
Predicción de Interacciones entre Proteínas Basada en Información Evolutiva

Florencio Pazos (CNB-CSIC)

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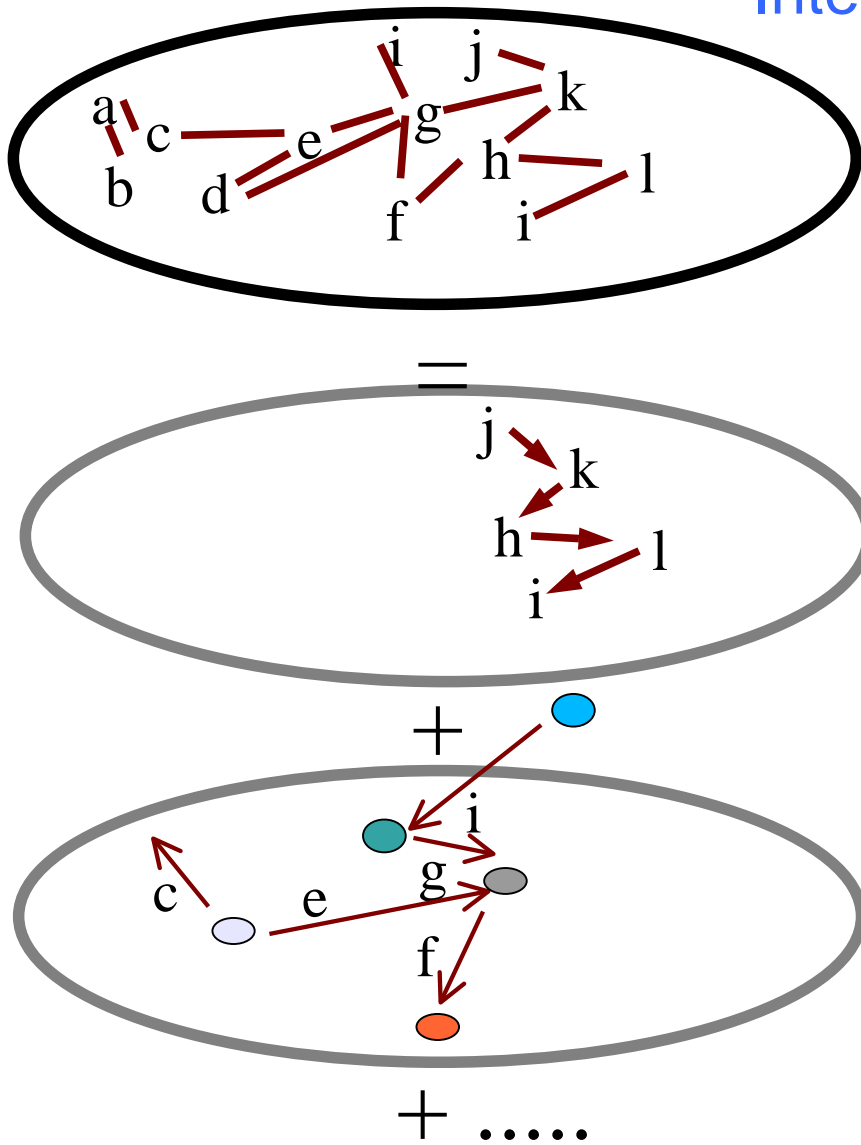
- El “interactoma”
- Determinación experimental masiva (*high throughput*) de interactomas
- Métodos computacionales de base evolutiva para predicción de interacciones
 - Conservación de cercanía genómica
 - Fusión génica
 - Perfiles filogenéticos
 - Mutaciones correlacionadas
 - Similitud de árboles filogenéticos
- Bibliografía

Biología de Sistemas

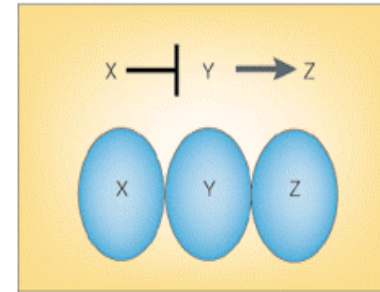
Caracterización masiva de componentes moleculares y sus relaciones

- Genome sequencing (“genome”).
- Transcript characterization (mRNA) (“transcriptome”)
- Characteristics of the protein repertory (“proteome”)
- Cellular localization of the components (“localizome”)
- Gene regulation network (“regulome”)
- **Protein interaction network (“interactome”)**
- Massive gene-phenotype studies (“fenoma”)
- Metabolic networks (“metabolome”)
-

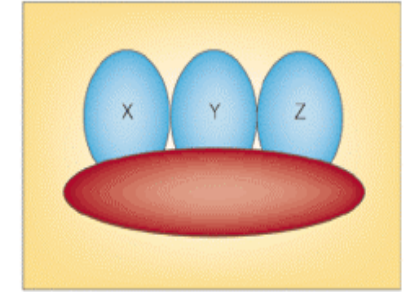
Interactoma



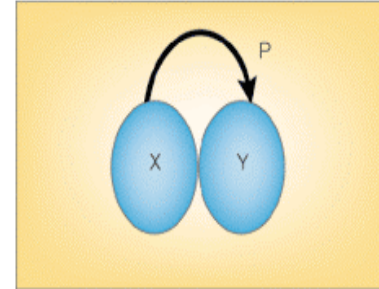
a Genetic pathways



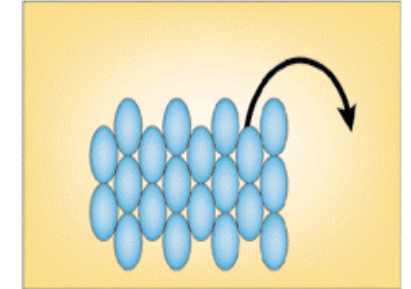
b Pathway scaffolding



c Enzymatic reactions

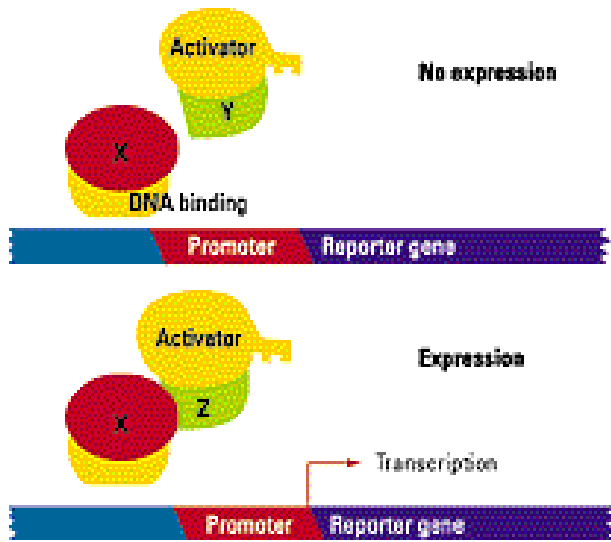


d Molecular machines

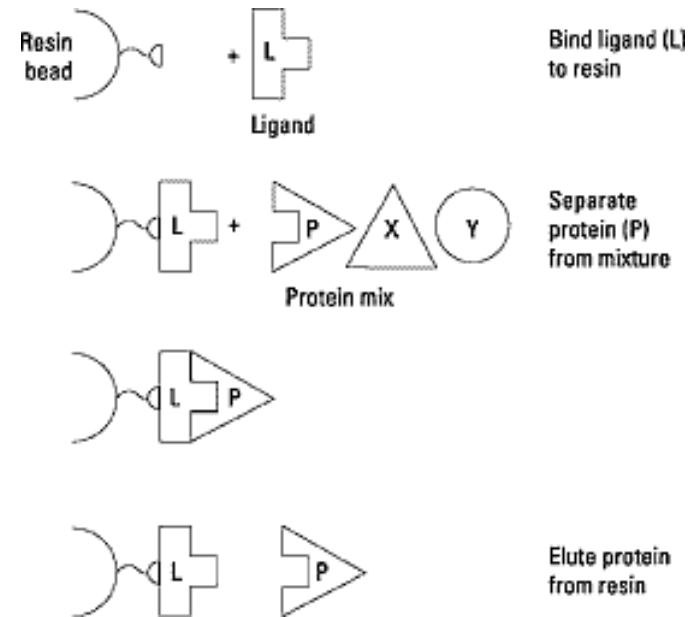


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Determinación Experimental Masiva del Interactoma



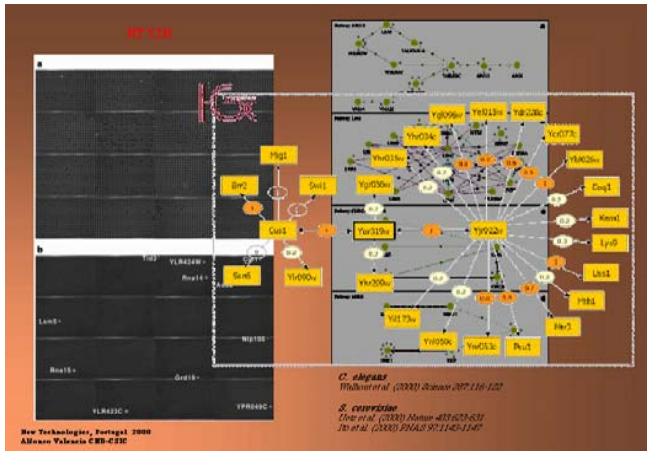
Y2H



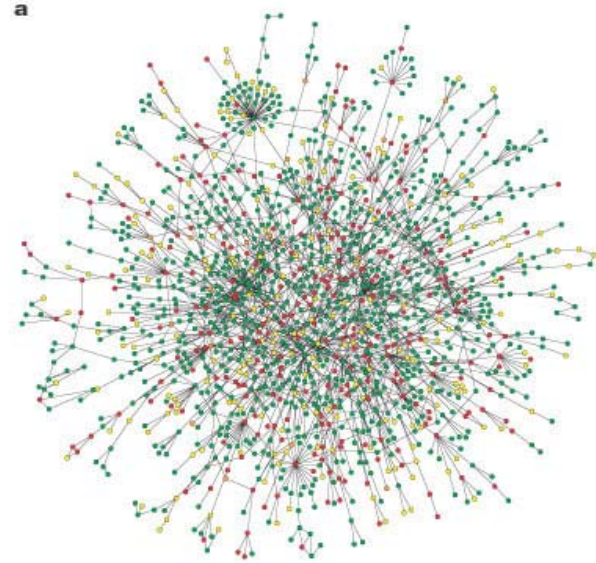
TAP/MS

<http://pubs.acs.org/hotartcl/mdd/00/sep/edwards.html>

Interactomas determinados experimentalmente (*high throughput*)

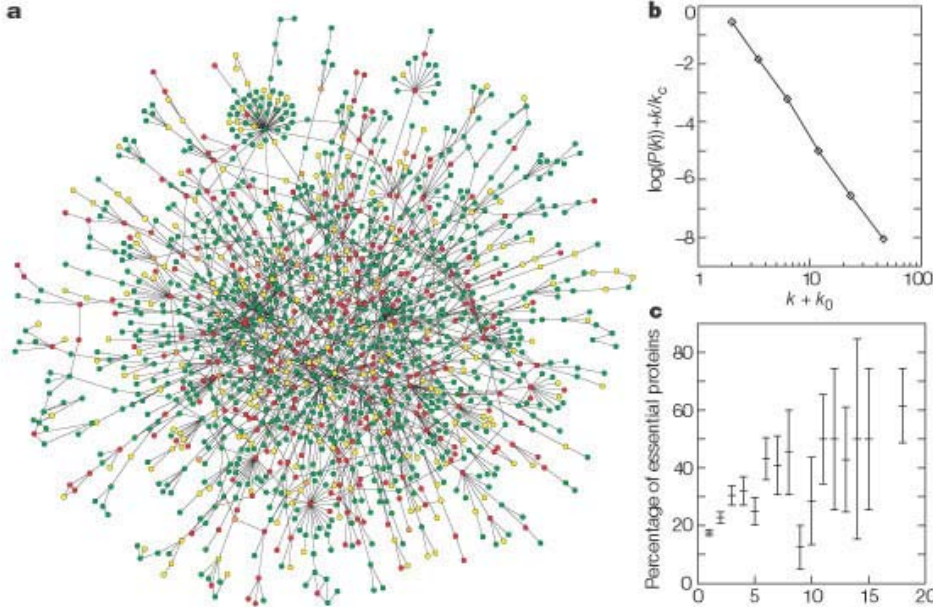


A.Valencia

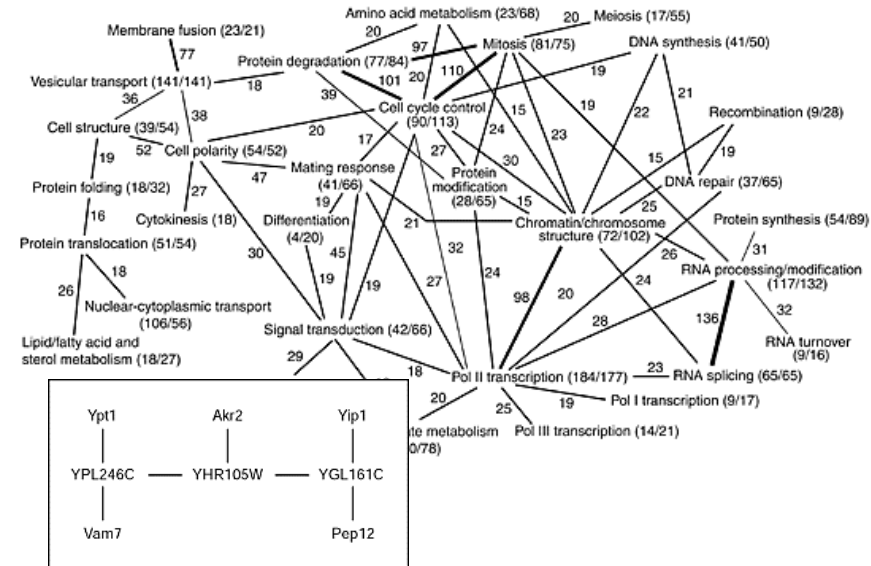
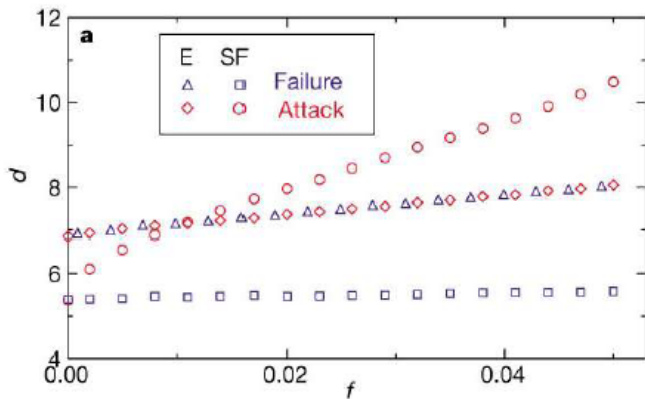


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- Ito, T., et al. (2000) Toward a protein-protein interaction map of the budding yeast: A comprehensive system to examine two-hybrid interactions in all possible combinations between the yeast proteins. *Proc Natl Acad Sci USA*, **97**, 1143-1147.
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- Butland, G., Peregrin-Alvarez, J.M., Li, J., et al. (2005) Interaction network containing conserved and essential protein complexes in *Escherichia coli*. *Nature*, **433**, 531-537.
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- Uetz, P., Dong, Y.A., Zeretzke, C., Atzler, C., Baiker, A., Berger, B., Rajagopala, S.V., Roupelieva, M., Rose, D., Fossum, E., et al. (2006) Herpesviral protein networks and their interaction with the human proteome. *Science*, **311**, 239-242.

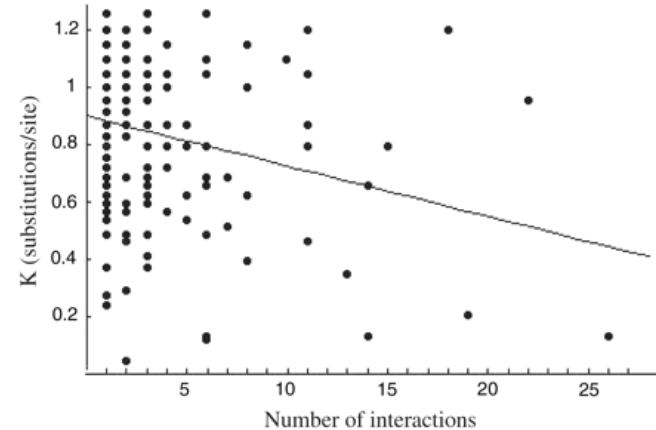
Estudio de los interactomas (*top-down*)



Jeong, H., Mason, S. P., Barabasi, A. L. & Oltvai, Z. N. (2001). Lethality and centrality in protein networks. *Nature* **411**, 41-42.



Schwikowski, B., Uetz, P. & Fields, S. (2002). A network of protein-protein interactions in yeast. *Nature Biotech* **18**, 1257-1261.



Fraser, H.B., Hirsh, A.E., Steinmetz, L.M., Scharfe, C. and Feldman, M.W. (2002) Evolutionary rate in the protein interaction network. *Science*, **296**, 750-752.

Calidad de los datos de interacciones *high throughput*

Table 1
Large protein interaction screens for eukaryotes

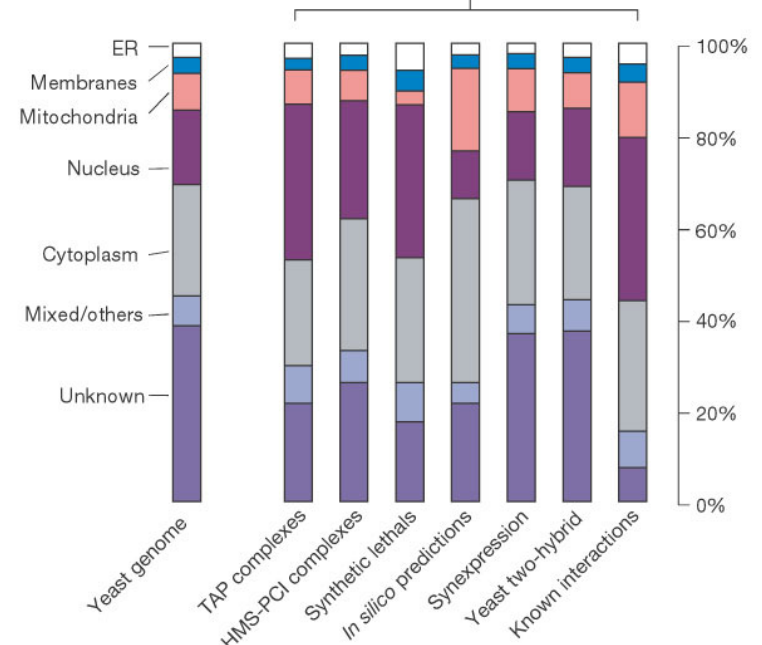
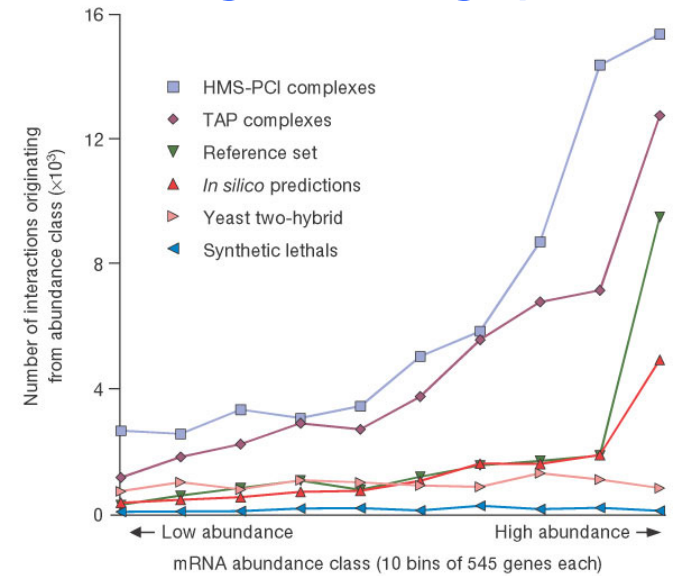
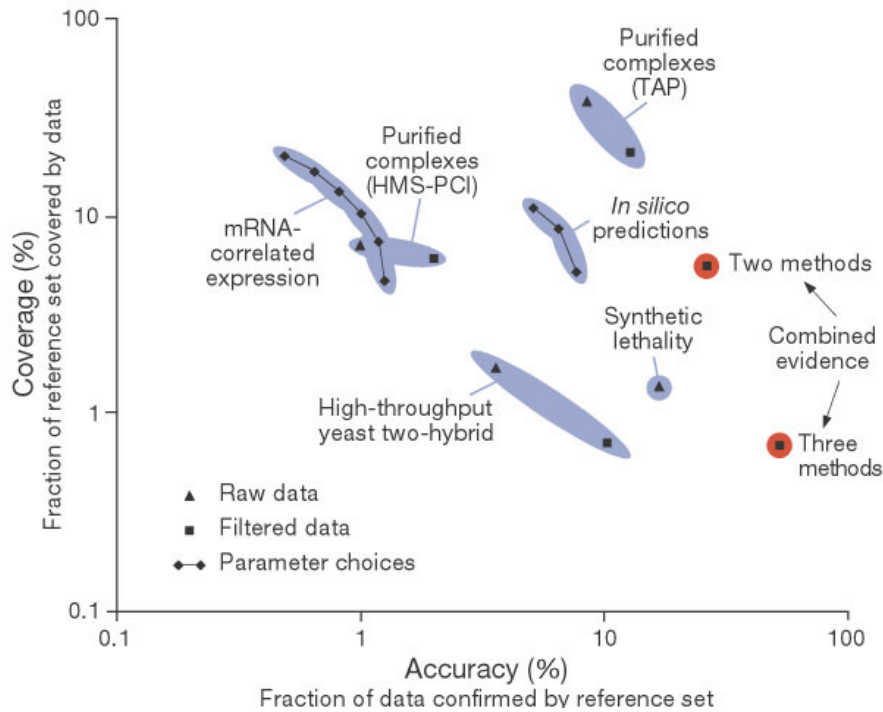
Organism (genes)	Method	Interactions ^a	Proteins	Reference
Yeast (~6000)	Yeast two-hybrid	967	1004	[63]
	Yeast two-hybrid	4549	3278	[13]
	Yeast two-hybrid	420	271	[64,65]
	Co-AP/MS	9421	1665	[66]
	Co-AP/MS	3878	1578	[67]
<i>Drosophila</i> (~14 000)	Yeast two-hybrid	20 405	7048	[49]
	Yeast two-hybrid	1814	488	[14]
Worm (~20 000)	Yeast two-hybrid	4027	1926	[68]

Overlap:
6 int !

^aFor two-hybrid screens, the approximate number of unique binary interactions is shown. For co-AP/MS screens, the approximate number of binary interactions that would result if each bait protein contacted every protein that co-purified with it (the “hub and spoke” model) is shown. Data can be retrieved from one of the databases cited [42–44].

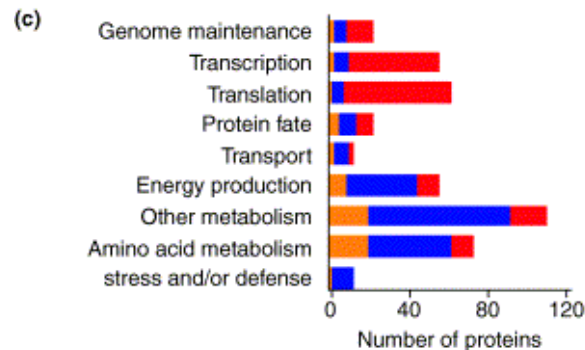
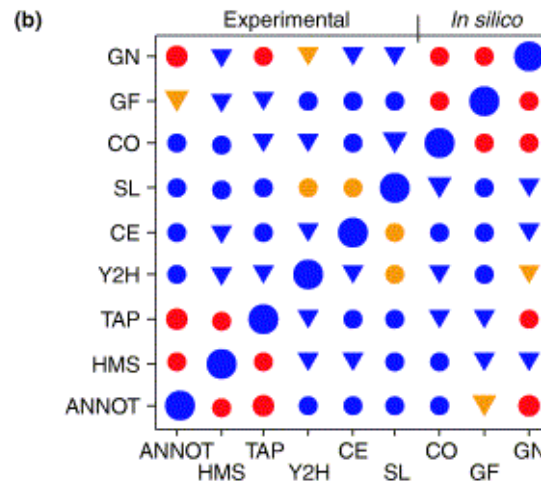
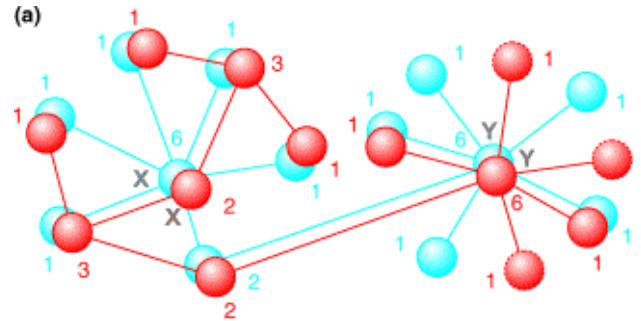
Estimation (yeast): 12.000-40000 (6000)

Calidad de los datos de interacciones *high throughput*



von Mering, C., Krause, R., Snel, B., Cornell, M., Oliver, S.G., Fields, S. and Bork, P. (2002) Comparative assessment of large scale data sets of protein-protein interactions. *Nature*, **417**, 399-403.

Calidad de los datos de interacciones *high throughput*



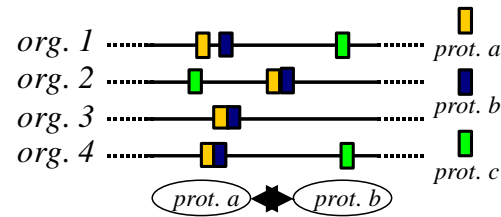
Predicción Computacional de Interacciones entre Proteínas

a) phylogenetic profiles

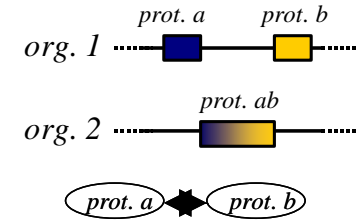
	prot. a	prot. b	prot. c	prot. d
org. 1	1	1	1	1
org. 2	0	1	0	1
org. 3	1	0	1	0
org. 4	1	0	1	1

(prot. a) ↔ (prot. c)

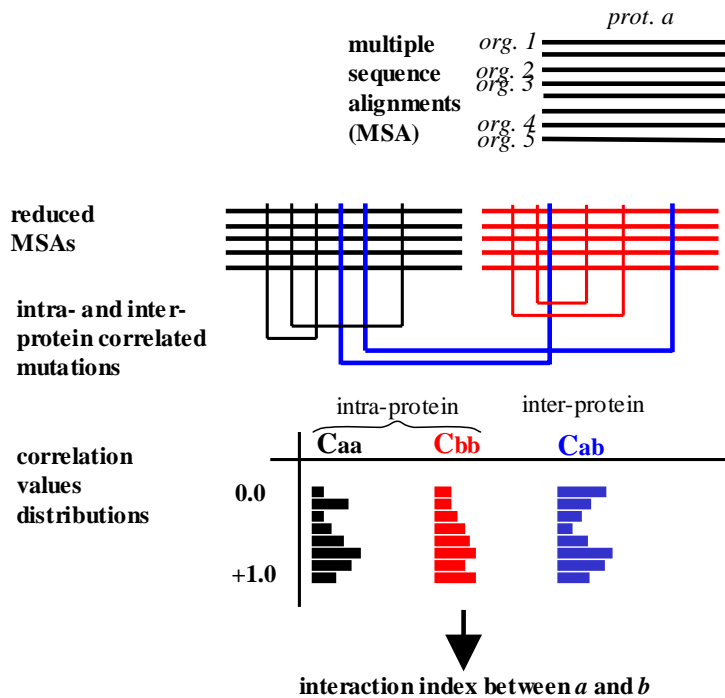
b) conservation of gene neighbouring



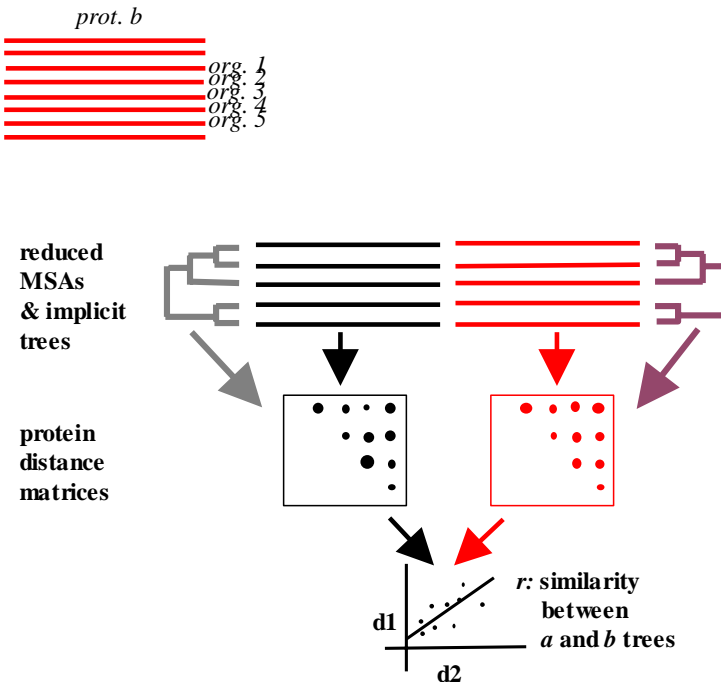
c) gene fusion



e) correlated mutations

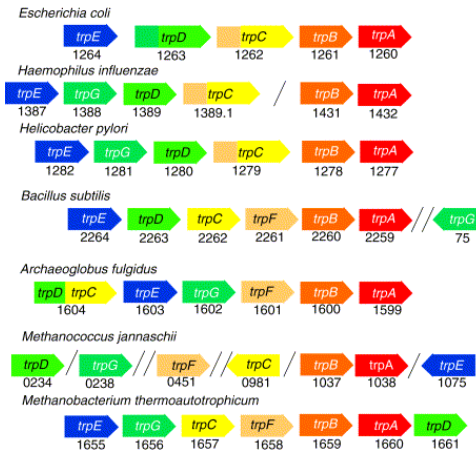
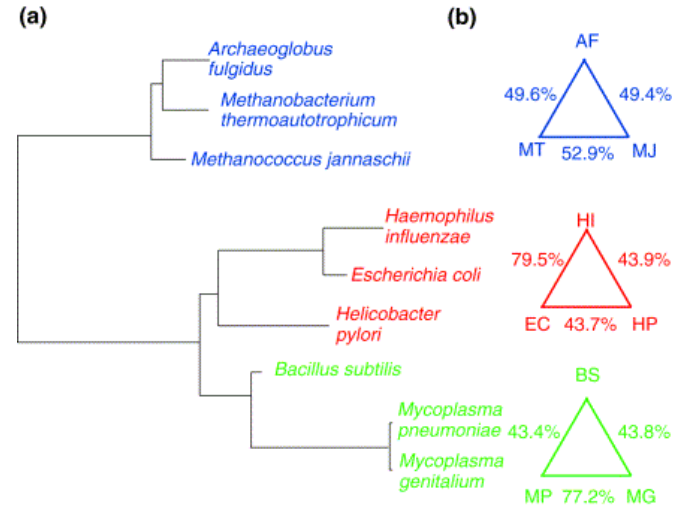
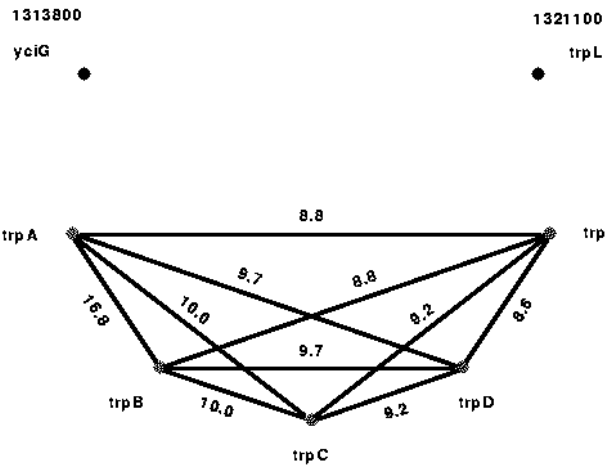
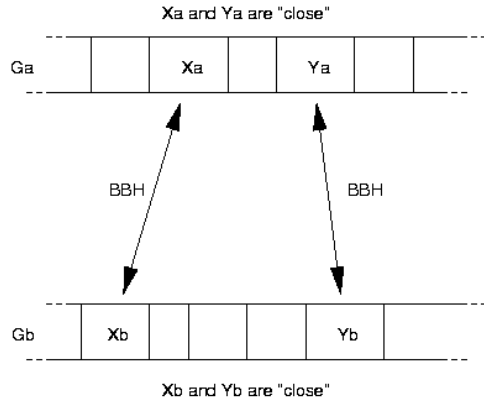


d) similarity of phylogenetic trees



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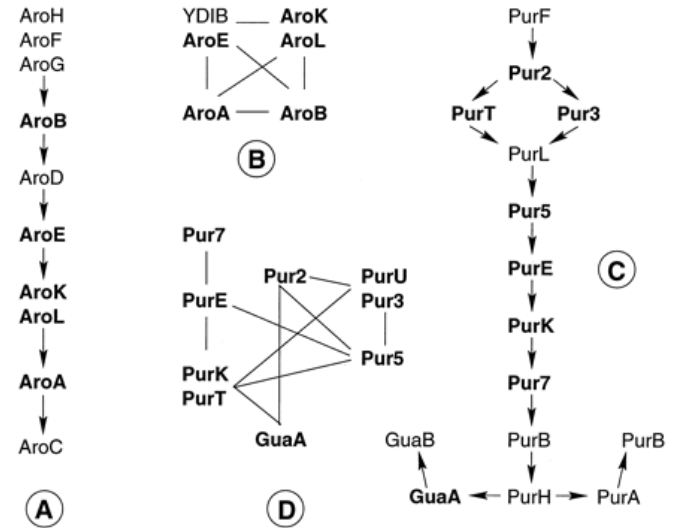
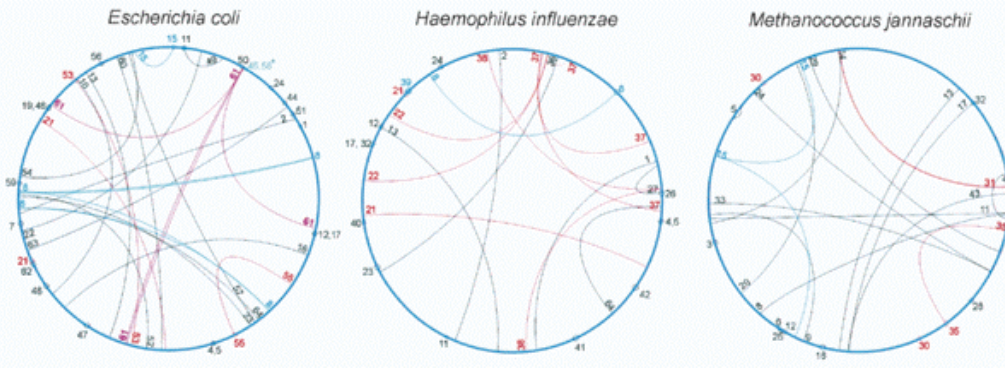
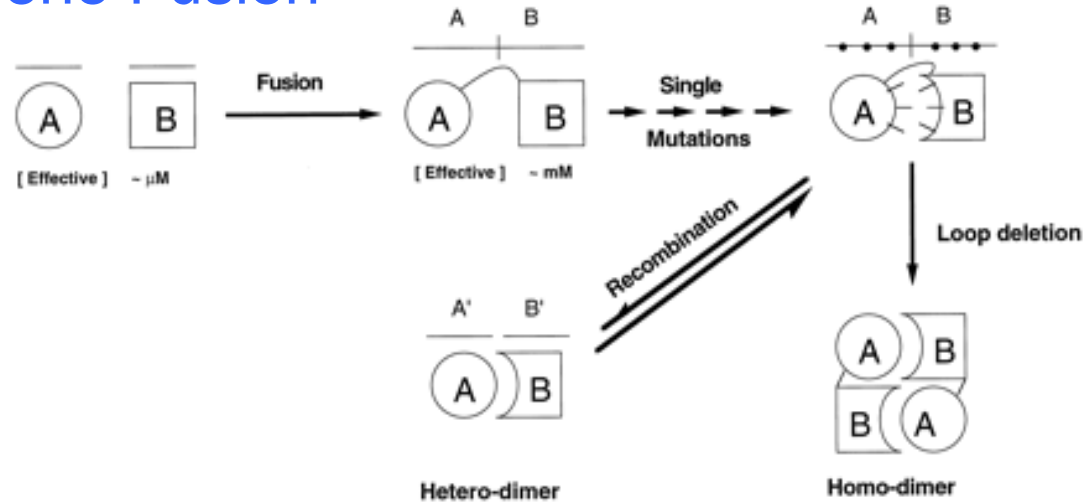
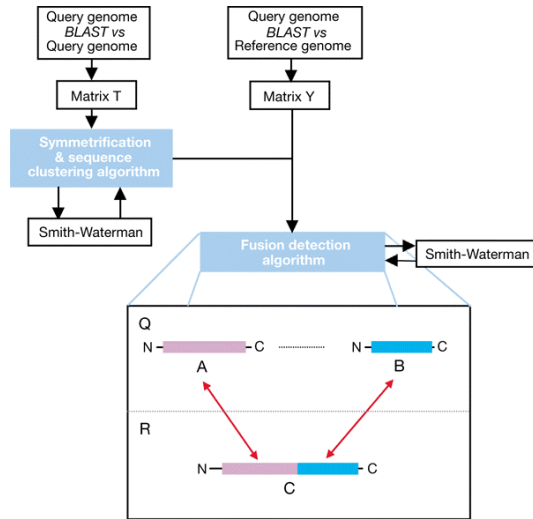
Conservation of gene neighboring



Overbeek, R., Fonstein, M., D'Souza, M., Pusch, G. D. & Maltsev, N. (1999). Use of contiguity on the chromosome to predict functional coupling. *In Silico Biol.* **1**, 93-108.

Dandekar, T., Snel, B., Huynen, M. & Bork, P. (1998). Conservation of gene order: a fingerprint of proteins that physically interact. *Trends Biochem Sci.* **23**, 324-328.

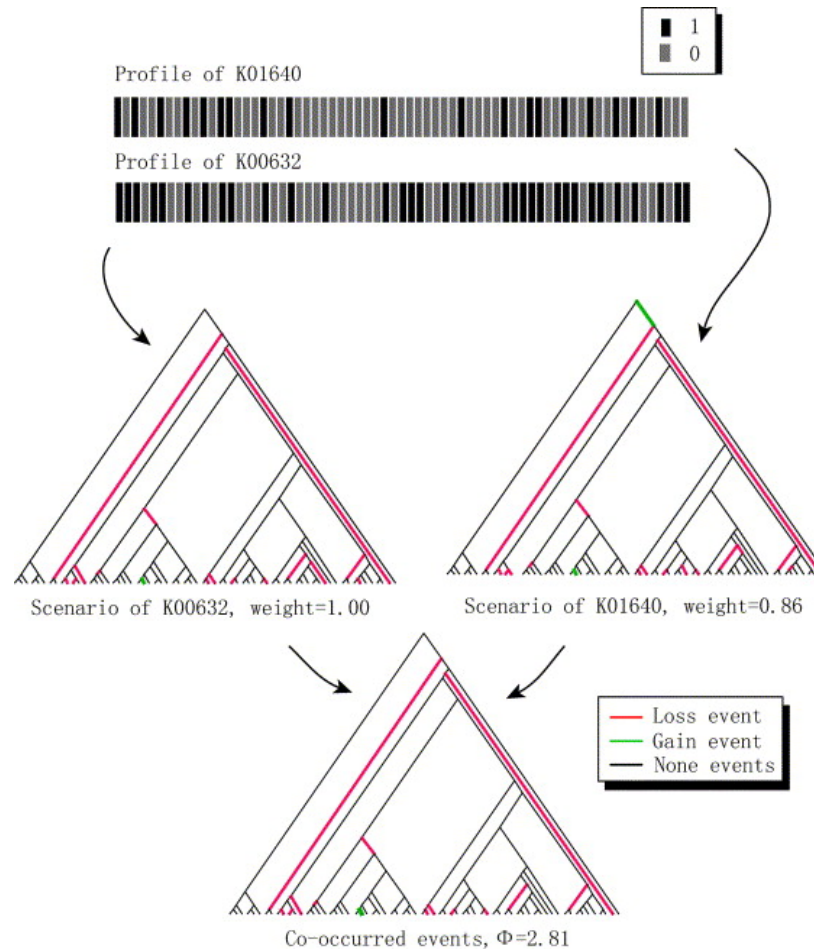
Gene Fusion



Enright, A. J., Iliopoulos, I., Kyripides, N. C. & Ouzounis, C. A. (1999). Protein interaction maps for complete genomes based on gene fusion events. *Nature*. **402**, 86-90.

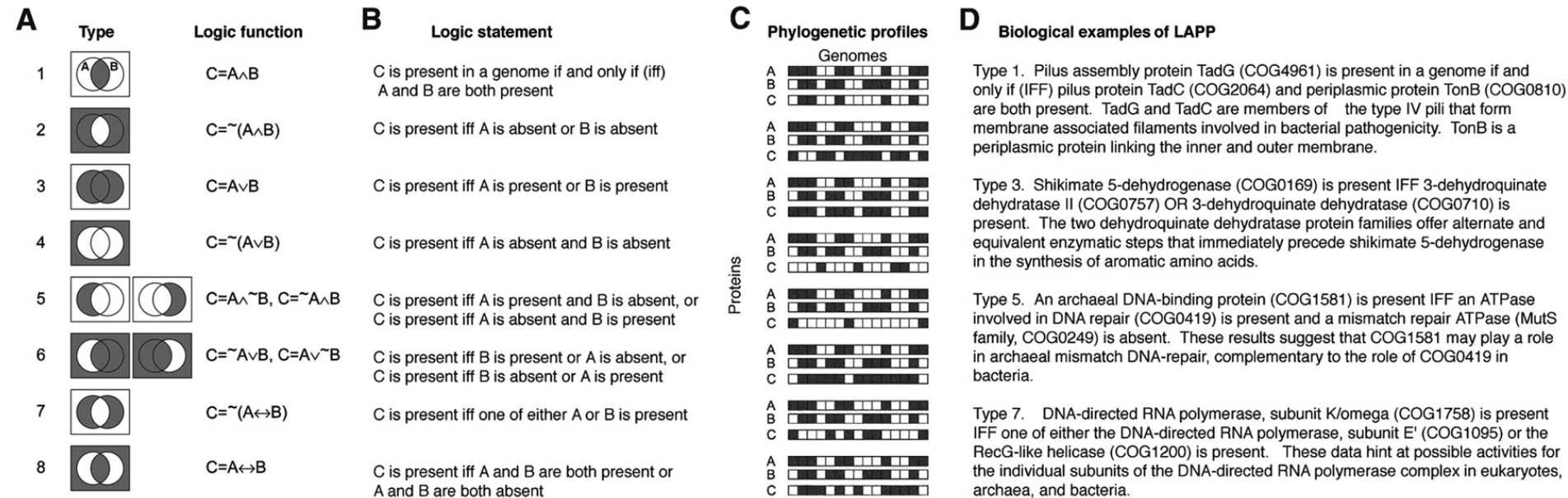
Marcotte, E. M., Pellegrini, M., Ho-Leung, N., Rice, D. W., Yeates, T. O. & Eisenberg, D. (1999). Detecting protein function and protein-protein interactions from genome sequences. *Science*. **285**, 751-753.

Phylogenetic Profiles

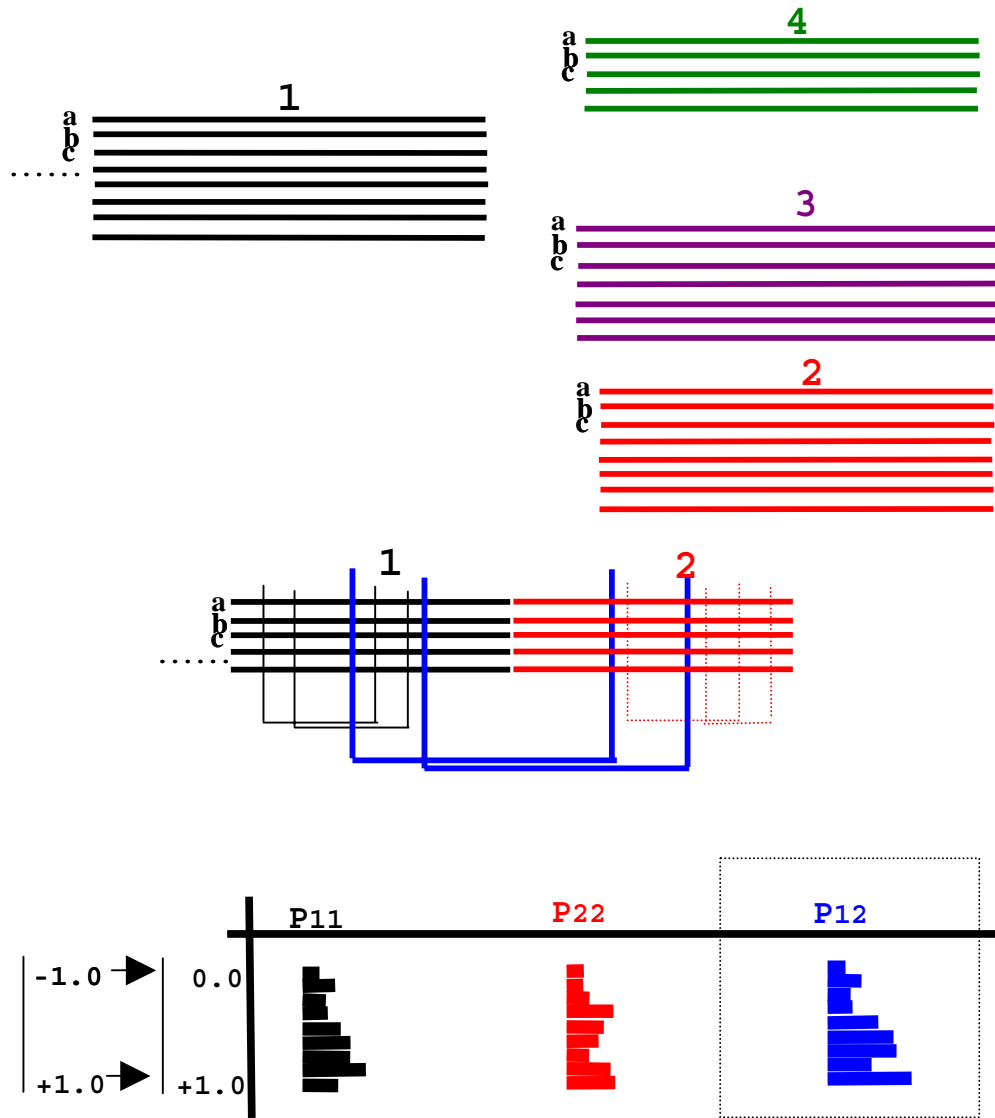


-
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Phylogenetic Profiles



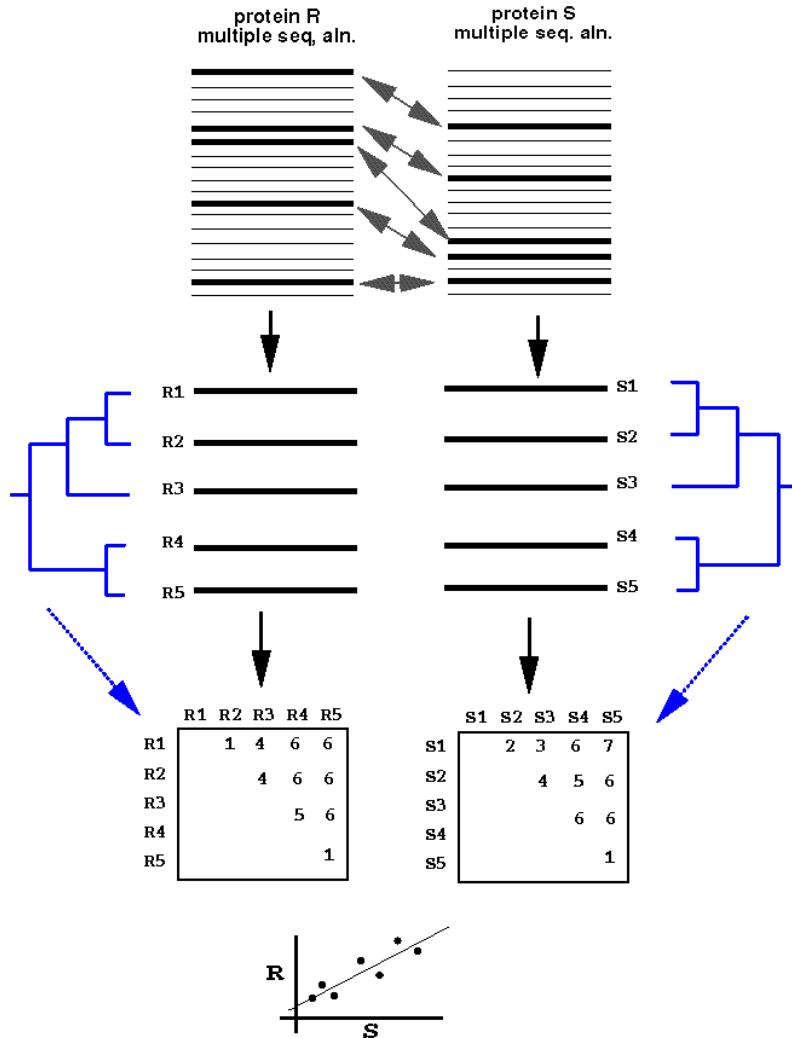
Based on correlated mutations (*i2h*)



Based on correlated mutations (*i2h*)

2c2c_2-1alc_1		3,503	1alc_1-1rnd_1		0,968
1sgt_2-4mt2_1		3,448	3adk_2-4tnc_2		0,961
9pap_1-9pap_2	*	3,042	1alc_1-1rnd_2		0,957
1alc_1-1alc_2	*	2,852	1sgt_1-2c2c_2		0,889
2c2c_1-4mt2_1		2,825	2c2c_2-3pgk_1		0,878
4tms_1-4tms_2	*	2,735	3trx_1-9pap_2		0,857
3trx_1-3trx_2	*	2,571	4tnc_1-4mt2_2		0,853
4mt2_1-4mt2_2	*	2,469	4tnc_2-4mt2_2		0,836
2c2c_2-4mt2_1		2,355	3trx_1-3pgk_2		0,829
2c2c_2-4mt2_2		2,331	3trx_1-9pap_1		0,814
4tnc_1-4tnc_2	*	2,238	2c2c_2-1rnd_2		0,813
3blm_1-3blm_2	*	2,206	4tms_2-3dfr_2		0,809
3pgk_1-3pgk_2	*	2,197	9pap_2-3adk_2		0,805
2c2c_1-4mt2_2		2,139	4tms_1-3dfr_2		0,804
1sgt_2-2c2c_1		2,068	1sgt_2-1alc_1		0,799
2c2c_1-1alc_1		2,011	9pap_1-3adk_2		0,790
2c2c_1-1alc_2		1,886	3trx_2-9pap_2		0,761
3adk_1-3adk_2	*	1,862	4tnc_2-4mt2_1		0,747
1sgt_2-2c2c_2		1,835	3adk_2-3pgk_2		0,726
2c2c_1-2c2c_2	*	1,787	4tnc_1-4mt2_1		0,718
3adk_1-3pgk_1		1,624	9pap_2-4tnc_2		0,702
1rnd_1-4mt2_1		1,530	3trx_1-3adk_1		0,673
2c2c_1-9pap_2		1,520	3dfr_1-3dfr_2	*	0,657
3adk_2-3dfr_2		1,507	2pf2_2-1alc_2		0,628
1sgt_2-2pf2_2		1,489	3adk_1-4tnc_1		0,617
9pap_1-3adk_1		1,488	3adk_1-4tnc_2		0,614
3adk_1-3pgk_2		1,444	2pf2_2-1alc_1		0,595
2c2c_2-1alc_2		1,415	3adk_2-4tnc_1		0,539
2c2c_1-3pgk_2		1,389	4tms_1-3dfr_1		0,507
1sgt_1-4mt2_1		1,387	3trx_2-3pgk_1		0,489
3adk_1-3dfr_1		1,367	3trx_2-3pgk_2		0,471
1rnd_2-4mt2_1		1,359	3trx_1-3adk_2		0,471
2c2c_2-3adk_1		1,319	1sgt_1-1alc_1		0,455
1rnd_1-1rnd_2	*	1,314	3trx_1-2c2c_2		0,453
3pgk_1-4tms_1		1,299	3trx_1-2c2c_1		0,446
2c2c_1-3adk_1		1,297	4tms_2-4tnc_2		0,444
3pgk_1-4tms_2		1,292	2c2c_1-1rnd_2		0,442
3trx_1-3pgk_1		1,279	1sgt_2-1alc_2		0,435
2c2c_1-3pgk_1		1,278	3trx_2-3adk_1		0,427
1alc_1-4mt2_1		1,278	4tms_1-4tnc_2		0,413
2c2c_2-9pap_2		1,274	1sgt_1-1rnd_1		0,403
1rnd_1-4mt2_2		1,258	4tms_1-4tnc_1		0,401
3adk_2-3pgk_1		1,252	4tms_2-3dfr_1		0,398
1rnd_2-4mt2_2		1,240	1alc_2-4mt2_2		0,362
3adk_1-3dfr_2		1,209	1sgt_1-1rnd_2		0,358
3trx_2-2c2c_1		1,196	1sgt_1-4mt2_2		0,356
3pgk_2-4tms_2		1,178	1sgt_2-1rnd_1		0,352
3pgk_2-4tms_1		1,170	3trx_1-4tnc_2		0,316
			2c2c_1-4tnc_1		0,303

MirrorTree



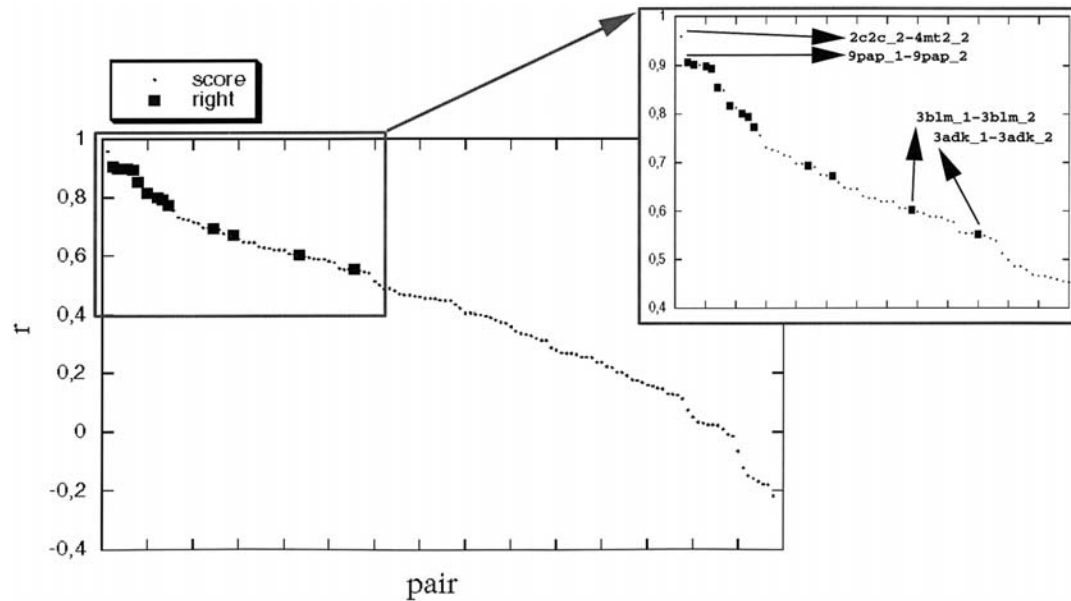
$$r = \frac{\sum_{i=1}^n (R_i - \bar{R}) \cdot (S_i - \bar{S})}{\sqrt{\sum_{i=1}^n (R_i - \bar{R})^2} \cdot \sqrt{\sum_{i=1}^n (S_i - \bar{S})^2}}$$

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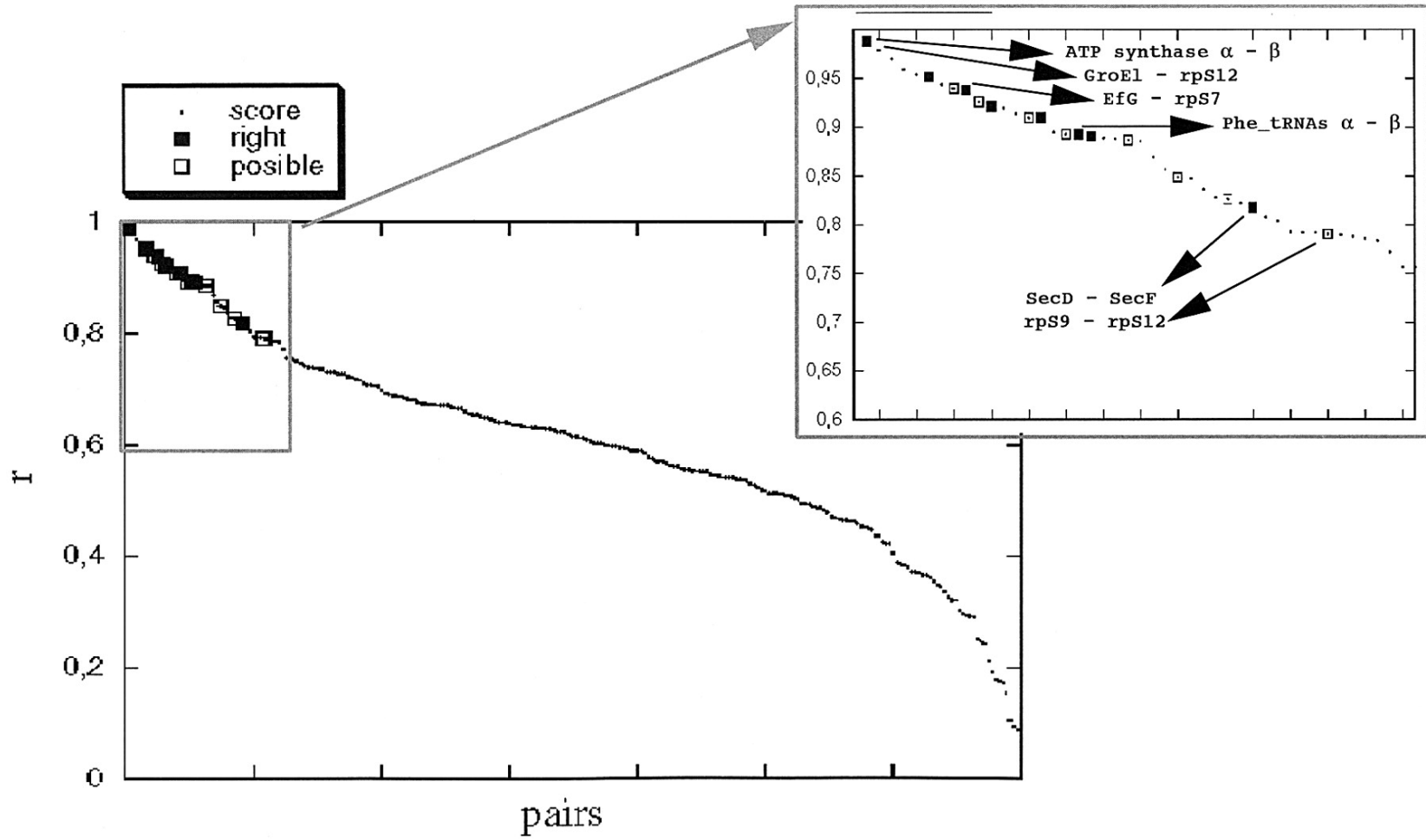
Pazos, F. and Valencia, A. (2001) Similarity of phylogenetic trees as indicator of protein-protein interaction. *Protein Eng*, **14**, 609-614.

MirrorTree

2c2c_2-4mt2_2	0,959	4tnc_1-4mt2_2	0,448
9pap_1-9pap_2 *	0,907	9pap_2-4tnc_1	0,446
2c2c_1-4mt2_2	0,901	1alc_2-4mt2_2	0,446
3pgk_1-3pgk_2 *	0,901	1sgt_2-4mt2_1	0,433
4mt2_1-4mt2_2 *	0,898	3adk_1-4tnc_2	0,421
3trx_1-3trx_2 *	0,894	1rnd_1-4mt2_2	0,405
4tms_1-4tms_2 *	0,854	4tnc_2-4mt2_2	0,405
2c2c_2-4mt2_1	0,849	2c2c_1-3adk_2	0,401
1rnd_1-1rnd_2 *	0,817	1sgt_2-2c2c_1	0,399
2c2c_1-4mt2_1	0,813	4tms_2-3dfr_2	0,394
1alc_1-1alc_2 *	0,801	3adk_1-3dfr_1	0,390
4tnc_1-4tnc_2 *	0,794	1sgt_2-2c2c_2	0,381
2c2c_1-2c2c_2 *	0,773	3adk_2-3dfr_1	0,372
3pgk_1-4tms_1	0,756	1sgt_2-1alc_1	0,371
3pgk_1-4tms_2	0,731	4tms_1-3dfr_2	0,358
2c2c_1-3adk_1	0,726	1sgt_1-4mt2_1	0,343
3pgk_2-4tms_1	0,723	1sgt_1-4mt2_2	0,336
2c2c_2-3pgk_1	0,715	9pap_2-4tnc_2	0,331
1alc_1-1rnd_1	0,712	4tms_1-3dfr_1	0,327
2c2c_2-3pgk_2	0,698	3trx_1-2c2c_2	0,319
1alc_2-1rnd_1	0,697	3trx_1-2c2c_1	0,312
1sgt_1-1sgt_2 *	0,693	1sgt_1-1alc_1	0,312
3pgk_2-4tms_2	0,691	3trx_2-2c2c_2	0,287
3adk_2-3dfr_2	0,675	3trx_2-2c2c_1	0,281
1sgt_2-2pf2_2	0,673	1sgt_1-2c2c_2	0,270
3dfr_1-3dfr_2 *	0,672	1alc_1-4mt2_2	0,268
2c2c_2-9pap_1	0,658	1sgt_1-2c2c_1	0,268
2c2c_1-3pgk_1	0,648	2c2c_1-1rnd_1	0,263
3trx_2-9pap_1	0,646	9pap_1-3adk_2	0,254
1sgt_1-2pf2_2	0,646	2c2c_2-3adk_2	0,254
2c2c_2-3adk_1	0,631	3adk_2-3pgk_1	0,251
3trx_1-9pap_1	0,627	1sgt_1-1rnd_1	0,238
2c2c_2-1alc_2	0,626	3adk_2-3pgk_2	0,238
2c2c_1-3pgk_2	0,620	9pap_2-3adk_2	0,221
3trx_2-9pap_2	0,620	1sgt_2-1alc_2	0,219
1rnd_2-4mt2_1	0,619	2c2c_2-1alc_1	0,203
1alc_2-1rnd_2	0,607	9pap_1-4tnc_1	0,202
1rnd_2-4mt2_2	0,606	1sgt_2-1rnd_1	0,191
3blm_1-3blm_2 *	0,603	1sgt_1-1alc_2	0,178
1alc_1-1rnd_2	0,599	3trx_2-3adk_2	0,175
3trx_1-3pgk_1	0,595	1sgt_1-1rnd_2	0,168
3trx_1-9pap_2	0,589	2pf2_2-1alc_1	0,160
1alc_2-4mt2_1	0,588	2c2c_1-1alc_1	0,155
2c2c_1-1alc_2	0,587	9pap_1-4tnc_2	0,149
2c2c_1-9pap_1	0,581	2c2c_2-1rnd_2	0,146
3trx_1-3pgk_2	0,577	4tms_2-3dfr_1	0,130
4tnc_1-4mt2_1	0,556	3trx_1-3adk_2	0,128
3adk_1-3pgk_1	0,554	2c2c_2-1rnd_1	0,125
		2c2c_1-1rnd_2	0,113



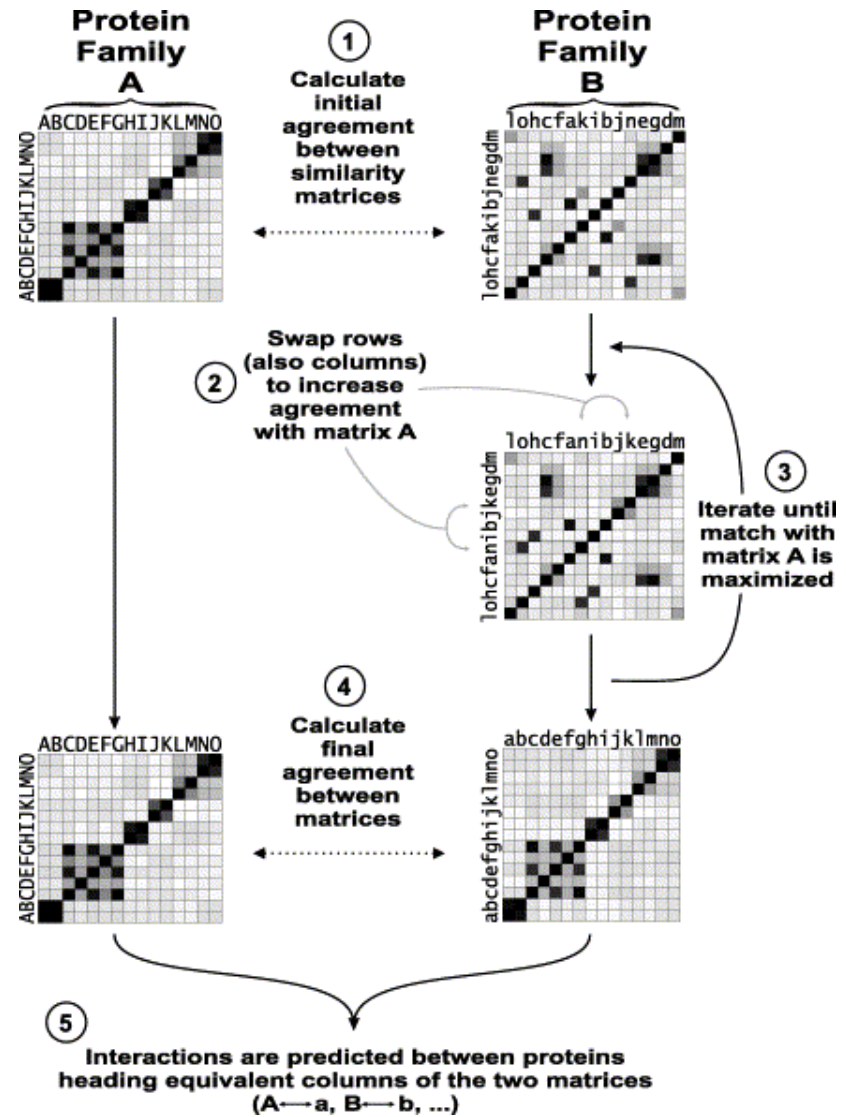
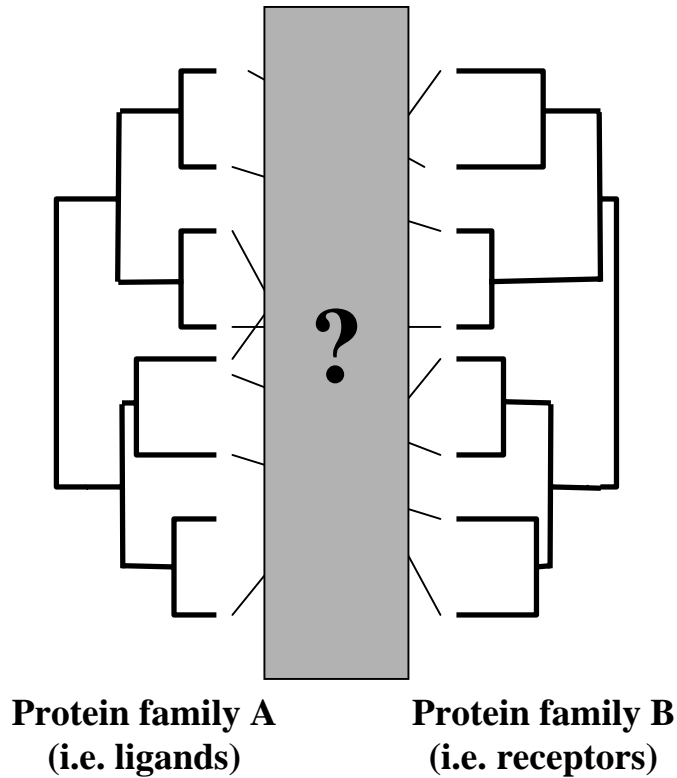
MirrorTree



MirrorTree - Variaciones

- Gertz, J., Elfond, G., Shustrova, A., Weisinger, M., Pellegrini, M., Cokus, S. and Rothschild, B. (2003) Inferring protein interactions from phylogenetic distance matrices. *Bioinformatics*, **19**, 2039-2045.
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- Jothi, R., Kann, M.G. and Przytycka, T.M. (2005) Predicting protein-protein interaction by searching evolutionary tree automorphism space. *Bioinformatics*, **21**, i241-i250.
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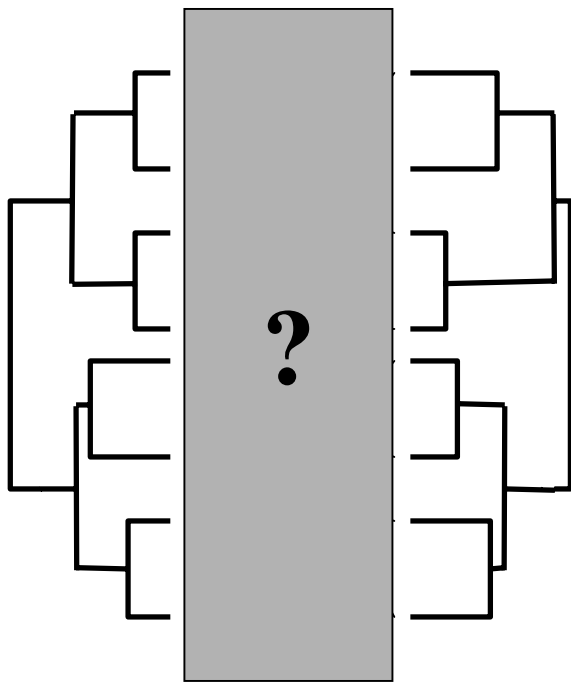
MirrorTree. Variaciones



• Ramani, A.K. & Marcotte, E.M. (2003) Exploiting the co-evolution of interacting proteins to discover interaction specificity. *J Mol Biol*, **327**, 273-284.

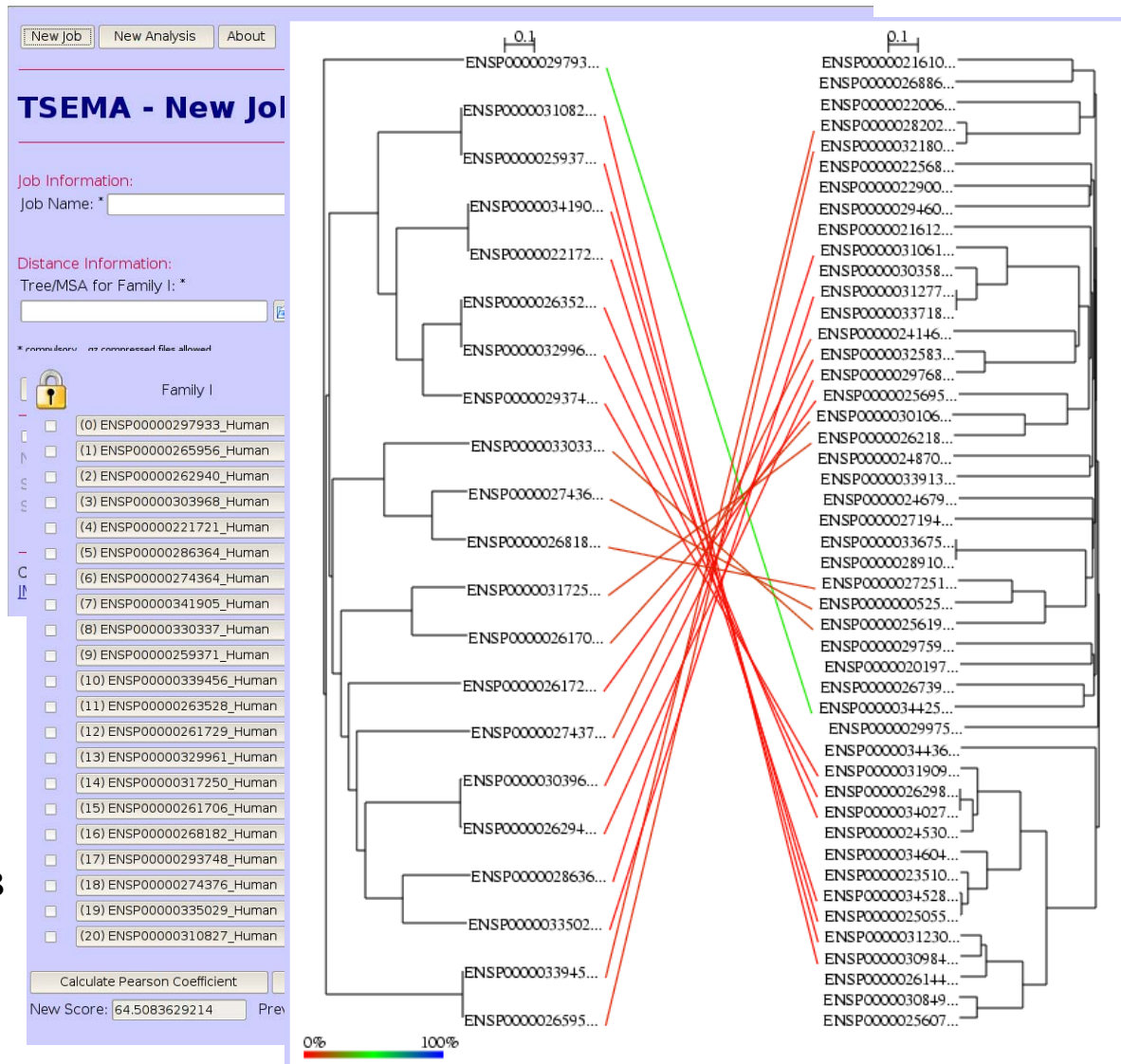
• Tillier, E.R., Biro, L., Li, G. and Tillo, D. (2006) Codep: maximizing co-evolutionary interdependencies to discover interacting proteins. *Proteins.*, **63**, 822-831.

Predicción interactiva del mapeo entre familias de proteínas



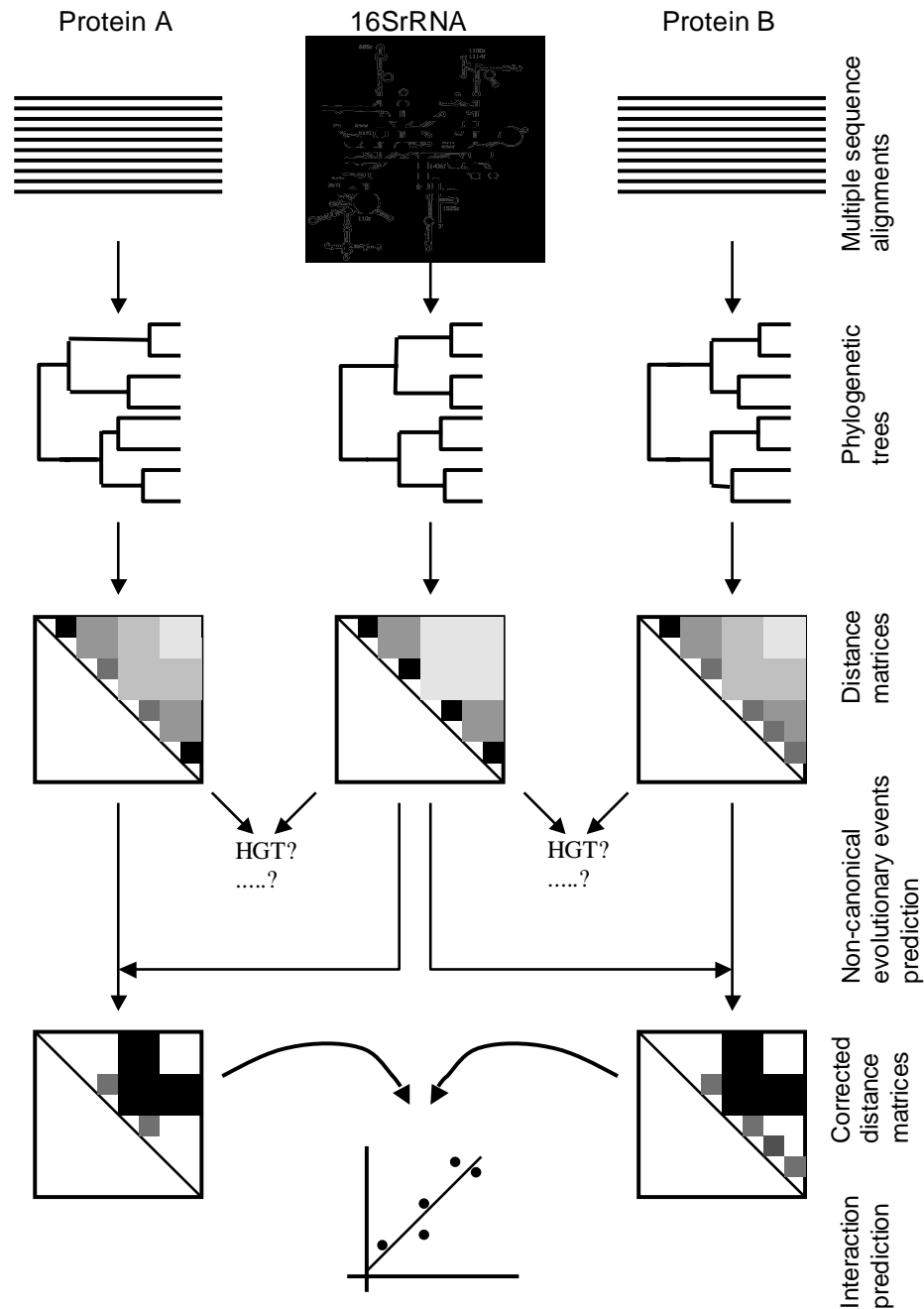
Protein family A
(i.e. ligands)

Protein family B
(i.e. receptors)



MirrorTree
Variations

tol-mirrortree



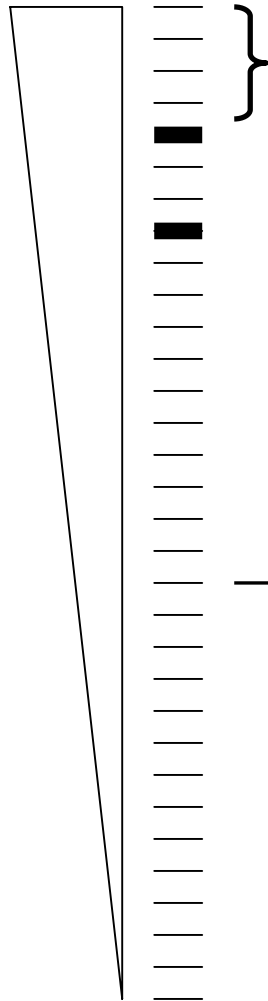
tol-mirrortree

DIP:
516 interactions (*E coli*)

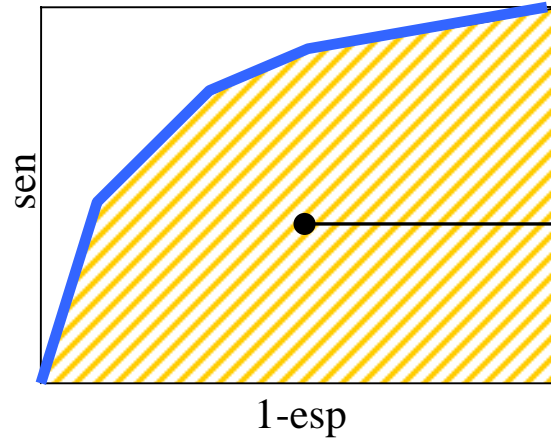
20,087 pairs calculated
(115 true)

118 proteins with
 ≥ 1 calculated true interactor

P00000
List of pairs
sorted by score

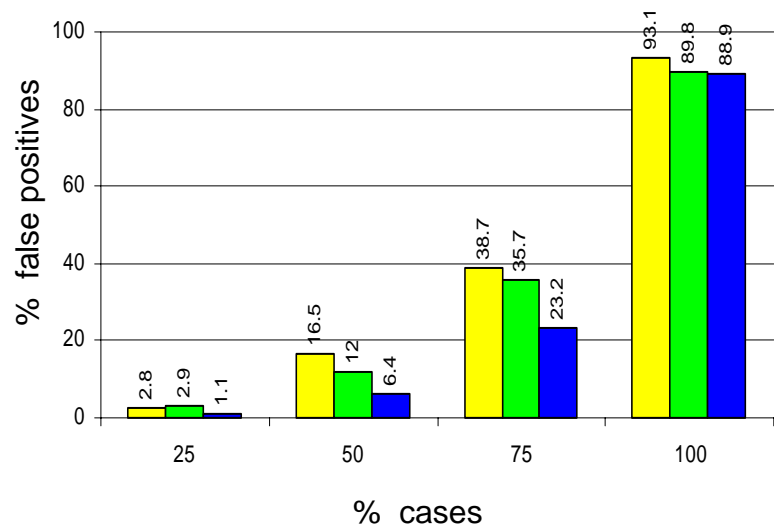
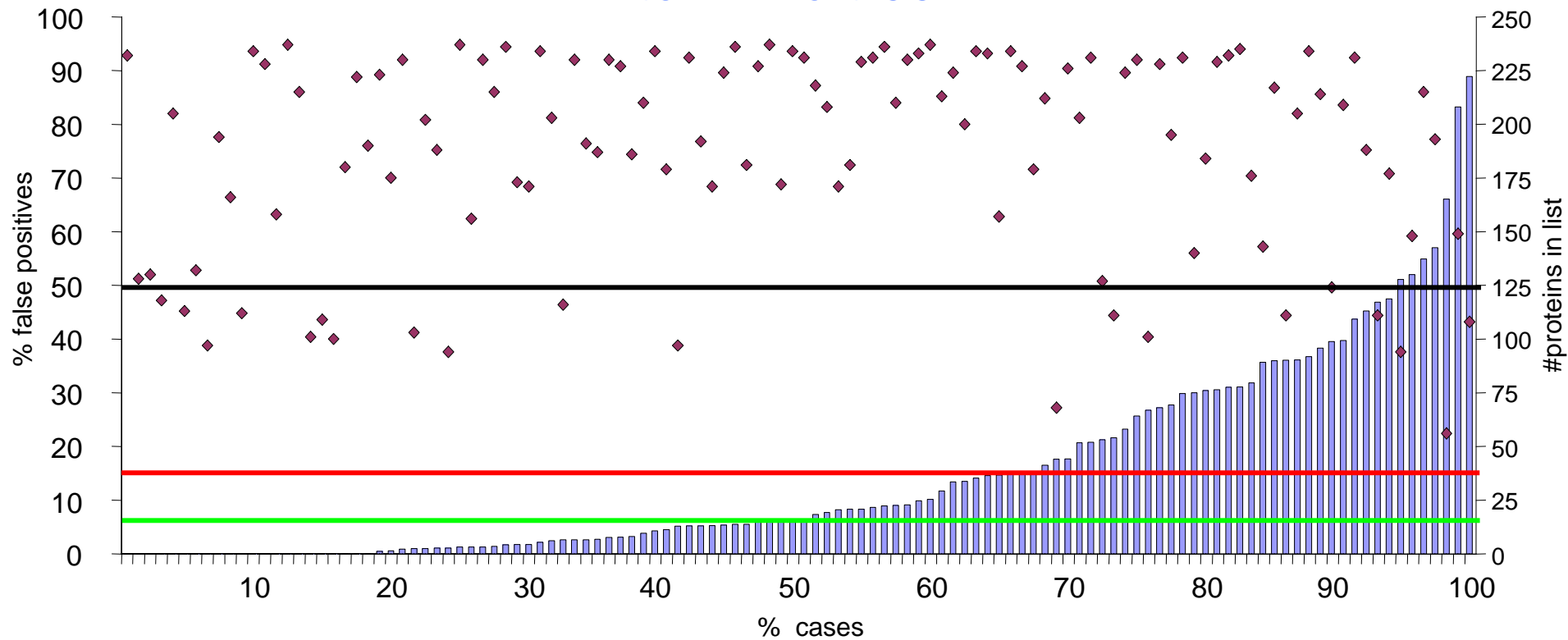


fraction of false positives
0%: perfect
50%: random
(1 int.)



ROC area
1.0: perfect
0.5: random

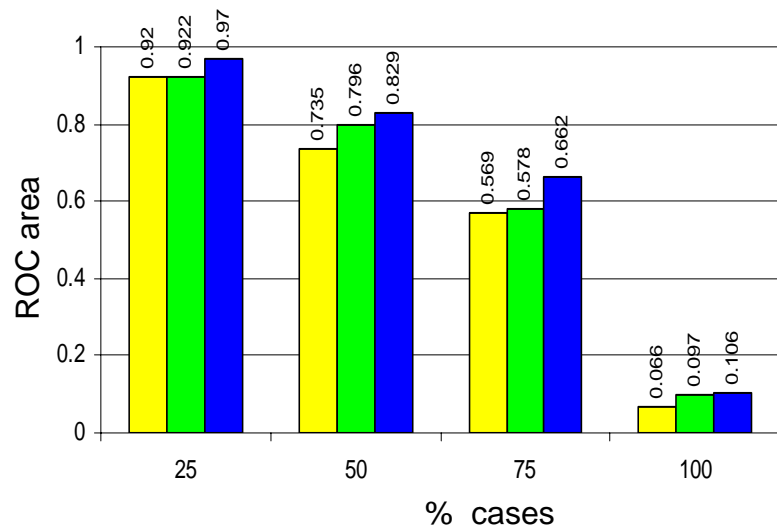
tol-mirrortree



mirrotree

mirrortree (tree dist.)

tol-mirrortree



Comparación con versiones anteriores de *mirrortree*

	% false positives	ROC area
<i>mirrortree</i>	23.4	0.71
<i>mirrortree</i> with tree distances	21.9	0.73
<i>tol-mirrortree</i>	14.9	0.79

P(N) values (sign test):

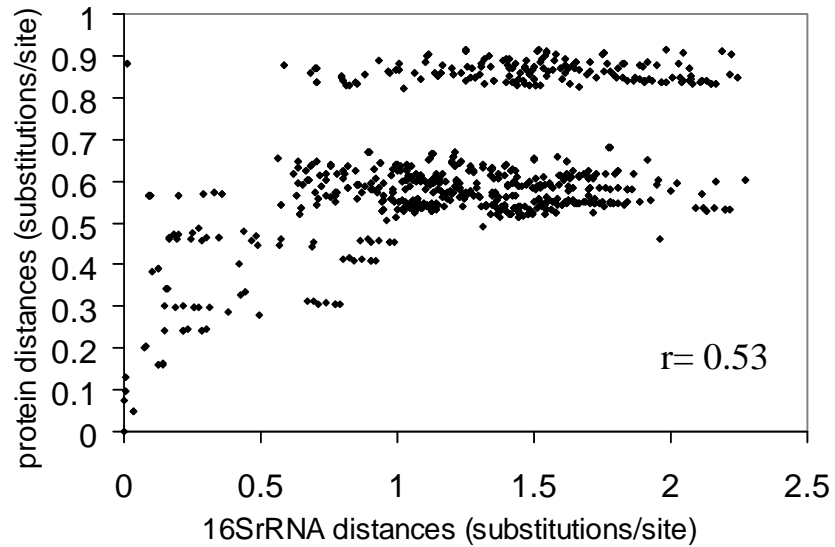
a \ b	<i>mirrortree</i>	<i>mirrortree</i> tree dist.	<i>tol-mirrortree</i>
<i>mirrortree</i>			
<i>mirrortree</i> tree dist.	0.276		
<i>tol-mirrortree</i>	$5.60 \cdot 10^{-6}$	$1.91 \cdot 10^{-5}$	

tol-mirrortree

Detección concomitante de eventos evolutivos no-estándar

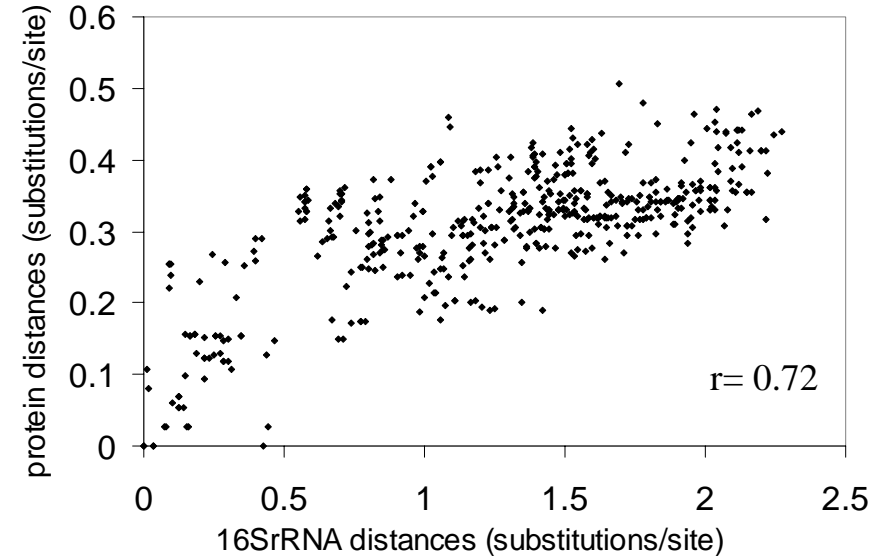
a)

Prolyl-tRNA synthetase



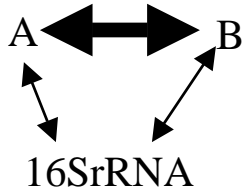
b)

Ribosomal protein L36

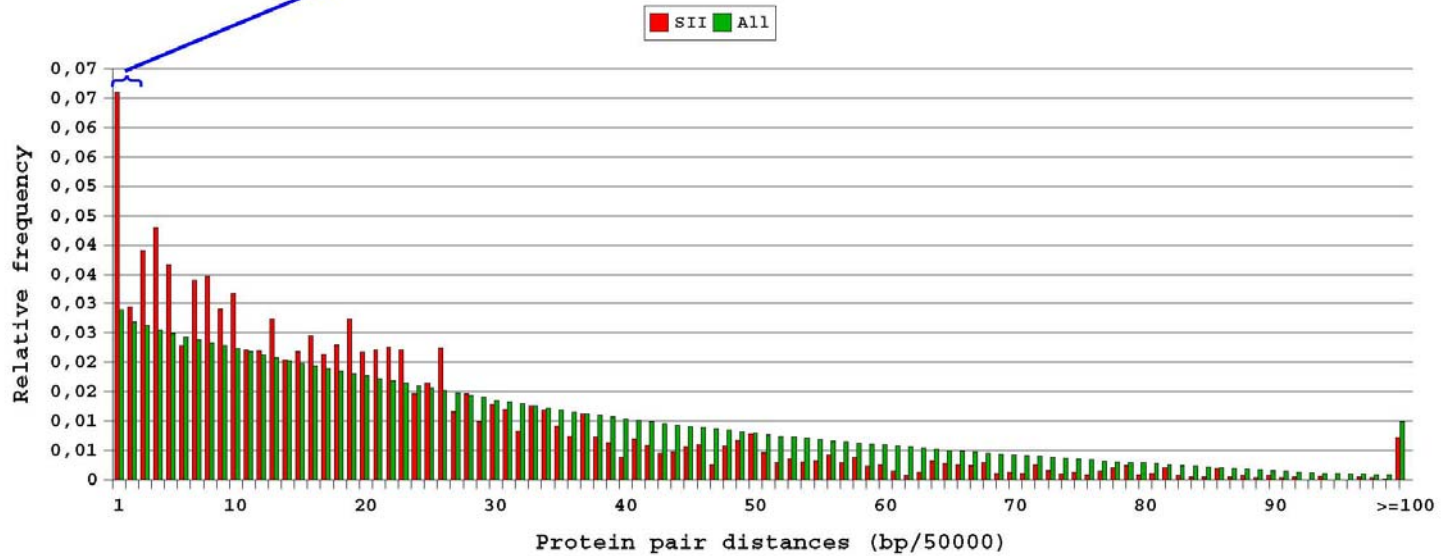
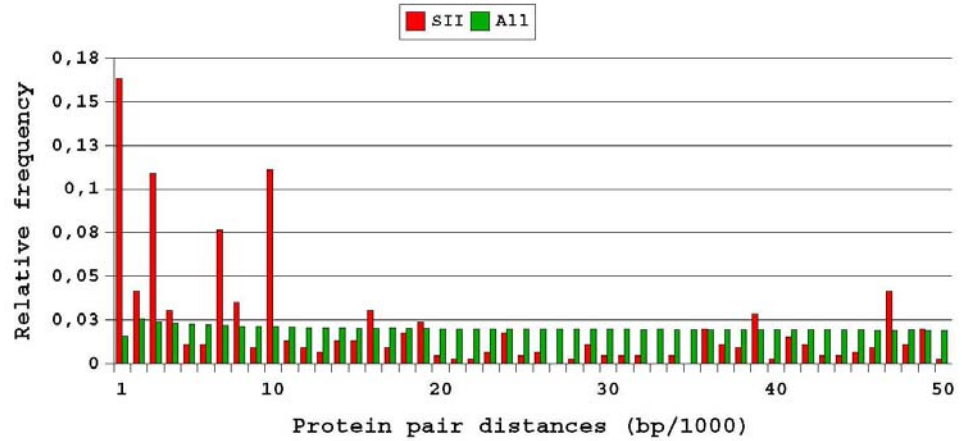


$r \leq 0.5 \rightarrow 25\%$ false pos (vs. 15%)
Excluding them: 13.7% false pos (vs. 15%)

Co-HGT events



SII vs All *E. coli* protein orthologous pair distances

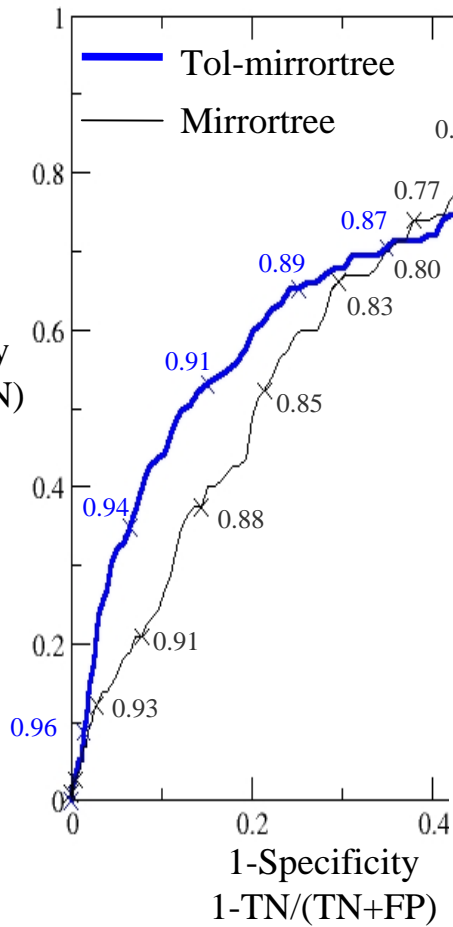


Protein
Multiple Sequences
Organism 1
Organism 2
Organism 3
Organism 4
Organism 5

Protein
Multiple Sequences
Organism 1
Organism 2
Organism 3
Organism 4
Organism 5

Protein Sensitivity
Multiple Sequences
Organism 1
Organism 2
Organism 3
Organism 4
Organism 5

Protein
Multiple Sequences
Organism 1
Organism 2
Organism 3
Organism 4
Organism 5



Correlation Coefficient
(ρ^{16S})

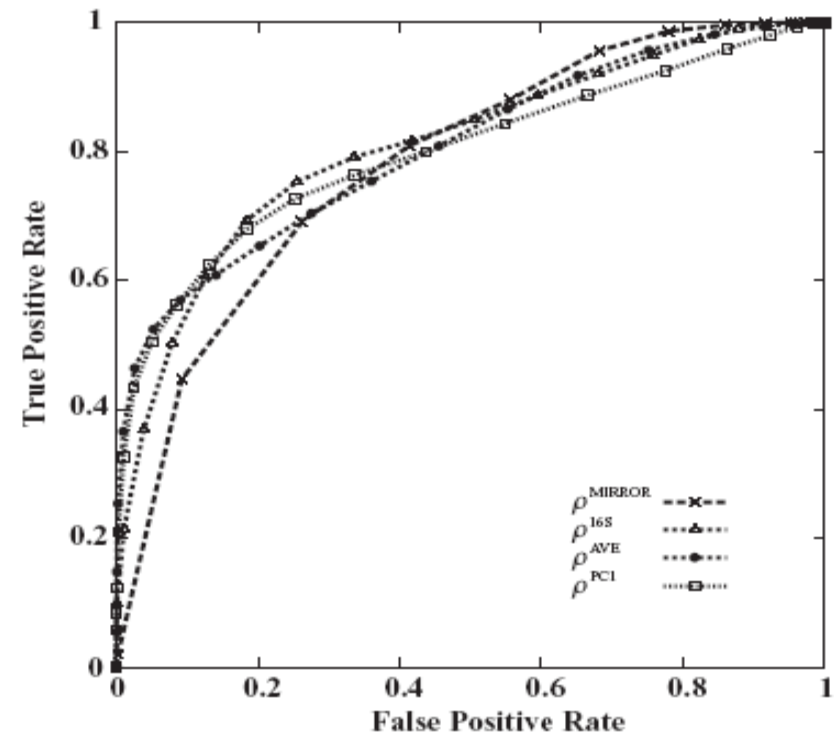
Protein A - Protein B
Protein A - Protein C
Protein A - Protein D
Protein B - Protein C
Protein B - Protein D
Protein C - Protein D

Correlation Coefficient
(ρ^{AVE})

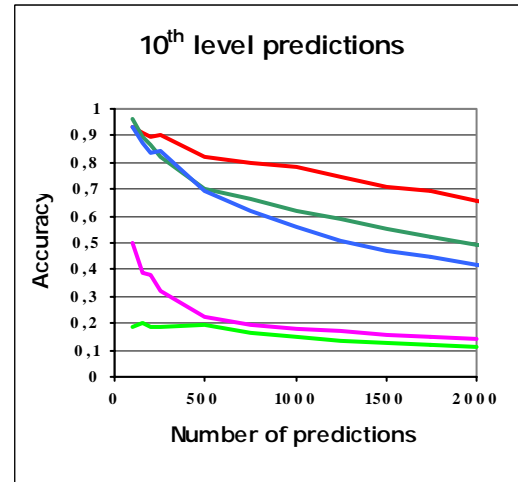
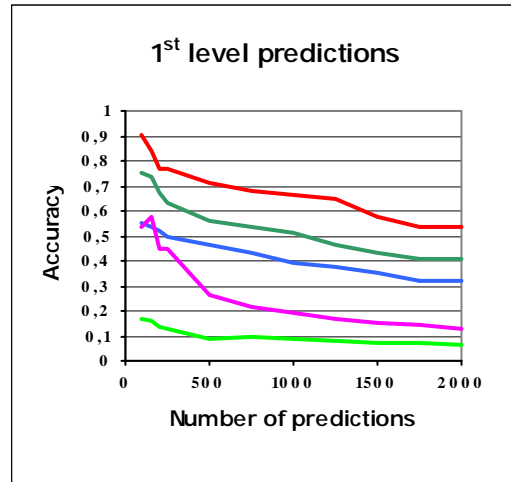
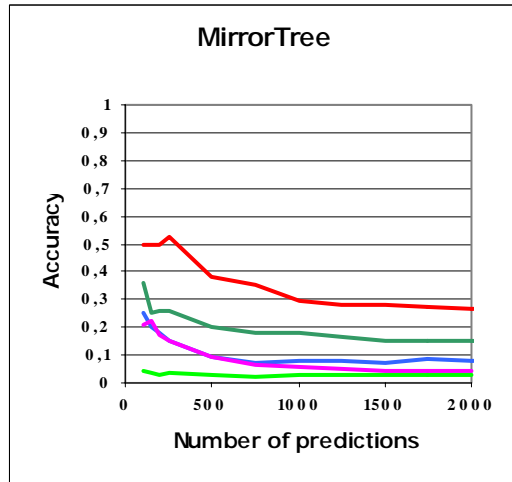
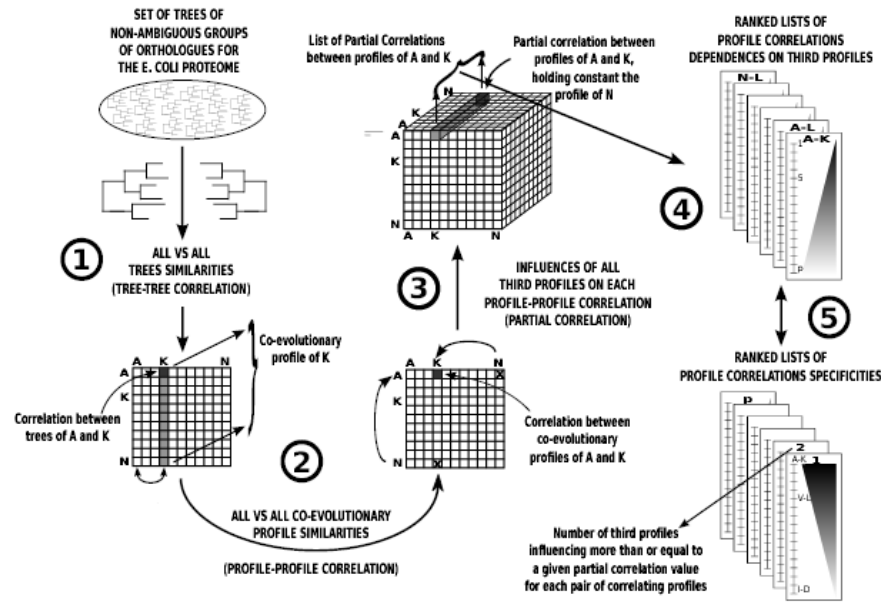
Protein B
Protein C
Protein D
Protein C
Protein D
Protein D

Correlation Coefficient
(ρ^{PC1})

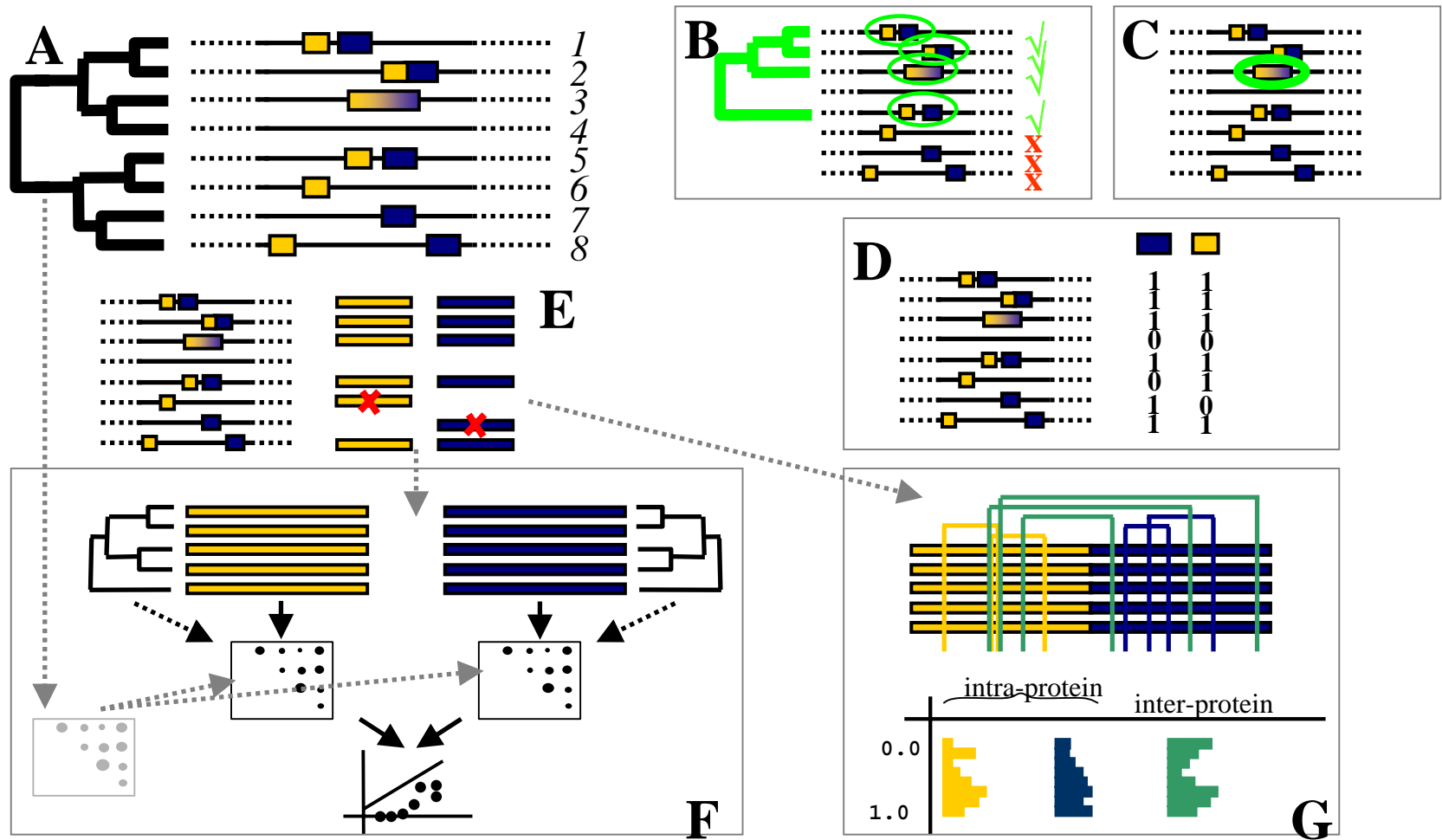
Protein B
Protein C
Protein D
Protein C
Protein D
Protein D



Genome-wide co-evolutionary networks



Métodos Computacionales de Predicción de Compañeros de Interacción



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