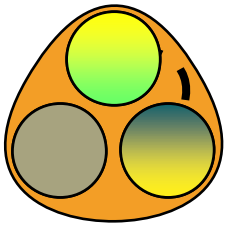


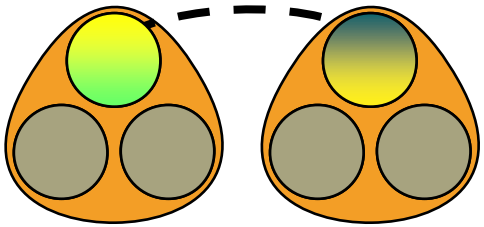
Dominating fate of paralogs (~40x enrichment)

But there's more to it:

- mRNA dosage (cRP, co-expr ~1)
- interacting homologs (co-expr ~0.4)
- module variants (co-expr ~0.2)



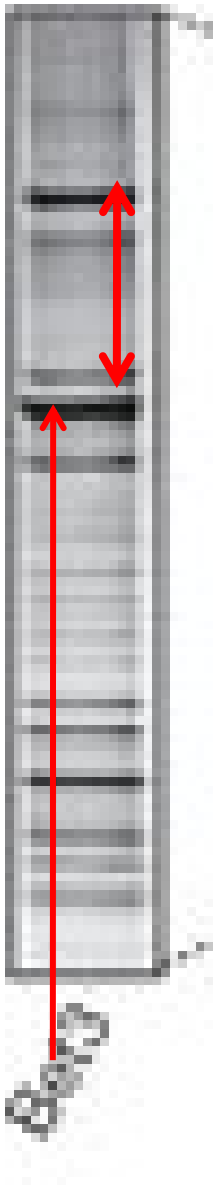


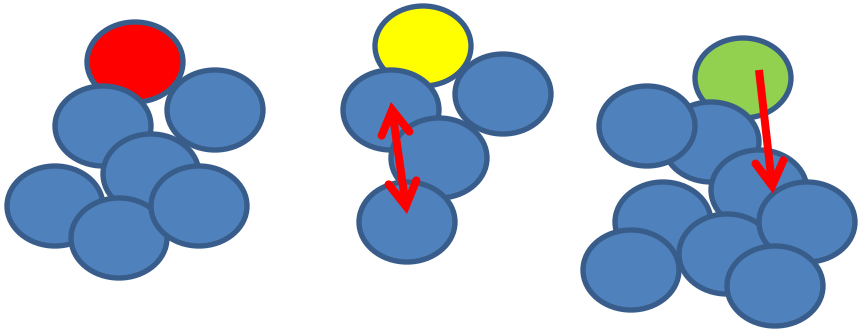


Also can be seen

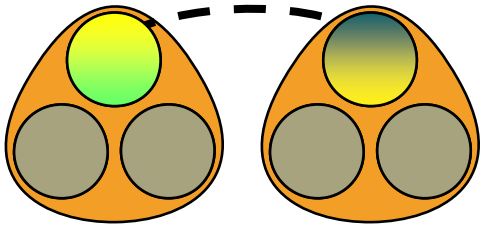
from mass-spec data

Prey-prey vs bait-prey





Module variants

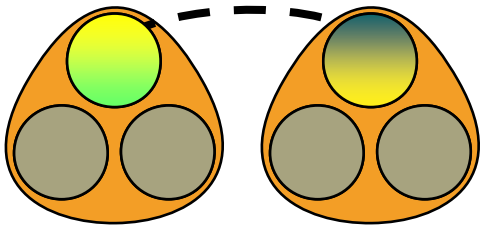


WGD, redundant (non-lethal)

complementary pattern of growth rates

Module variant paralogs	Deletion phenotype
COX5A/COX5B	COX5A knockout: reduced fitness when no glucose
KIP1/CIN8	CIN8 knockout: unrestricted growth only on glycine
BUL2/BUL1	BUL1 knockout: reduced fitness on ethanol
DID4/VPS24	DID4 knockout: severely reduced growth on lactate
NOT5/NOT3	NOT3 knockout: severely impaired growth on glycine NOT5 knockout: growth severely impaired in all conditions tested
REG2/REG1	REG1 knockout: limited growth on glucose

Module variants



re-use of a complex

additional functions, environments it can operate

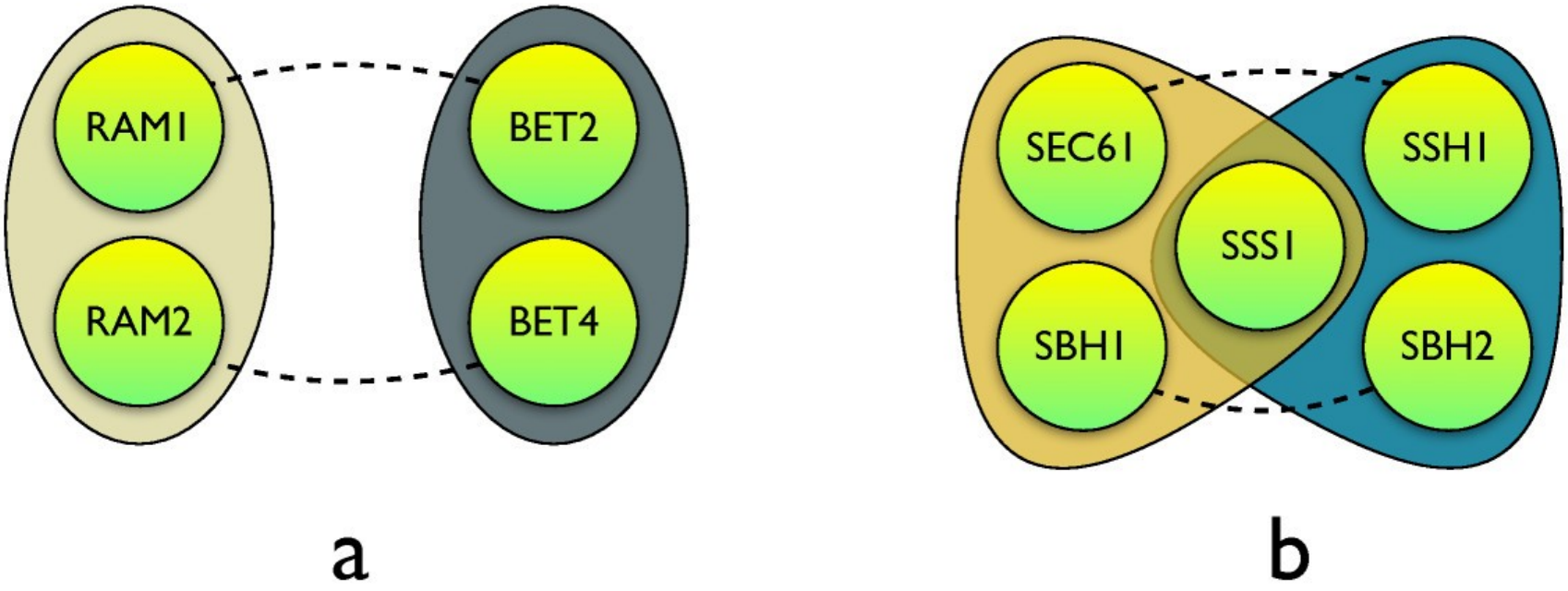
Relation to KO data

Type of intra-complex paralogs and viability of single-gene knockouts in rich medium.

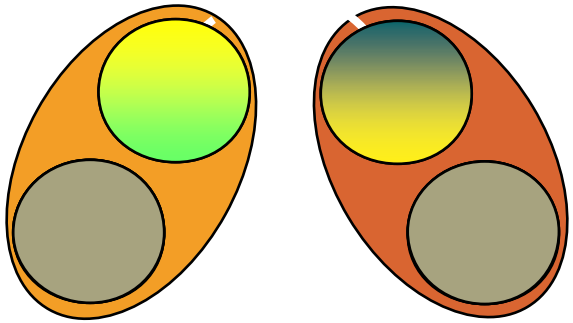
Intra-complex duplication type	**Fraction essential**
Interacting homologs	50% (12/24)
Module variants	19% (10/54)
Average*	32% (71/225)

*) calculated among all paralogs involved in modules.

Examplex of whole-complex duplication



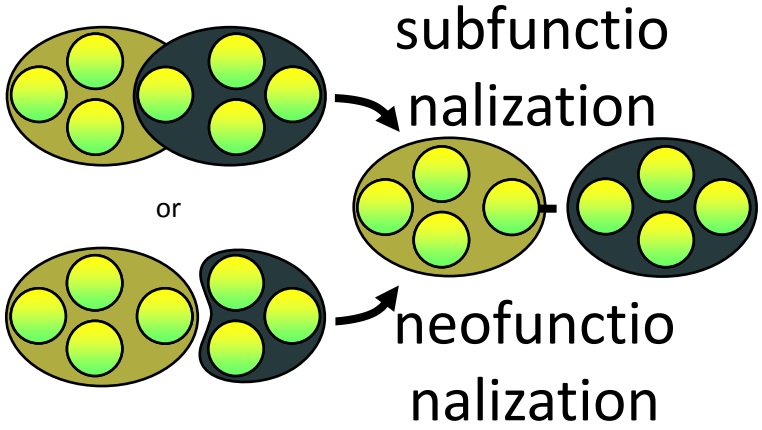
shared subunits / bi-complex

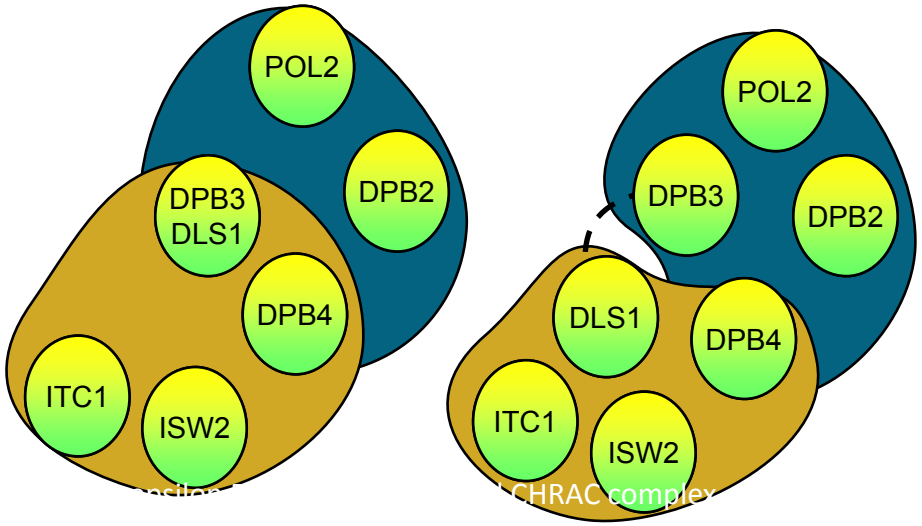


When homologs participate in different modules

underrepresented, only 20% are WGD paralogs

BUT: aren't module variants also bi-complex in a sense? -> zipper model of protein evolution





Research

Open Access

Chromatin Central: towards the comparative proteome by accurate mapping of the yeast proteomic environment

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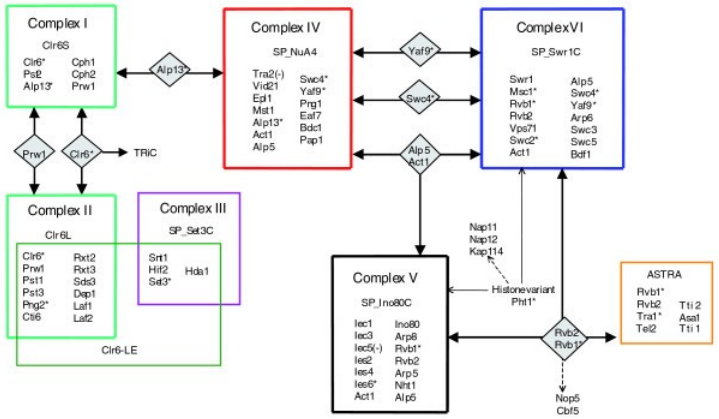
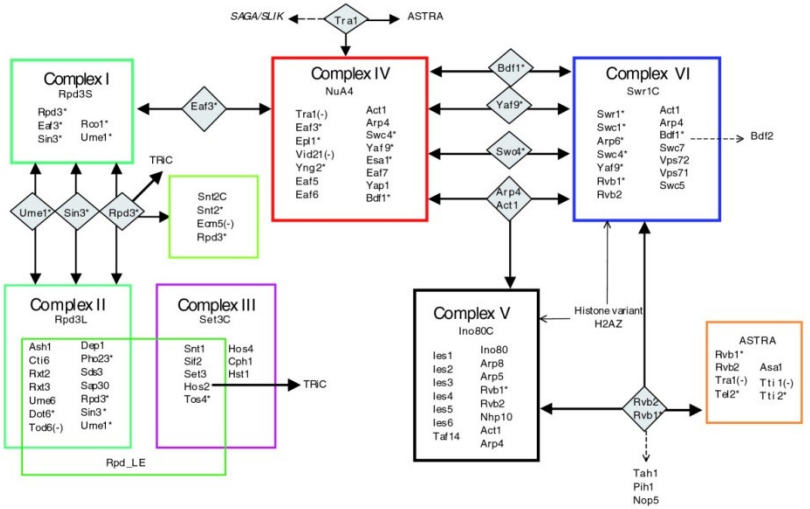
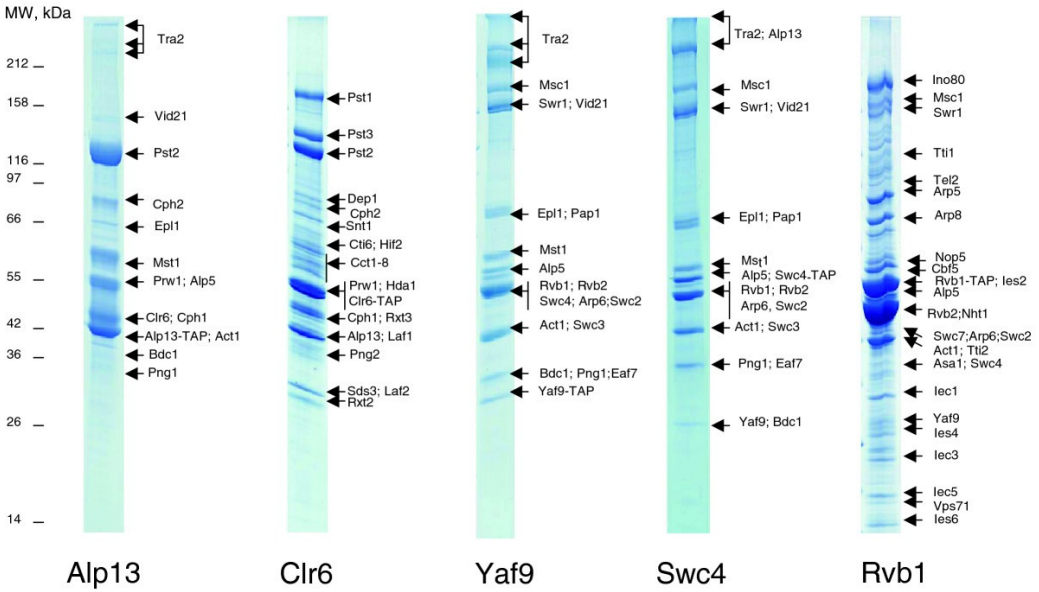
pombe

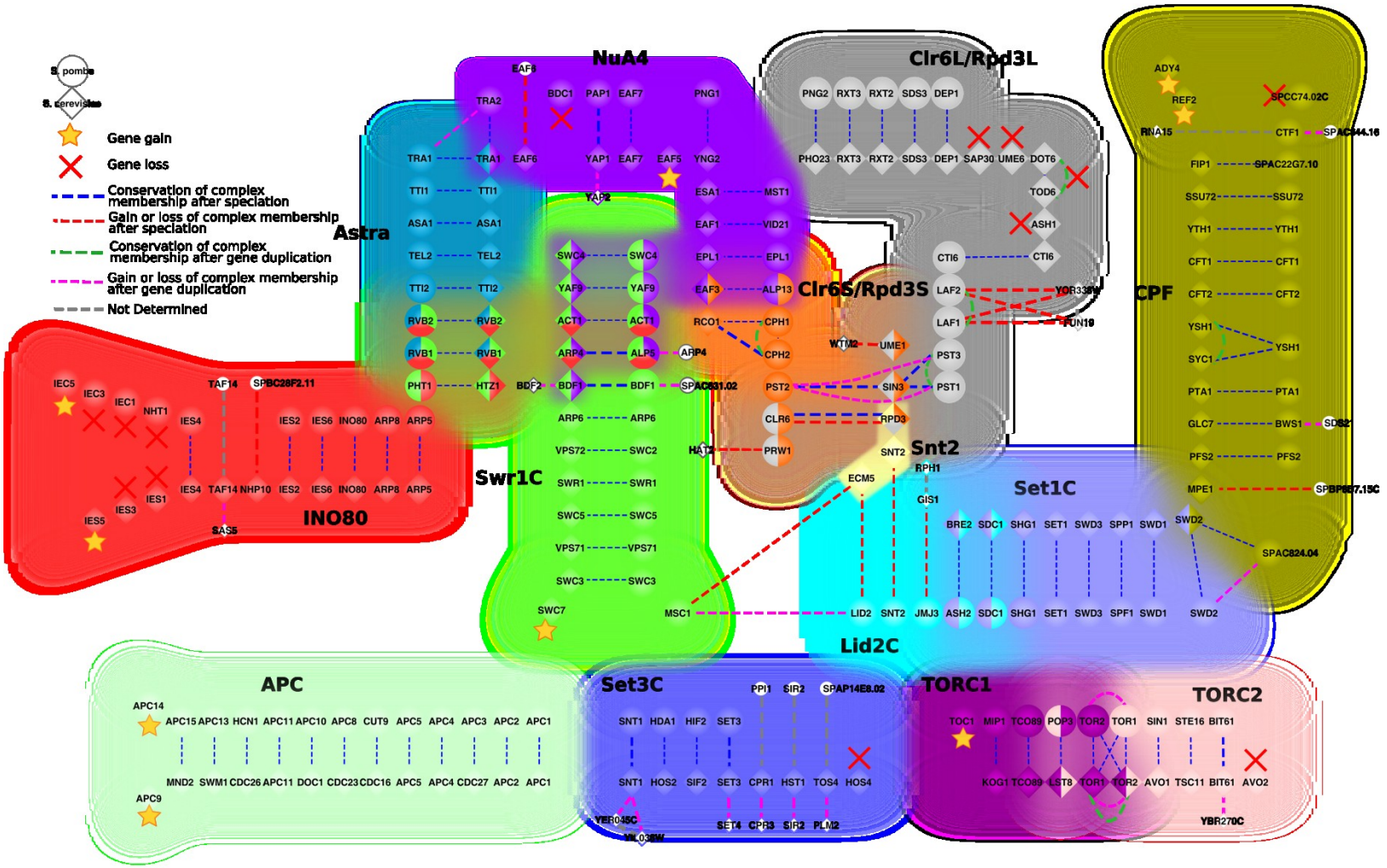
cerevisiae

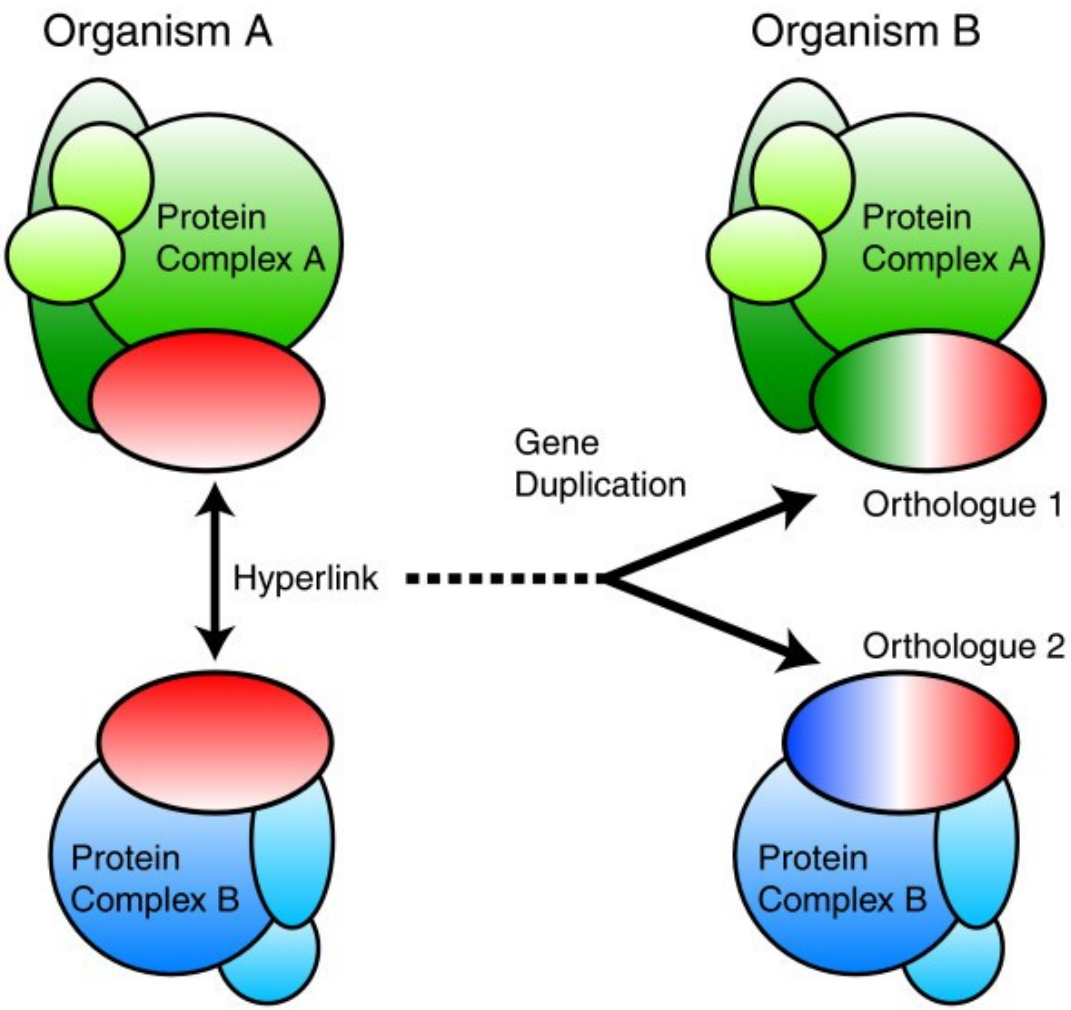


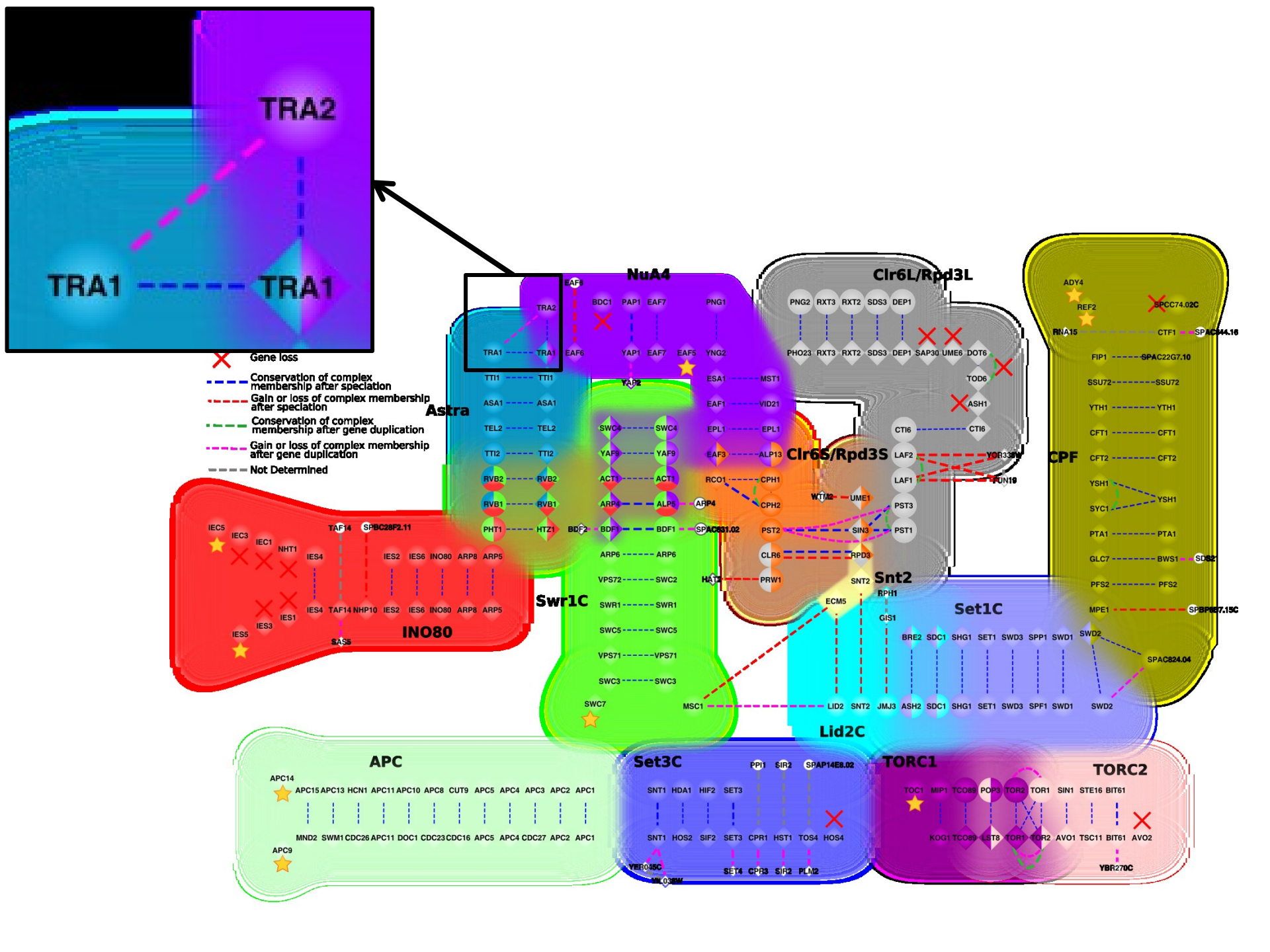


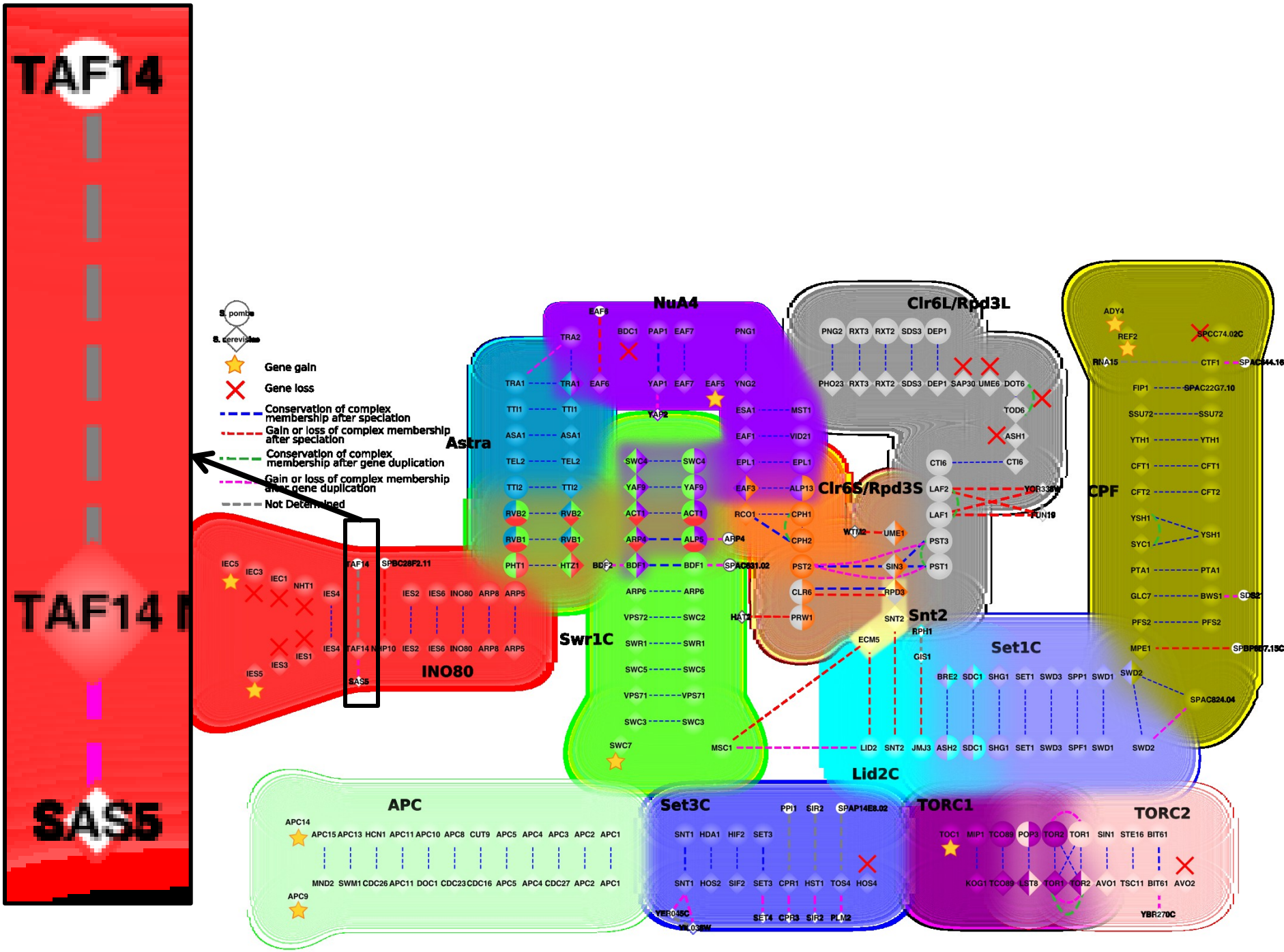


Protein-complex alignment




Organism A
Organism B
Protein Complex A
Protein Complex A
Gene Duplication
Orthologue 1
Hyperlink
Orthologue 2
Protein Complex B
Protein Complex B


TRA2
TRA1
TRA1
Gene loss
Conservation of complex membership after speciation
Gain or loss of complex membership after speciation
Conservation of complex membership after gene duplication
Gain or loss of complex membership after gene duplication
Not Determined
NuA4
Astra
Clr6L/Rpd3L
Clr6S/Rpd3S
CPF
Swr1C
INO80
Snt2
Set1C
Lid2C
APC
Set3C
TORC1
TORC2


TAF14
TAF14
SAS5
S. pombe
S. cerevisiae
Gene gain
Gene loss
Conservation of complex membership after speciation
Gain or loss of complex membership after speciation
Conservation of complex membership after gene duplication
Gain or loss of complex membership after gene duplication
Not Determined
NuA4
Astra
Swr1C
INO80
Clr6L/Rpd3L
Clr6S/Rpd3S
CPF
Snt2
Set1C
Lid2C
APC
Set3C
TORC1
TORC2

Research

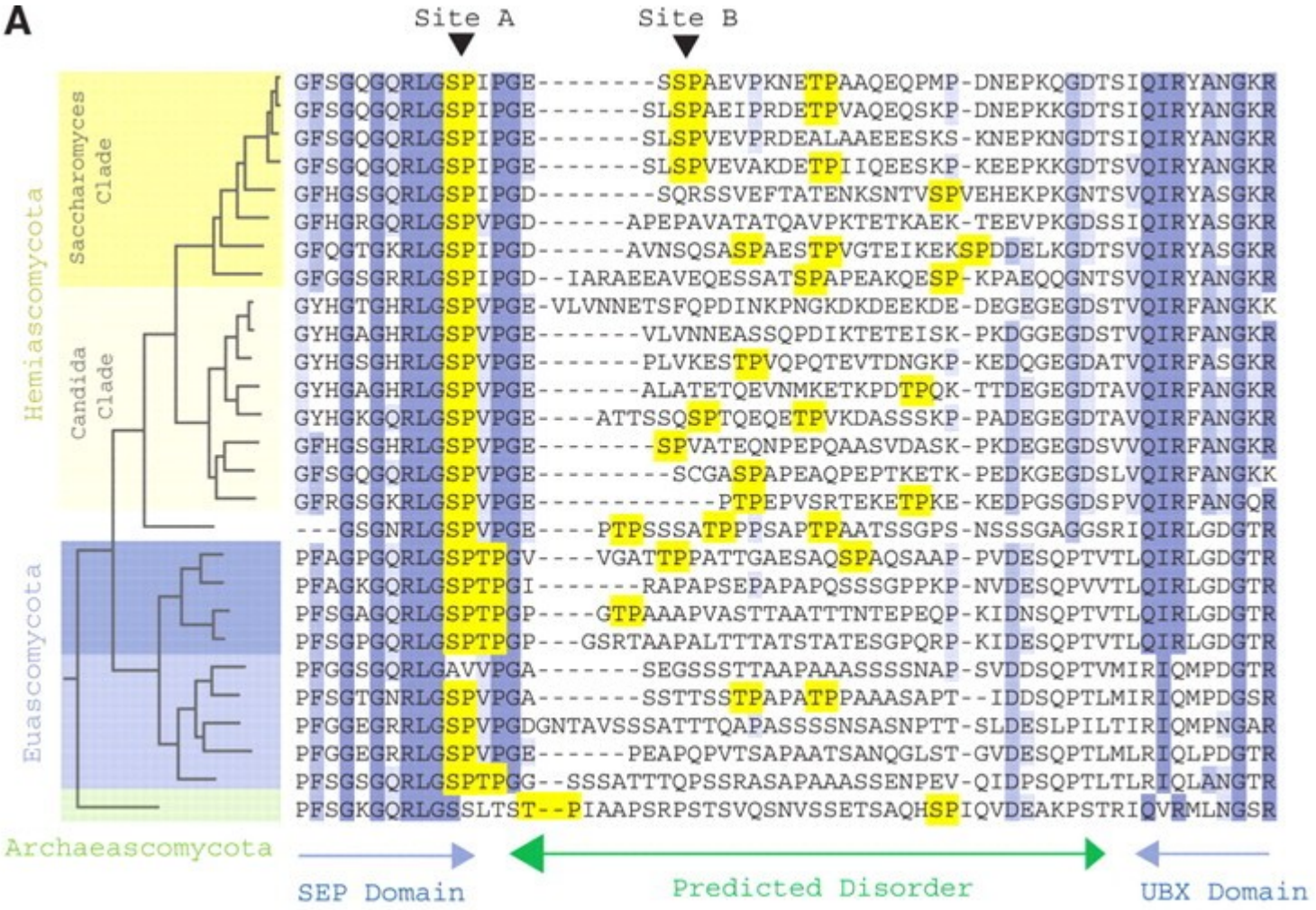
Open Access

Genome adaptation to chemical stress: clues from comparative transcriptomics in *Saccharomyces cerevisiae* and *Candida glabrata*

Gaëlle Lelandais*†, Véronique Tanty‡, Colette Geneix*§, Catherine Etchebest*, Claude Jacq†‡ and Frédéric Devaux†

- "We found that although the gene expression patterns characterizing the response to drugs were remarkably conserved between the two species, part of the underlying regulatory networks differed."

Evolution of phosphorylation



Science
AAAS

Global Analysis of Cdk1 Substrate Phosphorylation Sites Provides Insights into Evolution

Liam J. Holt *et al.*

Science **325**, 1682 (2009);
DOI: 10.1126/science.1172867

- position of most phosphorylation sites is not conserved in evolution; instead, clusters of sites shift position in rapidly evolving disordered regions.
- the regulation of protein function by phosphorylation often depends on simple nonspecific mechanisms that disrupt or enhance protein-protein interactions.

“dynamic conservation”

- Function / output is conserved but exact wiring / positions is not

- Also implied to play a large role in evolution of transcription factor binding sites.

Regulatory relations seem to evolve faster

- E.g. Phosphorylation (phosphoproteomics), expression (rna-seq, microarray), tf-binding (Chip-seq, chip-chip)

- Is all the binding / expression / modification functional?: likely not;
- does that completely explain the fast evolution?; likely not all. Also “dynamic conservation” and genuine changes. Can we accuratedly distinguish this, not so easily yet, “Similar signals”.

General considerations

- All HTP measure of function and definition of function come with a big set of issues
- Genome evolution (gene gain, gene loss, duplication) do shape the network to a very large extent
- Conservation at one level while flexible (neutral) at another level