Tesis Doctoral

Improving Co-evolution Based Methods for Protein-Protein Interaction Prediction

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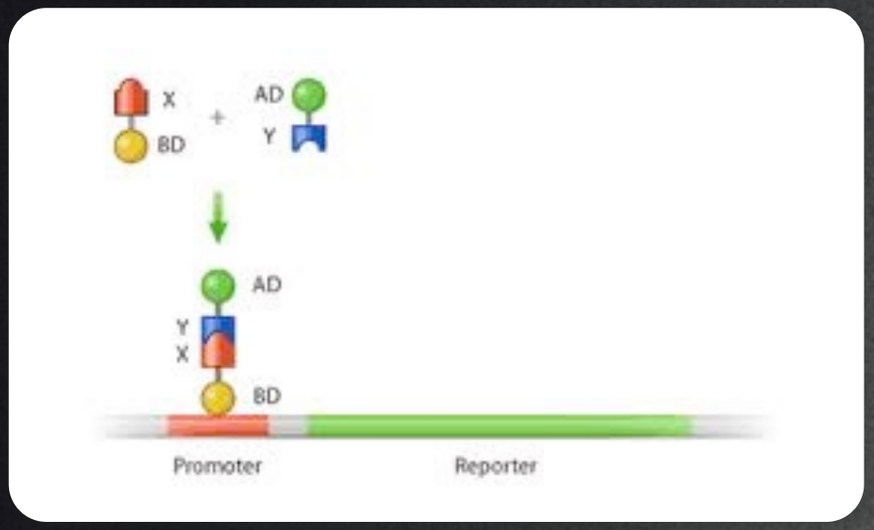
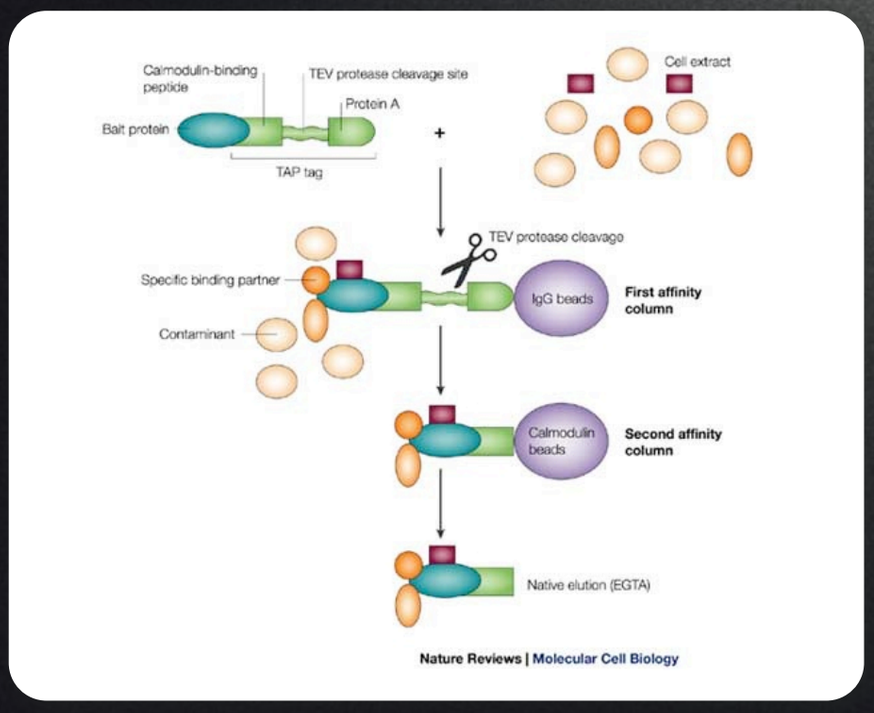
Supervisor: Florencio Pazos

Systems Biology and PPI Networks

- Complexity of biological processes
- Holistic point of view
- Network approaches
- Protein-Protein Interactions

Experimental methods for detecting PPIs

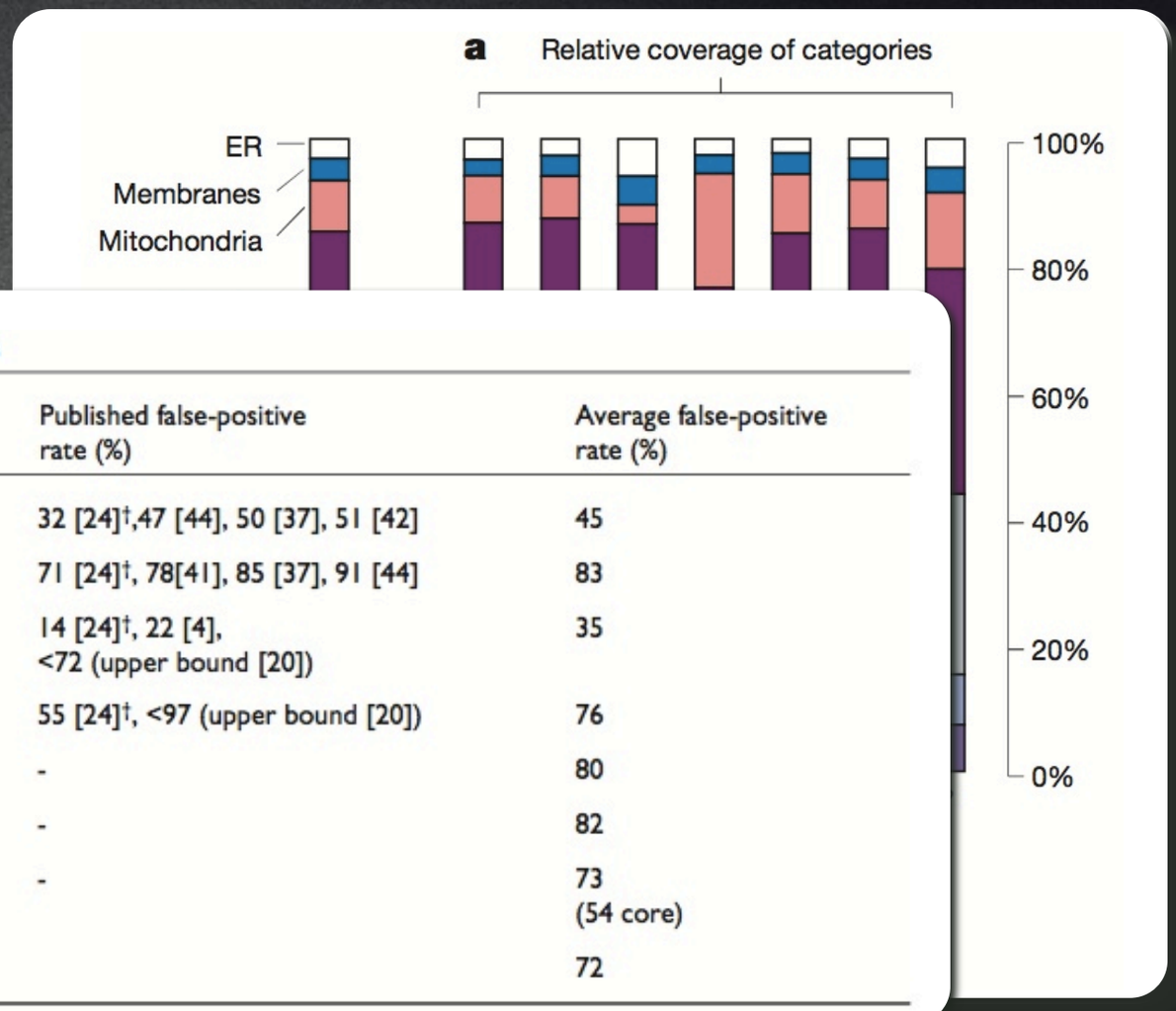




- Yeast two-hybrid
- Affinity purification - Mass Spectrometry
- Synthetic lethality
- Protein chips
- Phage display

Experimental problems

- High False-positives Rates
- Pr
- Pr



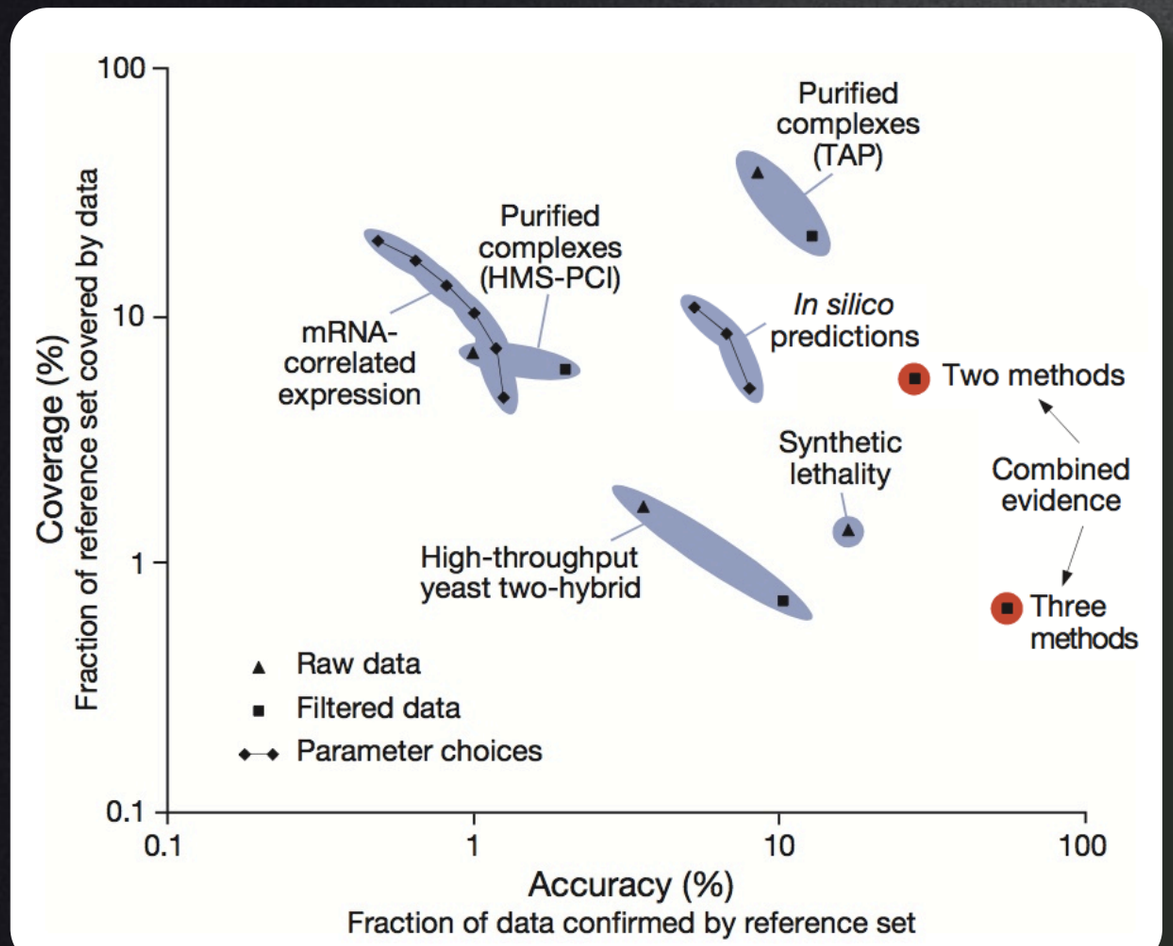
Yeast protein-interaction assay false-positive rates: yeast datasets

Dataset	Number of interactions	Derived false-positive rate* (%)	Published false-positive rate (%)	Average false-positive rate (%)
Uetz *et al.* [35]	854	46 [32]	32 [24]†,47 [44], 50 [37], 51 [42]	45
Ito [36]	4,393	89 [32]	71 [24]†, 78[41], 85 [37], 91 [44]	83
Gavin *et al.* [16]	3,180	68 [32]	14 [24]†, 22 [4], <72 (upper bound [20])	35
Ho *et al.* [17]	3,618	83 [32], 81, 82, 80	55 [24]†, <97 (upper bound [20])	76
Jansen *et al.* [22]	15,922	81, 79	-	80
Gavin *et al.* [27]	18,137	78, 82, 86‡	-	82
Krogan *et al.* [28]	14,317 (7,123 core)	75, 79, 66‡ (59, 65, 37‡ core)	-	73 (54 core)
Overall	51,419			72

Hart, G. T., Ramani, A. K., Marcotte, E. M. (2006) How complete are current yeast and human protein-interaction networks? Genome Biol 7, 120.

Mering, von, C. et al. Comparative assessment of large-scale data sets of protein-protein interactions. Nature 417, 399–403 (2002).

Possible Solutions

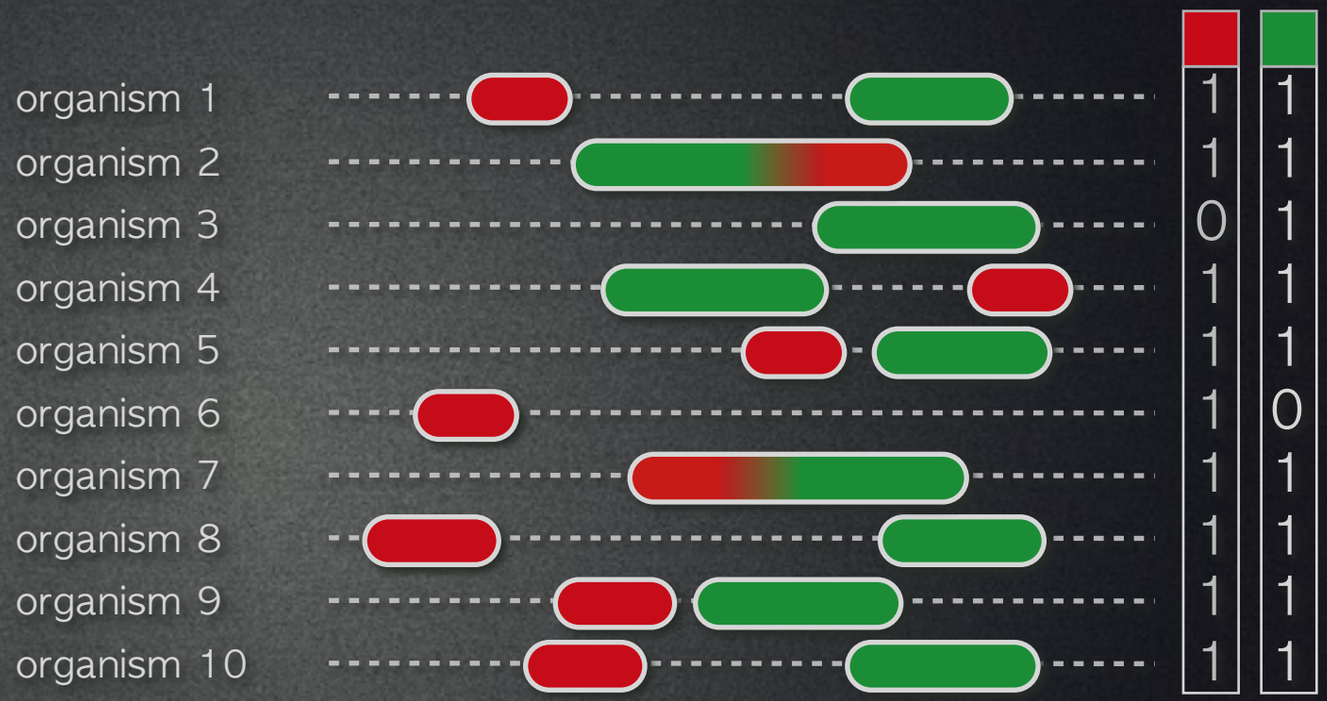


- Repeated screenings
- Combining evidences
- Confidence evaluation

Mering, von, C. et al. Comparative assessment of large-scale data sets of protein-protein interactions. Nature 417, 399–403 (2002).

Computational Methods

- Gene Fusion Events
- Conservation of Gene Neighborhood
- Similarity of Phylogenetic Profiles
- Similarity of Phylogenetic Trees



Enright et al. Protein interaction maps for complete genomes based on gene fusion events. Nature (1999) vol. 402 (6757) pp. 86-90

Overbeek et al. Use of contiguity on the chromosome to predict functional coupling. In Silico Biol (1999) vol. 1 (2) pp. 93-108

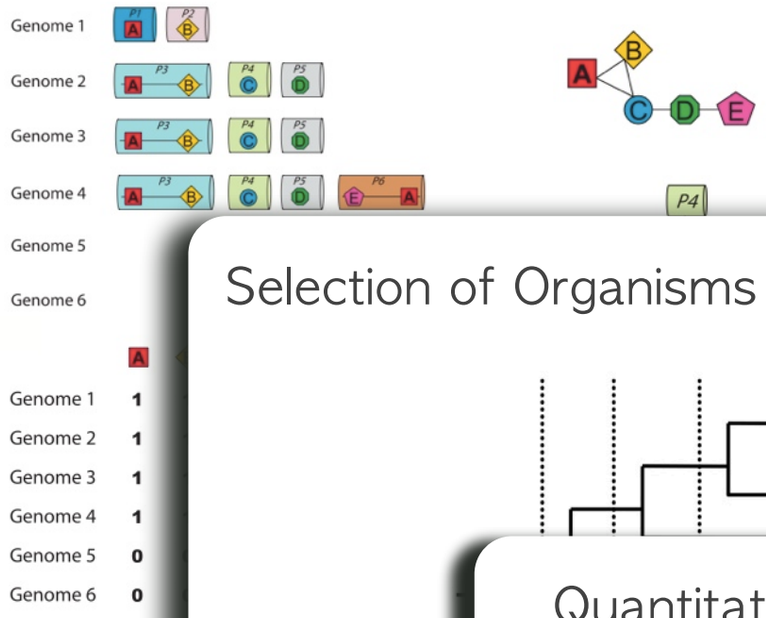
Dandekar et al. Conservation of gene order: a fingerprint of proteins that physically interact. Trends Biochem Sci (1998) vol. 23 (9) pp. 324-328

Pellegrini et al. Assigning protein functions by comparative genome analysis: protein phylogenetic profiles. Proc Natl Acad Sci U S A (1999) vol. 96 (8) pp. 4285-4288

Date y Marcotte. Discovery of uncharacterized cellular systems by genome-wide analysis of functional linkages. Nat Biotechnol (2003) vol. 21 (9) pp. 1055-1062

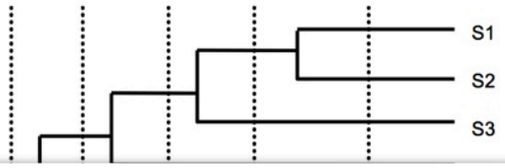
organism 1	1	1
organism 2	1	1
organism 3	0	1
organism 4	1	1
organism 5	1	1
organism 6	1	0
organism 7	1	1
organism 8	1	1
organism 9	1	1
organism 10	1	1

Local Profiles: Domains



Pagel, P., Wong,
phylogenetic p

Selection of Organisms

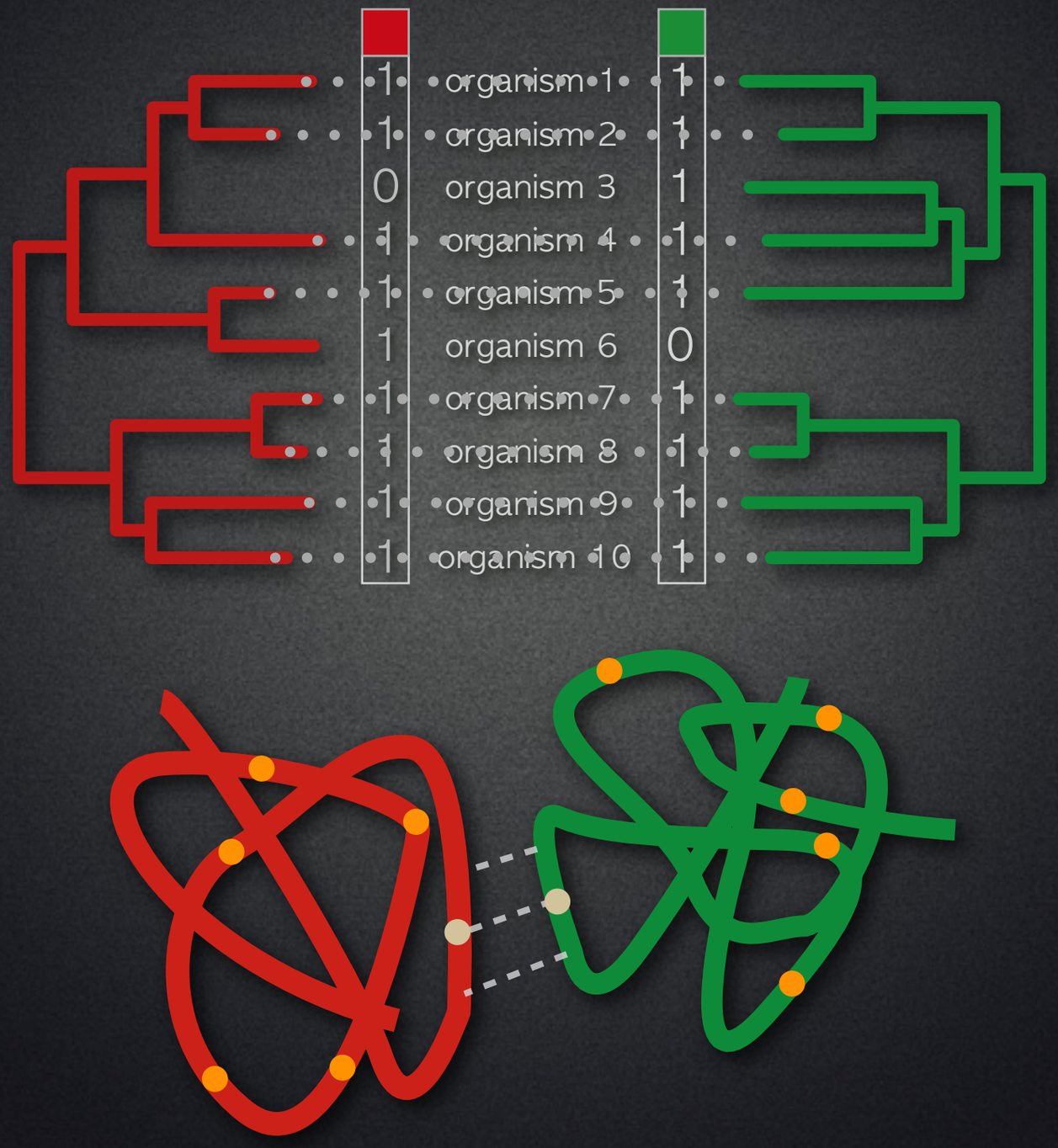


Sun, J., Li, Y. &
protein intera
Res Commu

Quantitative Profiles

Date, S. V. & Marcotte, E. M. Discovery of uncharacterized cellular systems by genome-wide analysis of functional linkages. Nat Biotechnol 21, 1055–1062 (2003)

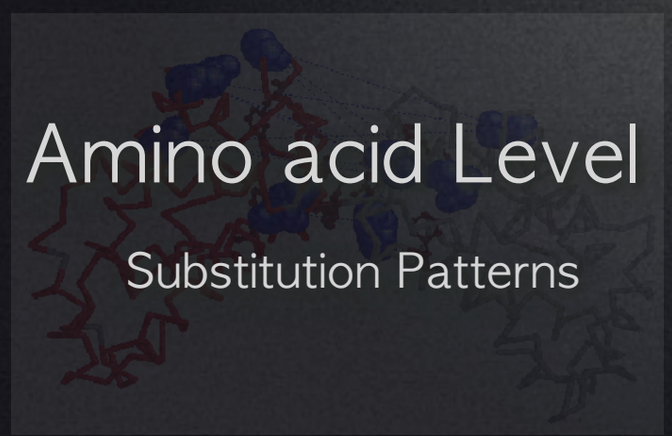
Similarity of Phylogenetic Trees



Fryxell, K. J. The coevolution of gene family trees. Trends Genet 12, 364–369 (1996).

Co-evolution

"reciprocal evolutionary change in interacting species" Thompson 1994

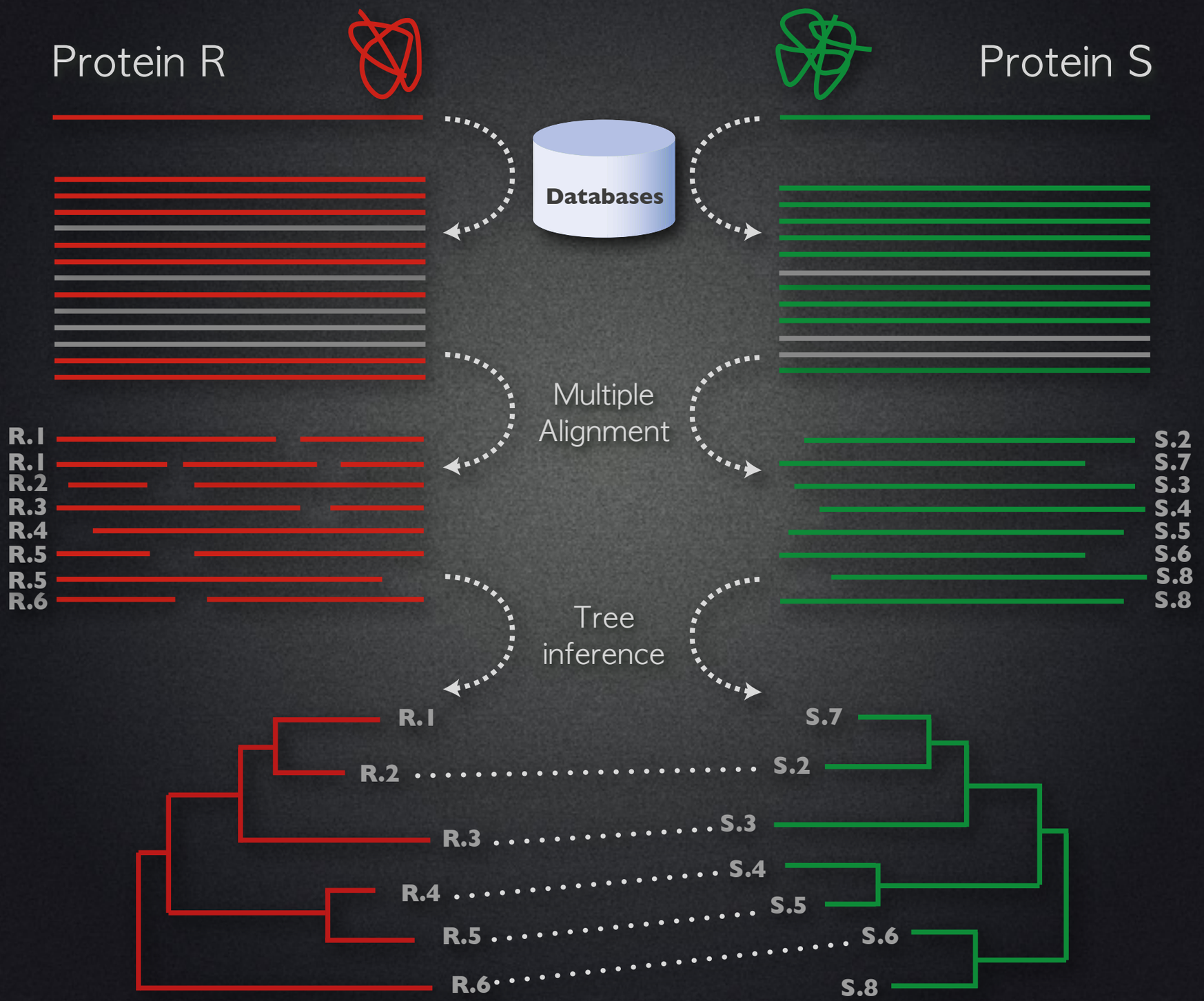


Ecological Factors
Trophic networks
Mutualisms
Symbioses
...

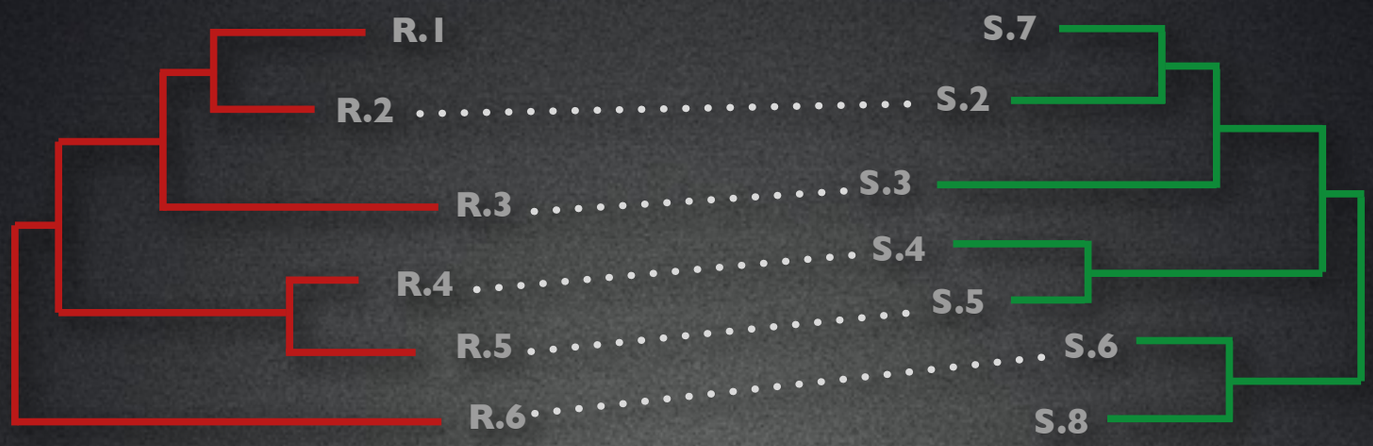
Protein Structure
Protein Function
Protein Networks
...

Local Structural Effects
Amino acid Contact Networks
Functional Sites
Protein-Protein Interfaces
...

MirrorTree

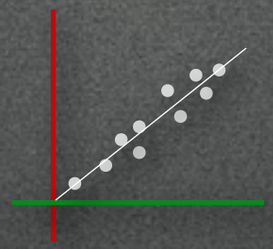

Protein R
Protein S
Databases
Multiple Alignment
R.1
R.1
R.2
R.3
R.4
R.5
R.5
R.6
S.2
S.7
S.3
S.4
S.5
S.6
S.8
S.8
Tree inference
R.1
R.2
R.3
R.4
R.5
R.6
S.7
S.2
S.3
S.4
S.5
S.6
S.8

MirrorTree



Distances matrix

	R1	R2	R3	R4	R5	R6
R1						
R2						
R3						
R4						
R5						
R6						



Pearson Correlation

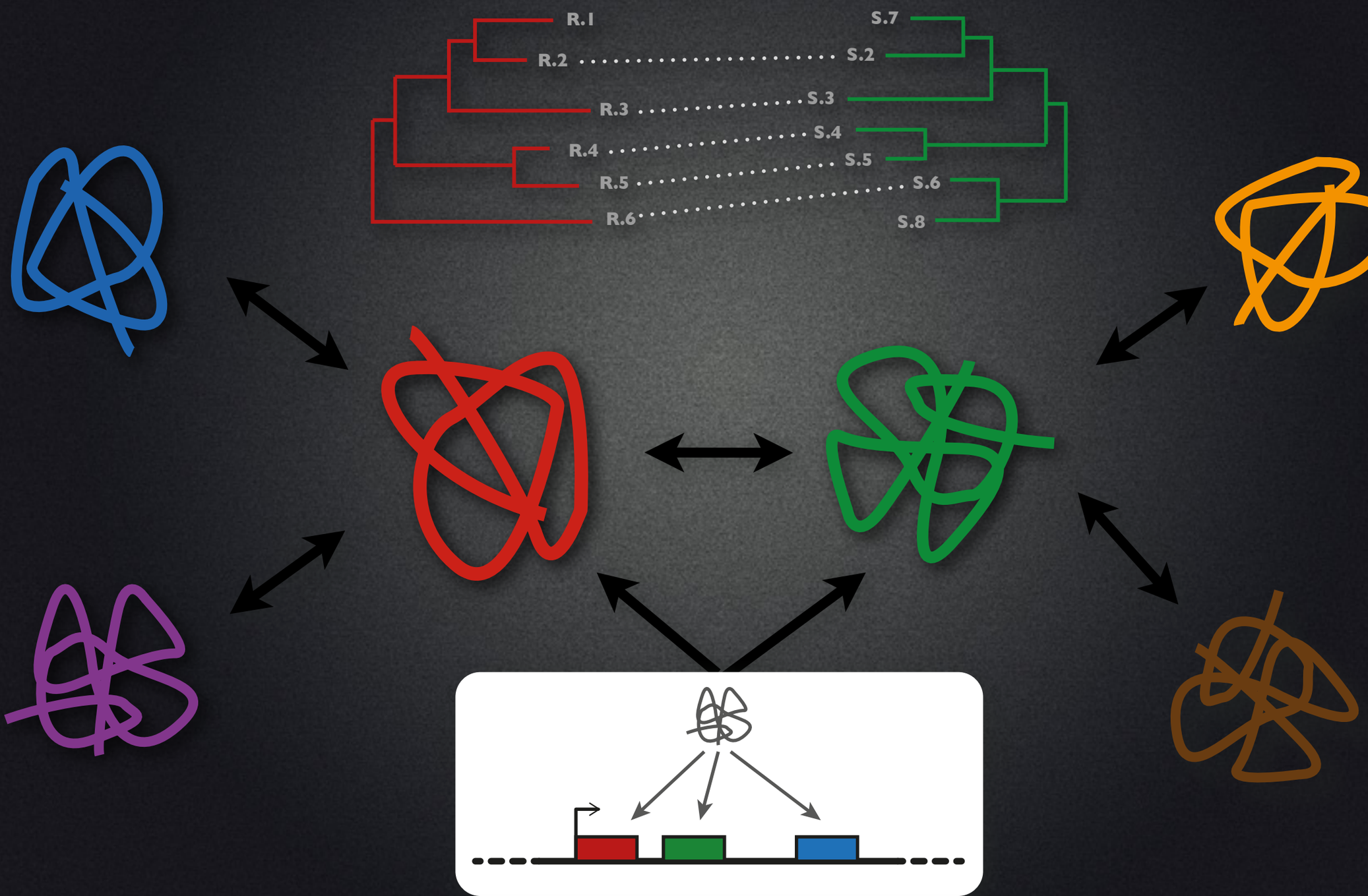
$$r = \frac{\sum_{i=1}^{n} (R_i - \bar{R})(S_i - \bar{S})}{\sqrt{\sum_{i=1}^{n} (R_i - \bar{R})^2} \sqrt{\sum_{i=1}^{n} (S_i - \bar{S})^2}}$$

Distances matrix

	S2	S3	S4	S5	S6	S7	S8
S2							
S3							
S4							
S5							
S6							
S7							
S8							

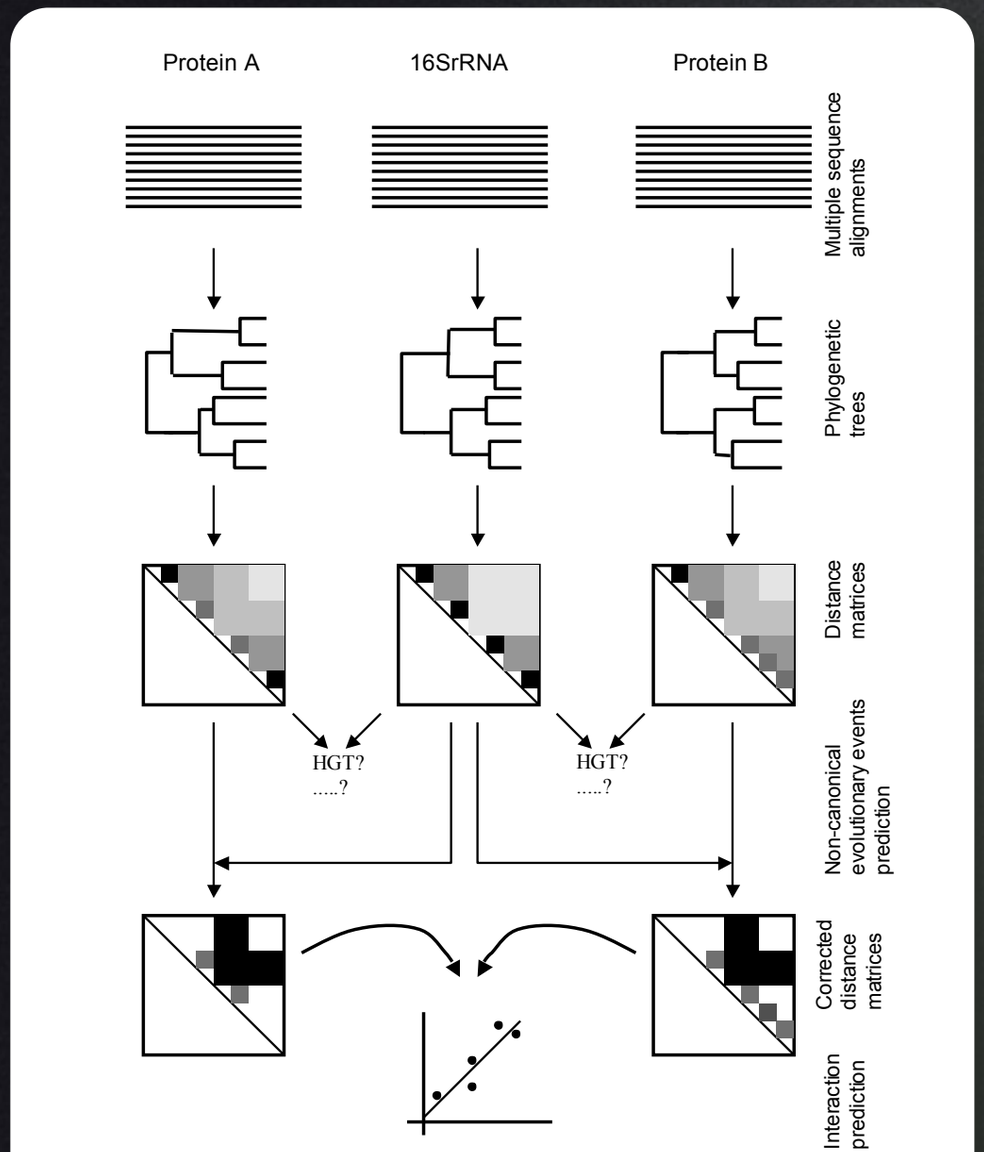
Pazos, F. & Valencia, A. Similarity of phylogenetic trees as indicator of protein-protein interaction. *Protein Eng* **14**, 609–614 (2001)

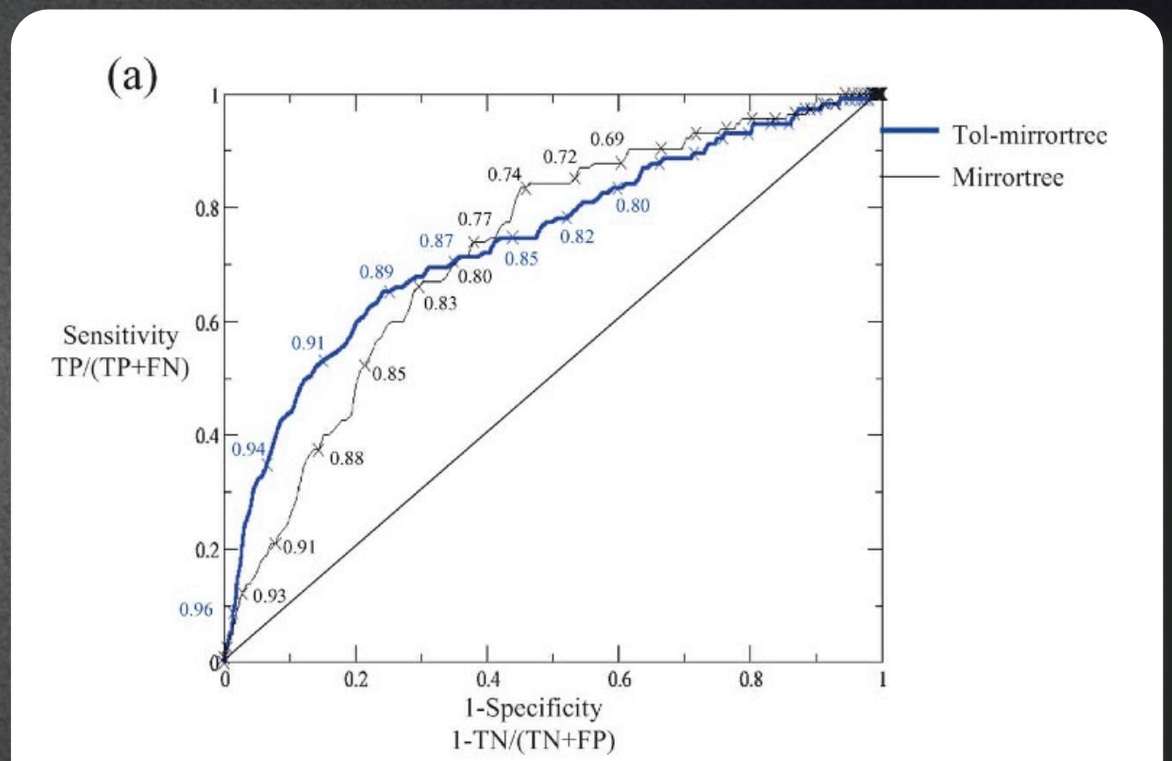
Possible causes of observed similarity



Pazos, F. & Valencia, A. Protein co-evolution, co-adaptation and interactions. EMBO J 27, 2648–2655 (2008).

TOL-MirrorTree

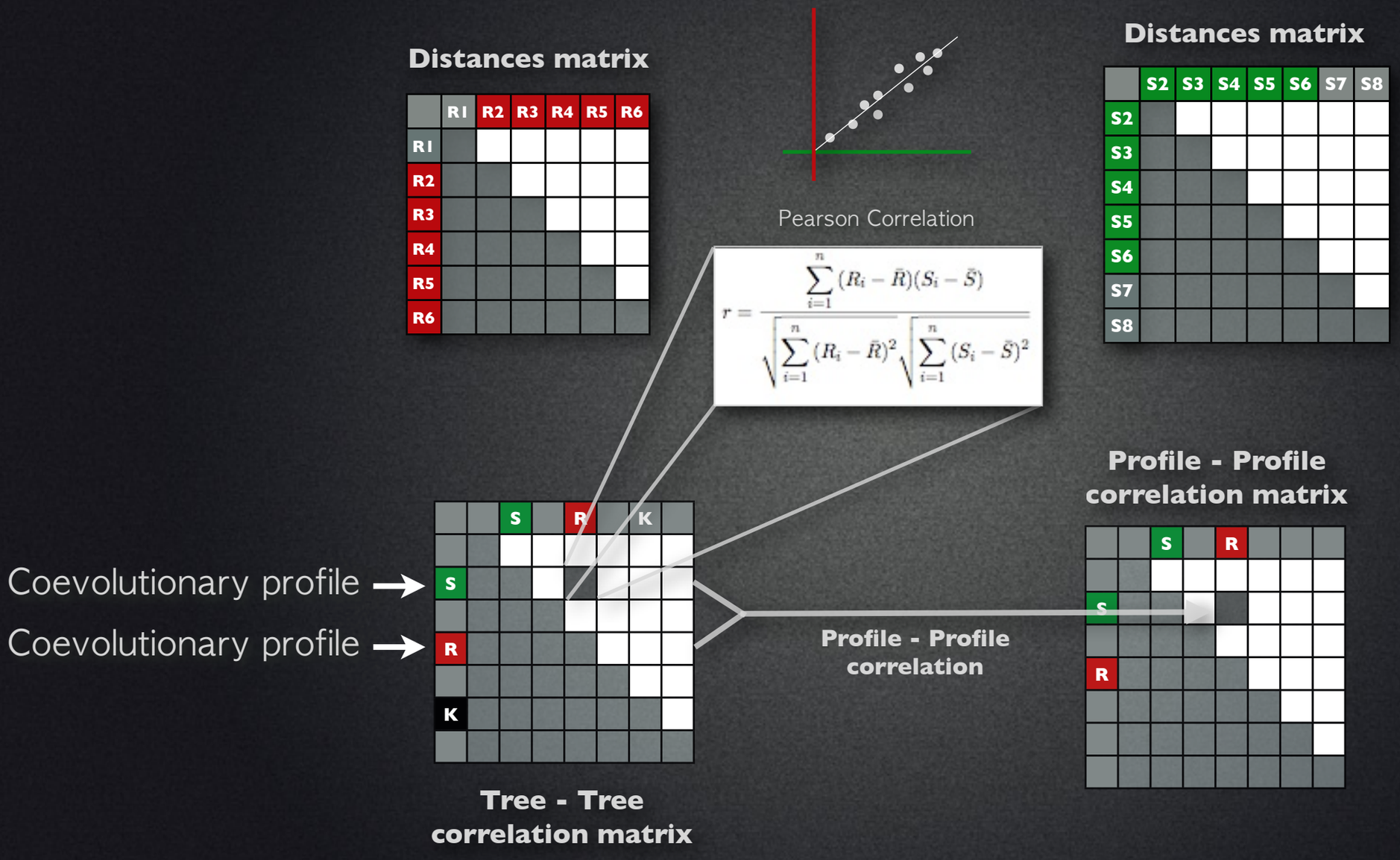




Sato, T., Yamanishi, Y., Kanehisa, M. & Toh, H. The inference of protein-protein interactions by co-evolutionary analysis is improved by excluding the information about the phylogenetic relationships. Bioinformatics 21, 3482–3489 (2005).

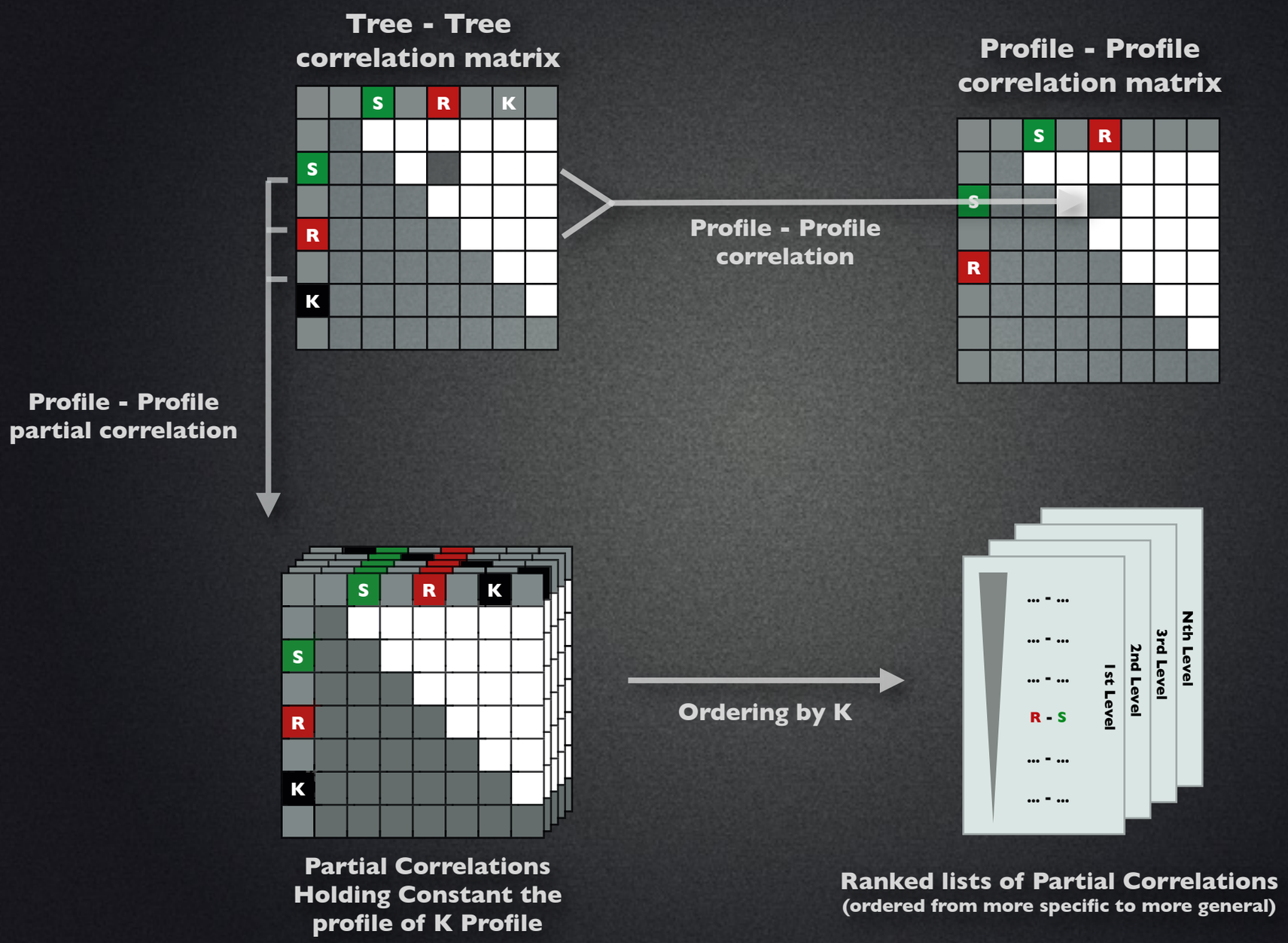
Pazos, F., Ranea, J. A. G., Juan, D. & Sternberg, M. J. E. Assessing protein co-evolution in the context of the tree of life assists in the prediction of the interactome. J Mol Biol 352, 1002–1015 (2005).

Profile Correlation



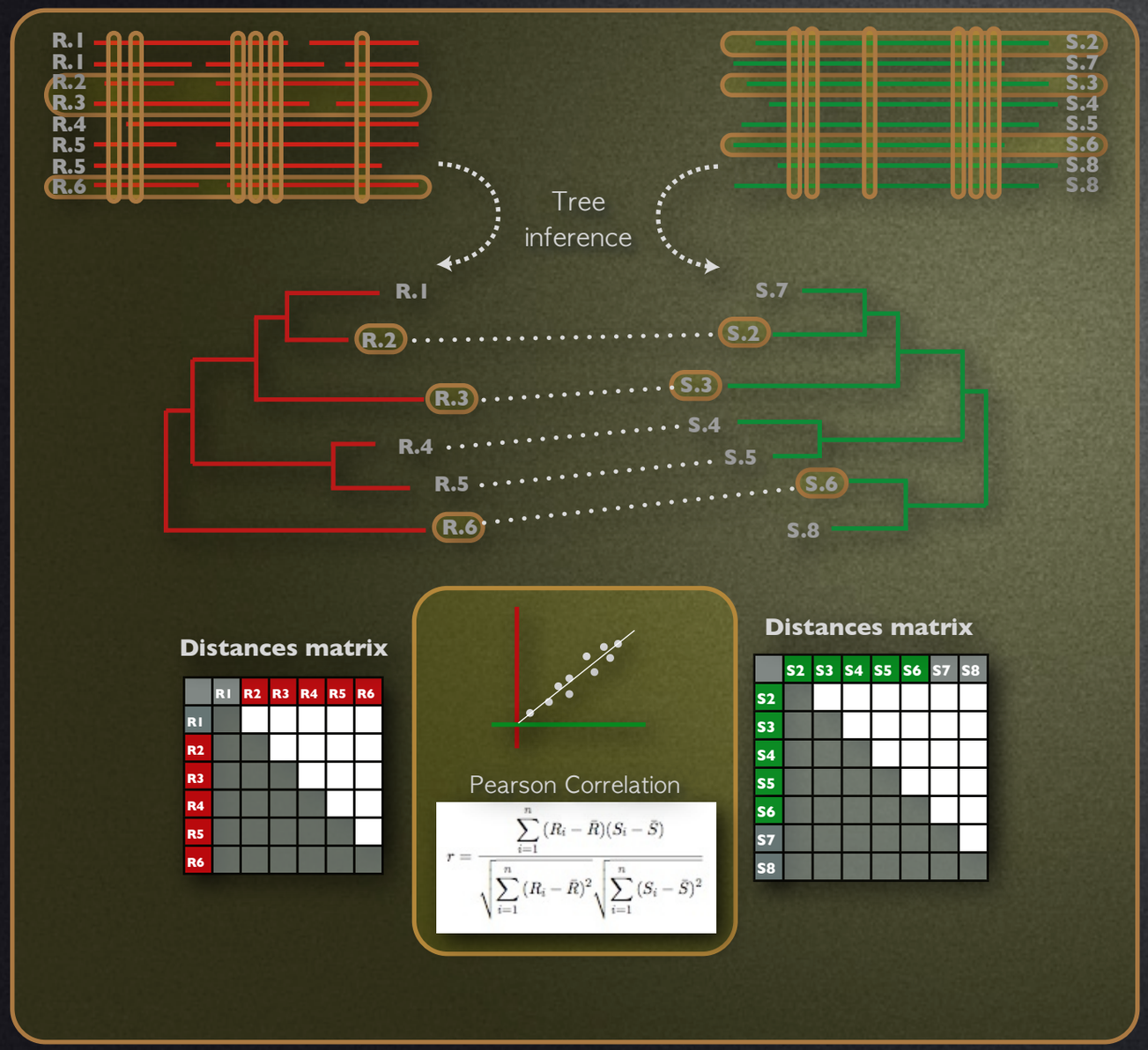
Juan, D., Pazos, F. & Valencia, A. High-confidence prediction of global interactomes based on genome-wide coevolutionary networks. *Proc Natl Acad Sci U S A* **105**, 934–939 (2008)

ContextMirror

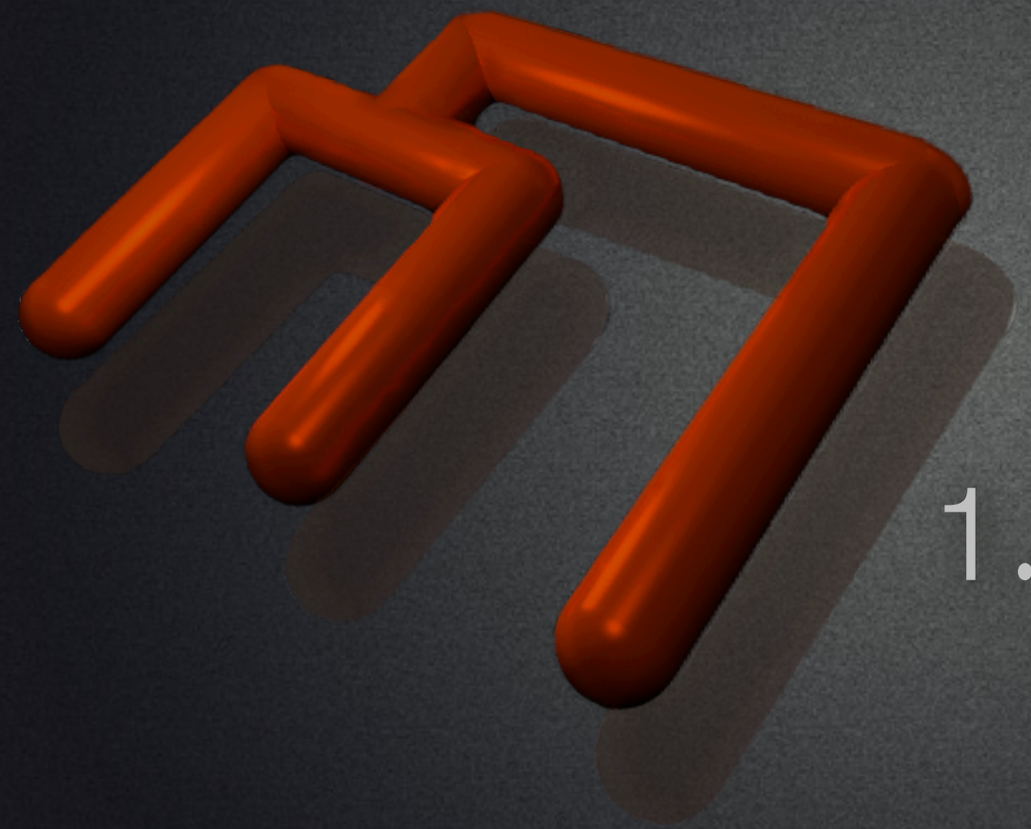


Juan, D., Pazos, F. & Valencia, A. High-confidence prediction of global interactomes based on genome-wide coevolutionary networks. *Proc Natl Acad Sci U S A* **105**, 934–939 (2008)

Objectives

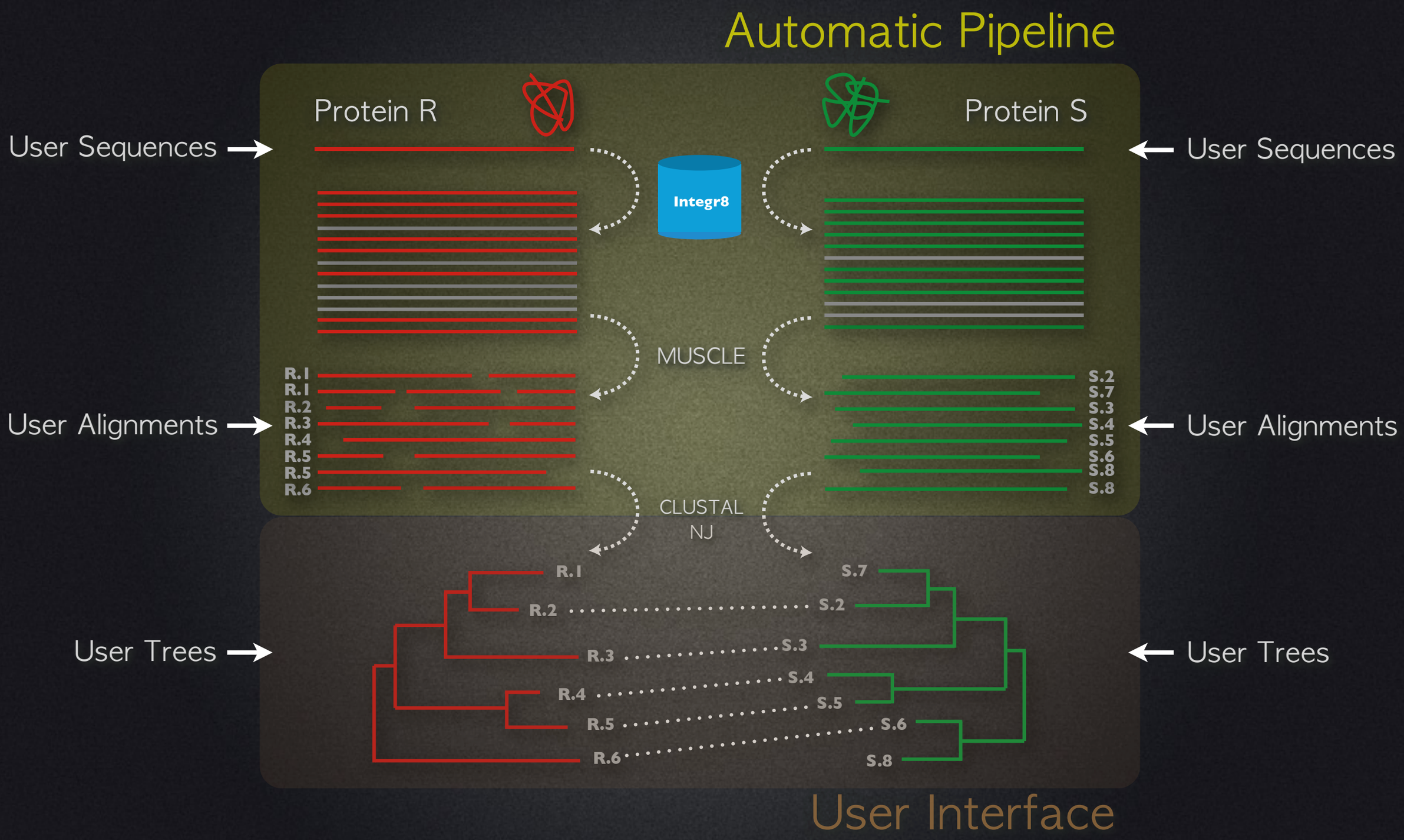


1. MirrorTree Server
2. Incorporating predicted accessibility
3. Selection of organisms
4. Co-evolution significance



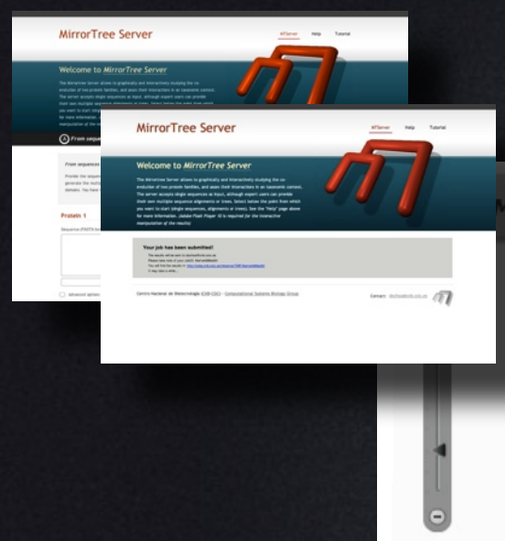
1. MirrorTree Server

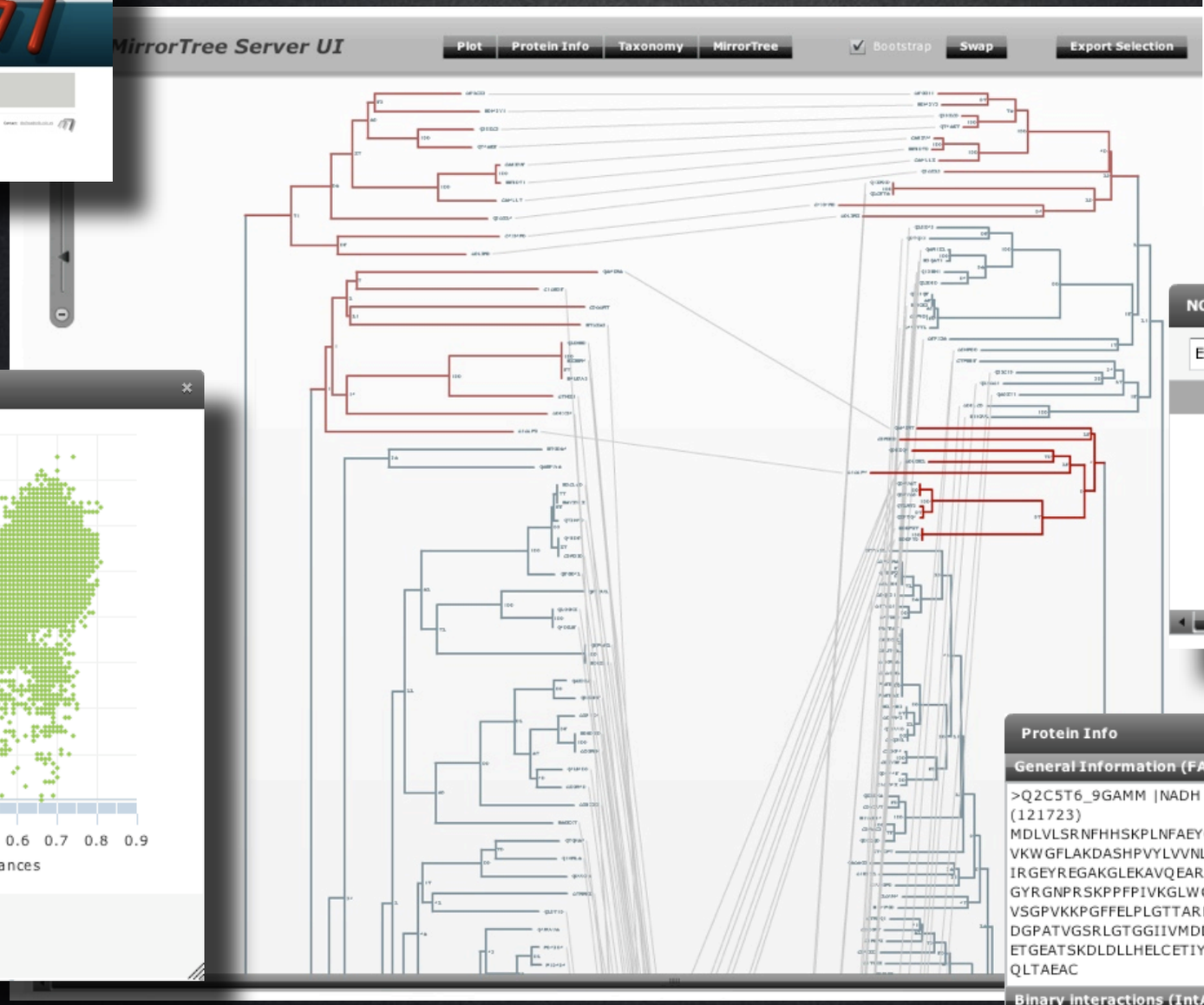
Ochoa, D. & Pazos, F. Studying the co-evolution of protein families with the Mirrortree web server. *Bioinformatics* **26**, 1370–1371 (2010)

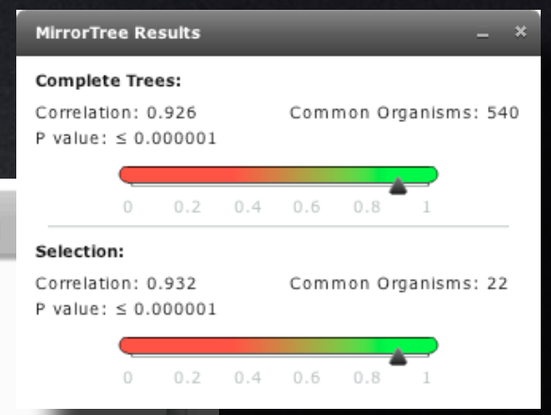

Automatic Pipeline
Protein R
Protein S
User Sequences
User Sequences
Integr8
MUSCLE
User Alignments
User Alignments
R.1
R.1
R.2
R.3
R.4
R.5
R.5
R.6
S.2
S.7
S.3
S.4
S.5
S.6
S.8
S.8
CLUSTAL
NJ
User Trees
User Trees
R.1
R.2
R.3
R.4
R.5
R.6
S.7
S.2
S.3
S.4
S.5
S.6
S.8
User Interface

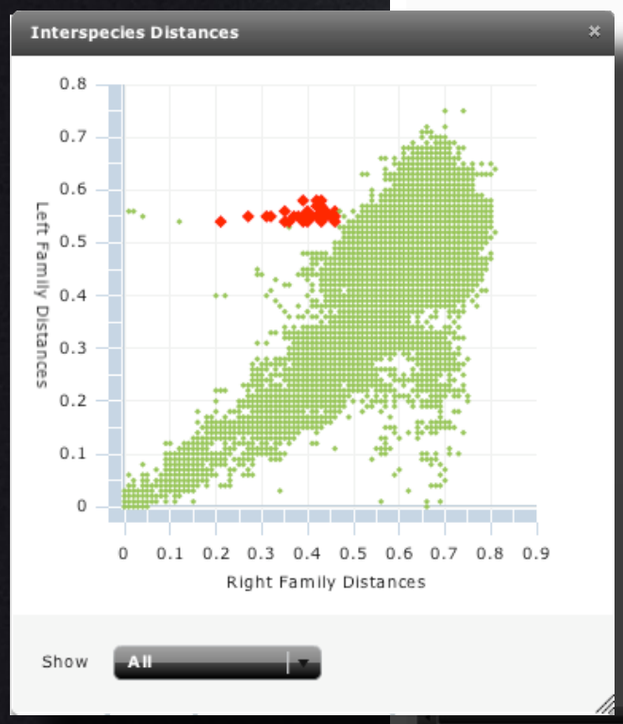
MirrorTree Server

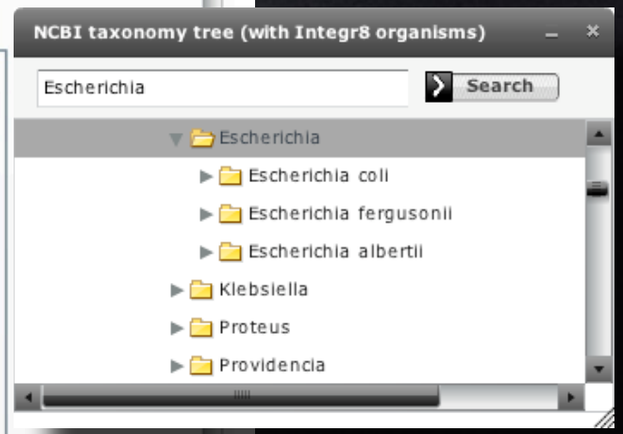
http://csbg.cnb.csic.es/mtserver

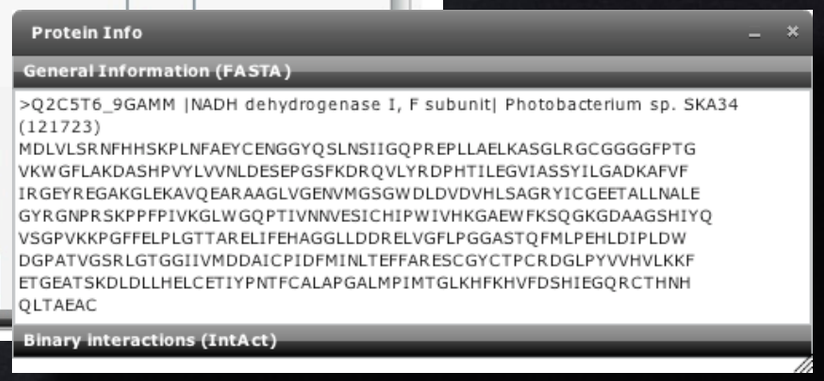




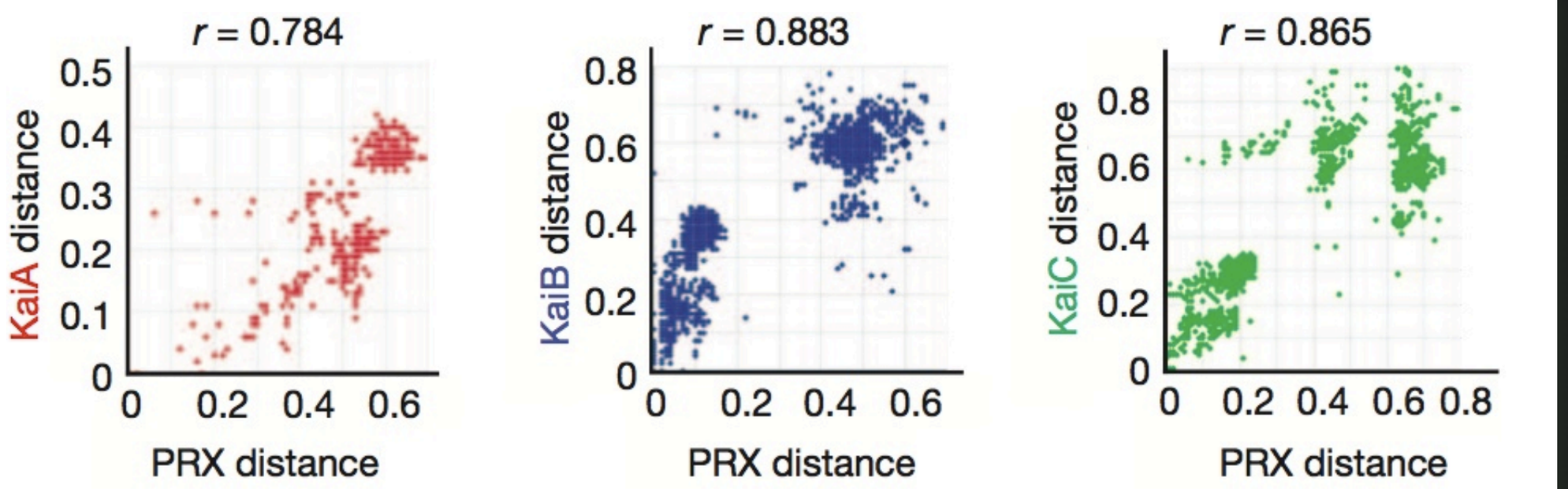




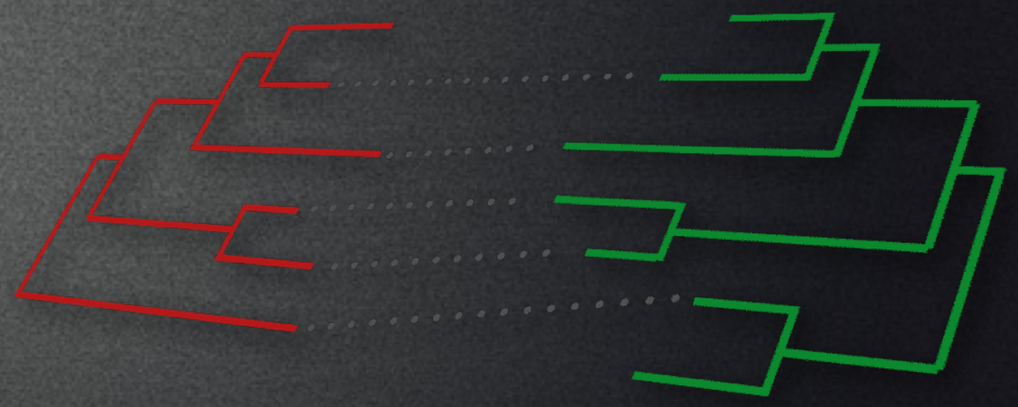




Peroxiredoxins



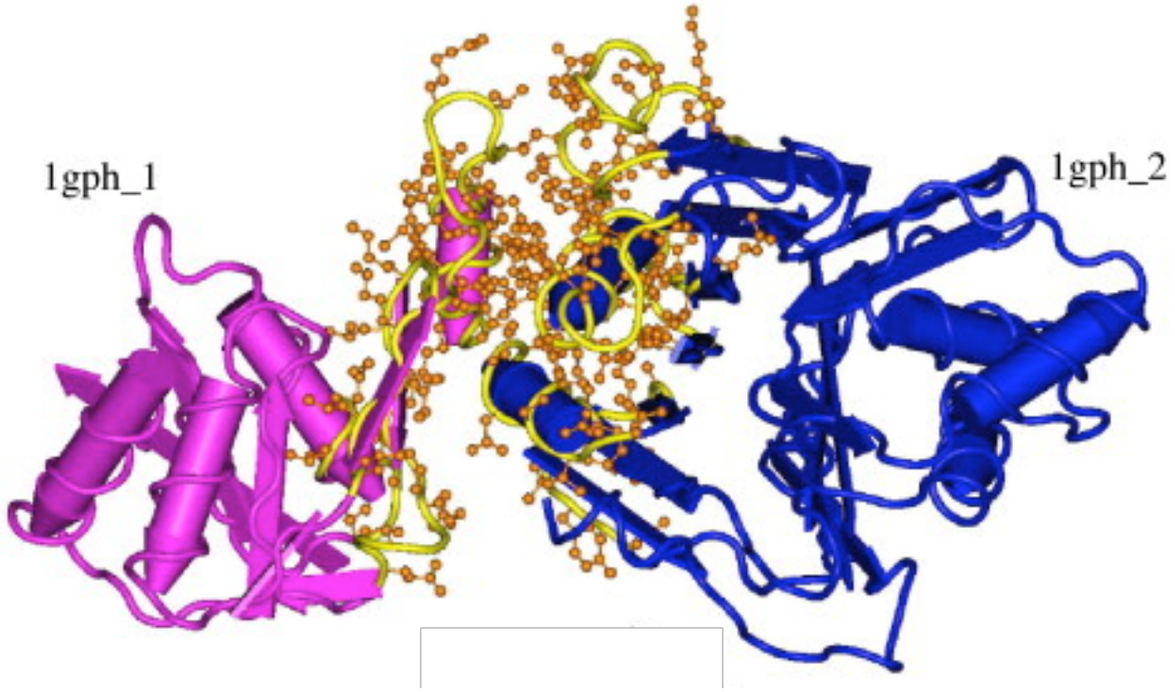
Edgar, R. S. et al. Peroxiredoxins are conserved markers of circadian rhythms. Nature 485, 459–464 (2012).

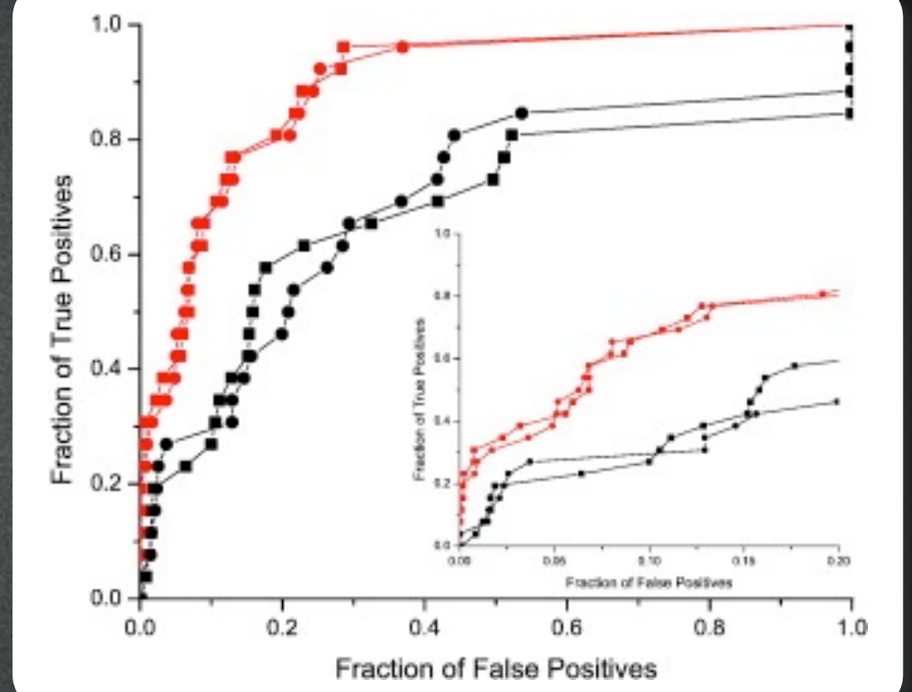


2. Incorporating Predicted Accessibility

Ochoa, D., García-Gutiérrez, P., Juan, D., Valencia, A. & Pazos, F. Incorporating information on predicted solvent accessibility to the co-evolution-based study of protein interactions. Molecular bioSystems 9, 70–76 (2013).

Residue filtering

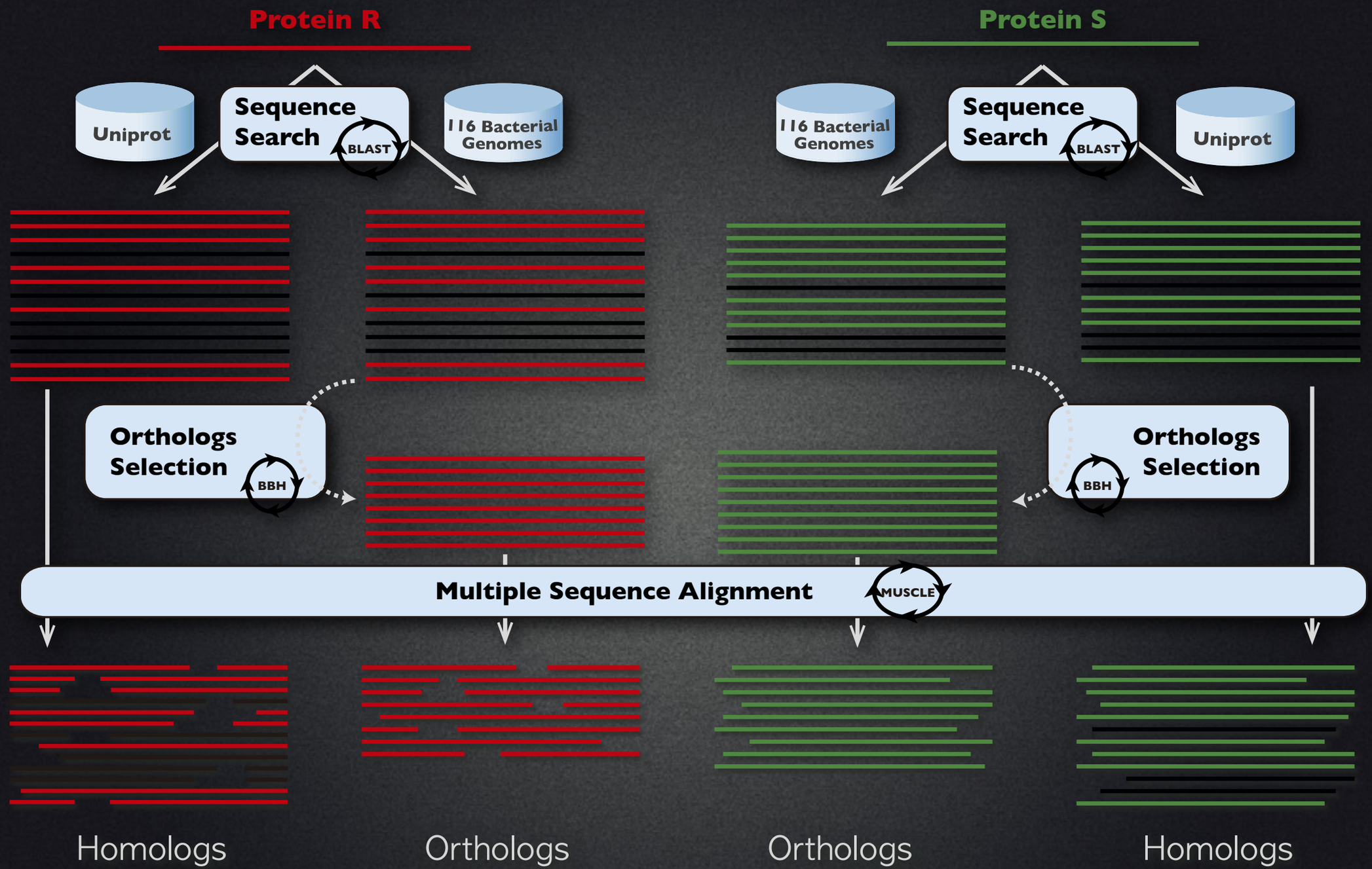




Kann, M. G., Shoemaker, B. A., Panchenko, A. R. & Przytycka, T. M. Correlated evolution of interacting proteins: looking behind the mirrortree. J Mol Biol 385, 91–98 (2009).

Objective

Asses the effect of including predicted solvent accessibility on the performance of the PPI inference based on similarity of phylogenetic trees


Protein R
Protein S
Uniprot
Sequence Search
BLAST
116 Bacterial Genomes
116 Bacterial Genomes
Sequence Search
BLAST
Uniprot
Orthologs Selection
BBH
Orthologs Selection
BBH
Multiple Sequence Alignment
MUSCLE
Homologs
Orthologs
Orthologs
Homologs

Homologs

Orthologs

Orthologs

Homologs

Accessibility Prediction (PROF)

Accessibility Prediction (PROF)

Tree Generation (CLUSTAL)

R.1
R.2
R.3
R.4
R.5
R.6

S.7
S.2
S.3
S.4
S.5
S.6
S.8

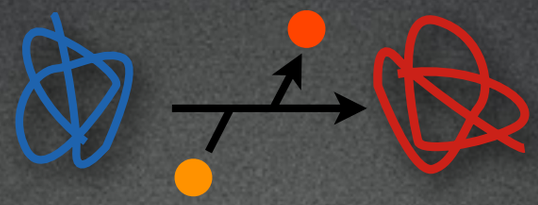
Mirrortree

Profile Correlation

ContextMirror

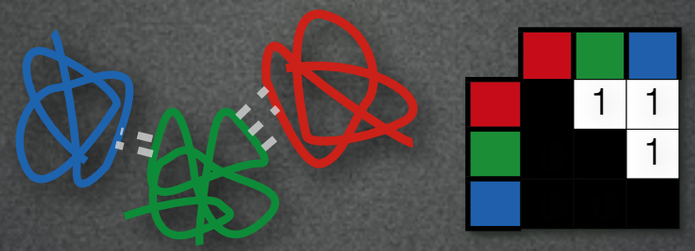
Gold Standards

Pathways
EcoCyc



719 proteins
4,491 evidences

Complexes
EcoCyc



591 proteins
1,354 evidences

Binary Physical
MPIDB

1,268 proteins
1,626 evidences

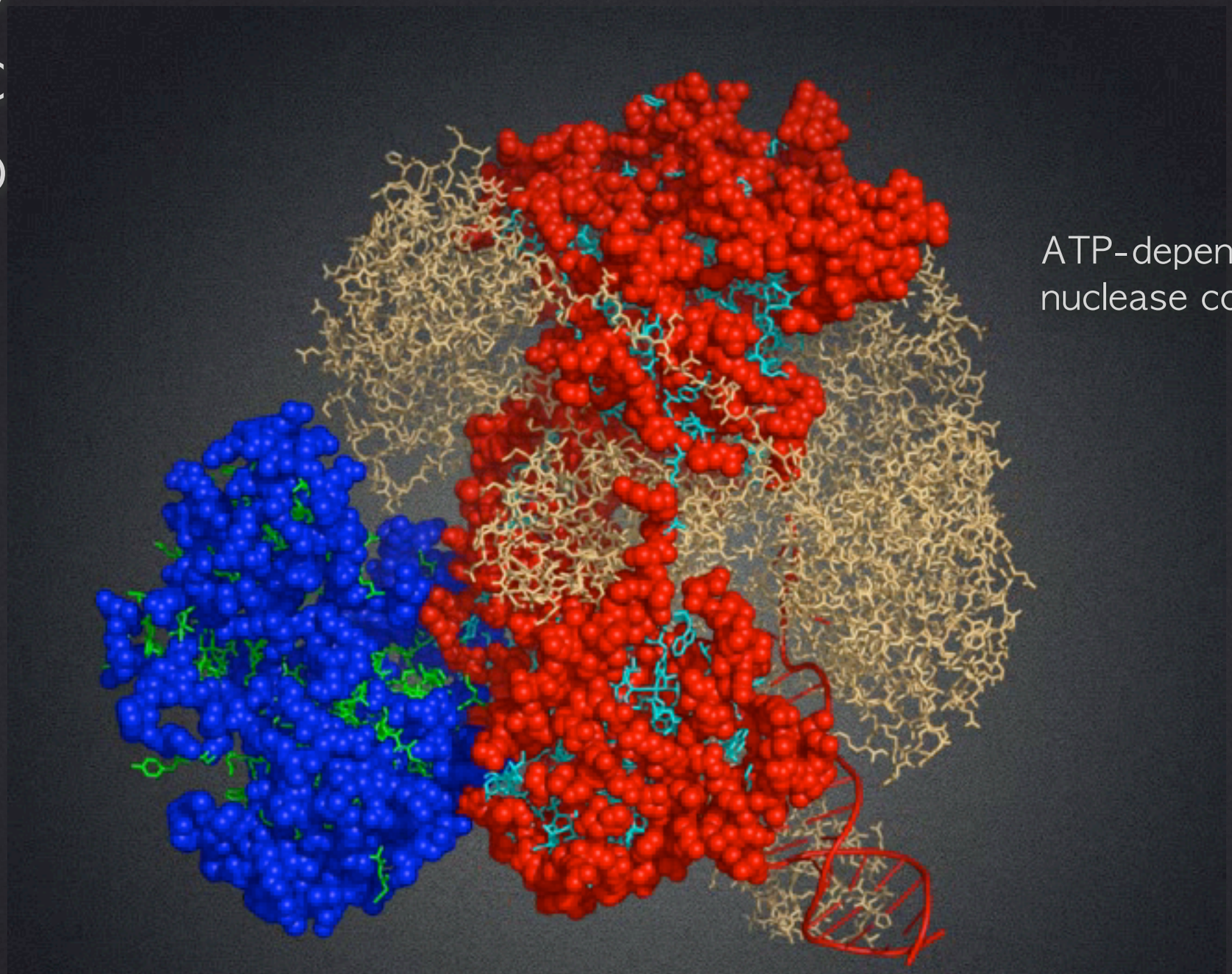
Keseler, I. M. et al. EcoCyc: a comprehensive database of *Escherichia coli* biology. Nucleic Acids Res 39, D583–90 (2011).
Goll, J. et al. MPIDB: the microbial protein interaction database. Bioinformatics 24, 1743–1744 (2008).

Ochoa, D., García-Gutiérrez, P., Juan, D., Valencia, A. & Pazos, F. Incorporating information on predicted solvent accessibility to the co-evolution-based study of protein interactions. Molecular bioSystems 9, 70–76 (2013).

RecB

RecC

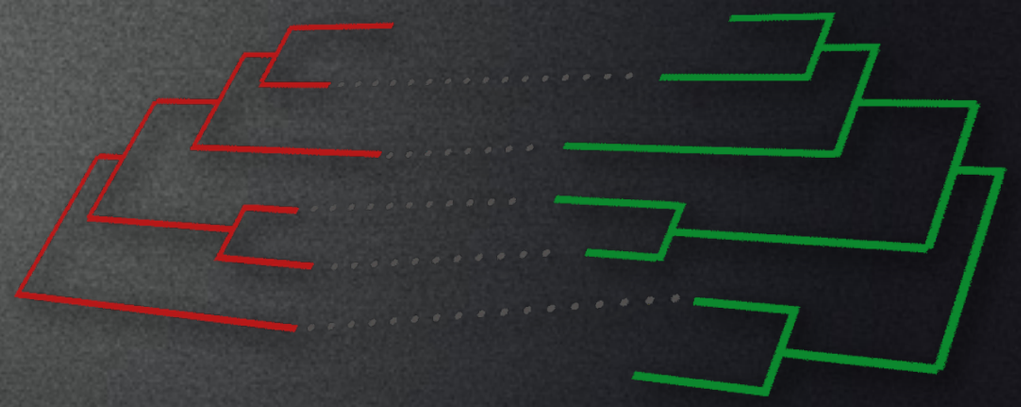
RecD



pACC2

ATP-dependent helicase/
nuclease complex

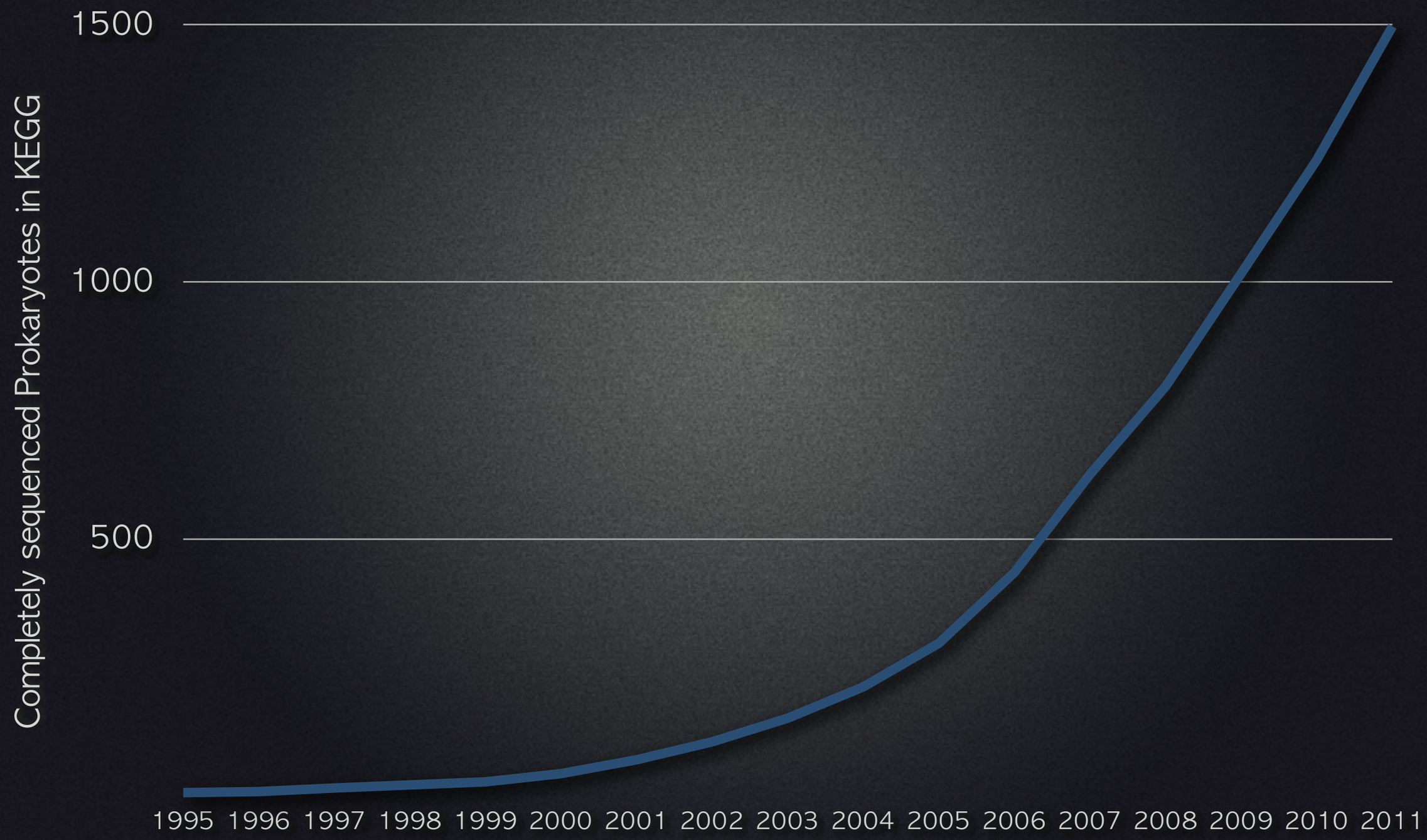
		ALL	eRIA0	eRIA3	pACC2	pACC12	pACC50
✔	RecC-RecD	0.701	0.768	Not significant	0.739	0.750	0.806
✘	RecB-RecD	0.427	Not significant	Not significant	Not significant	Not significant	Not significant



3. Selection of organisms

Herman, Dorota, David Ochoa, David Juan, Daniel Lopez, Alfonso Valencia, and Florencio Pazos. 2011. 'Selection of organisms for the co-evolution-based study of protein interactions.', BMC Bioinformatics, 12, 363

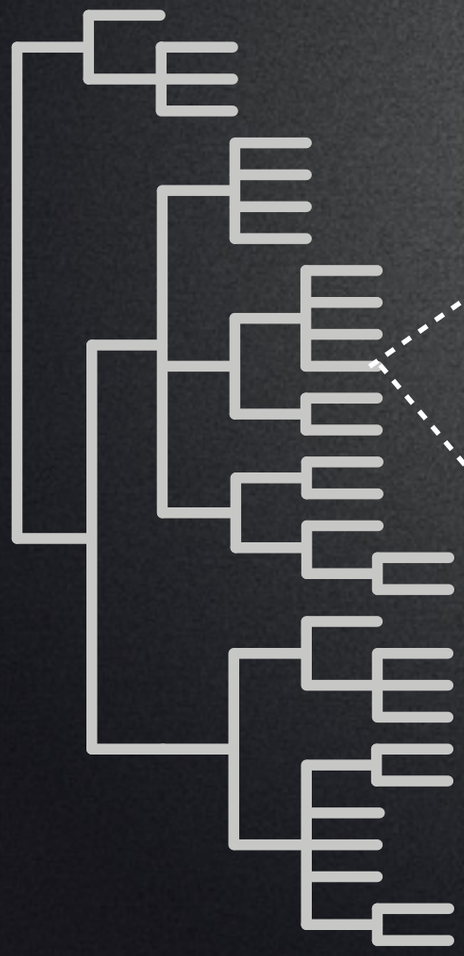
Sequence explosion



The redundancy problem

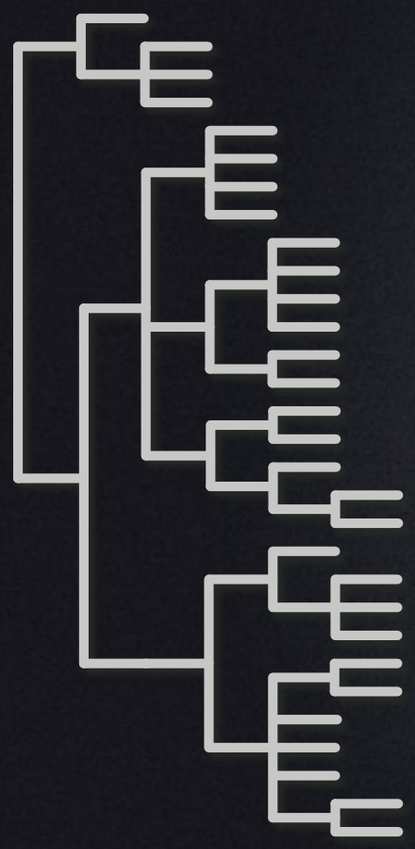
2001

70 sequenced prokaryotes



2011

1,498 sequenced prokaryotes

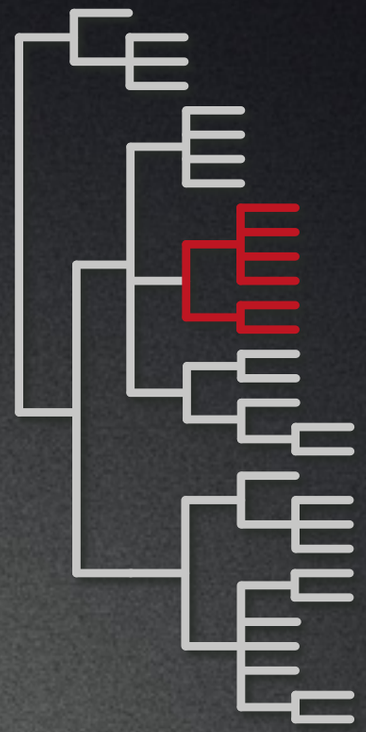


NCBI taxonomy tree

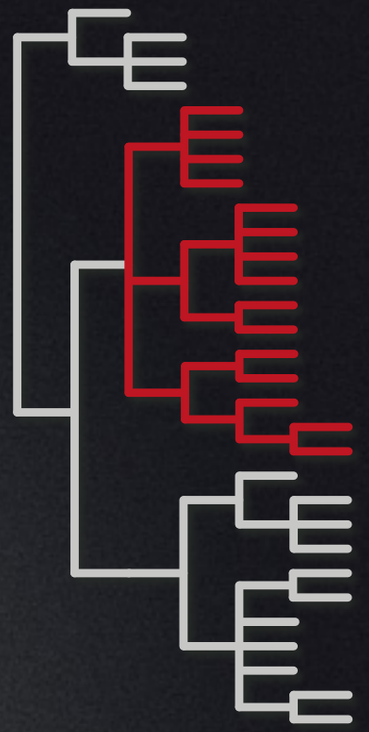
Nearest

Level

Nearest 1

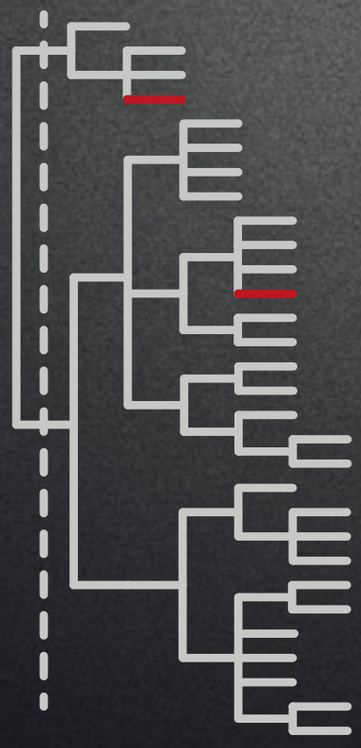


Nearest 2



Nearest 3

...

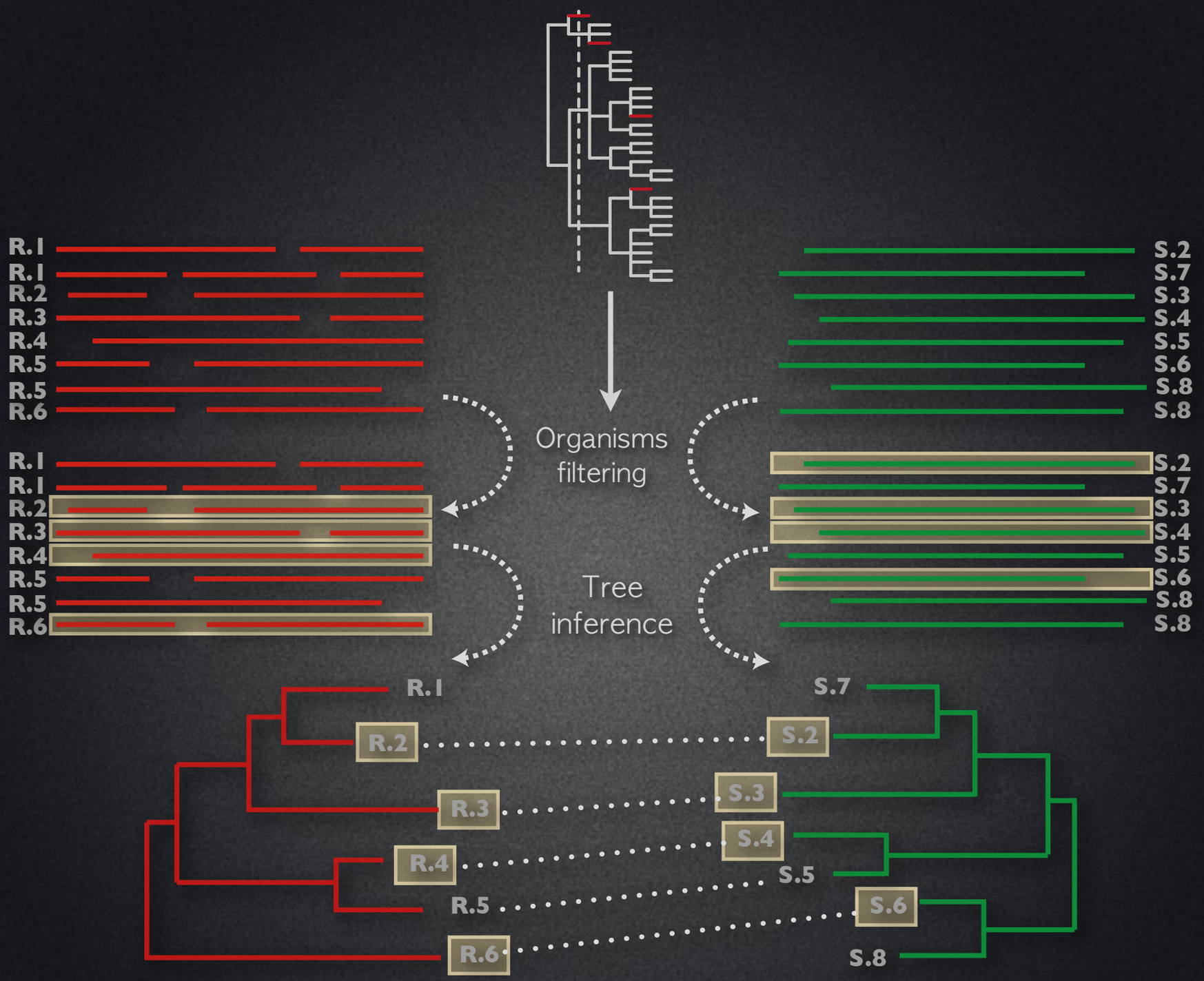


Level 1

Level 2

Level 3

...

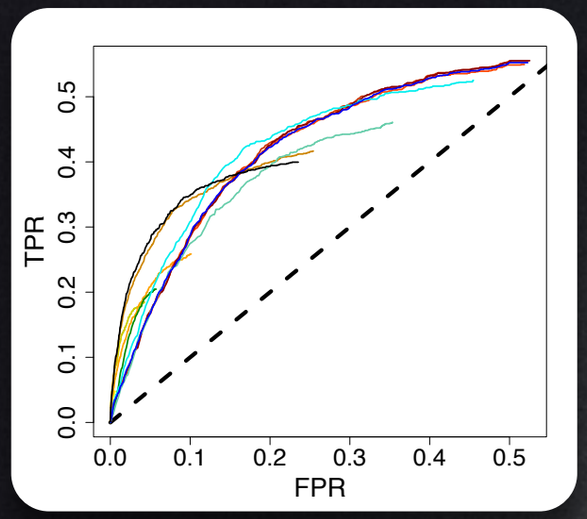

R.1
R.1
R.2
R.3
R.4
R.5
R.5
R.6
S.2
S.7
S.3
S.4
S.5
S.6
S.8
S.8
Organisms filtering
Tree inference
S.7
S.5
Mirrortree
Profile Correlation
ContextMirror

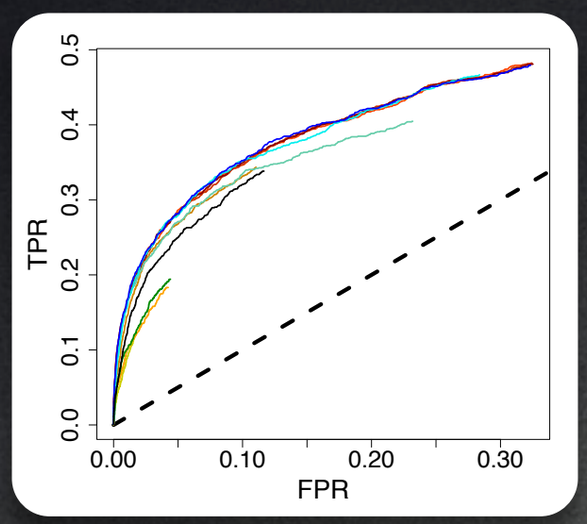
Mirrortree

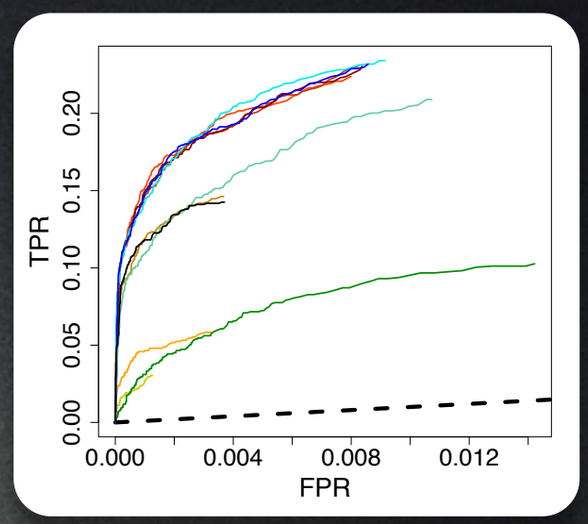
Profile Correlation

ContextMirror

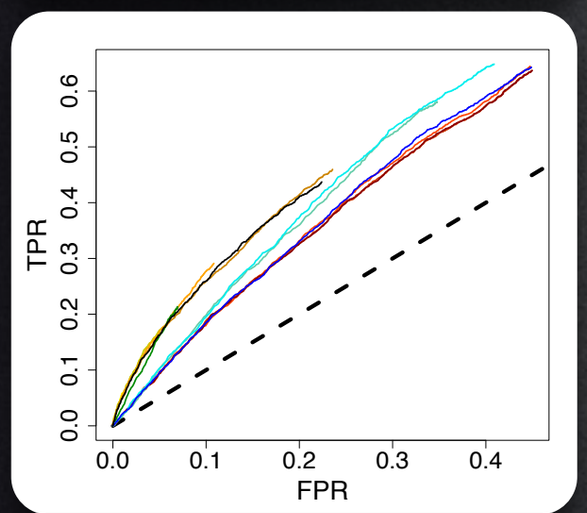
Complexes

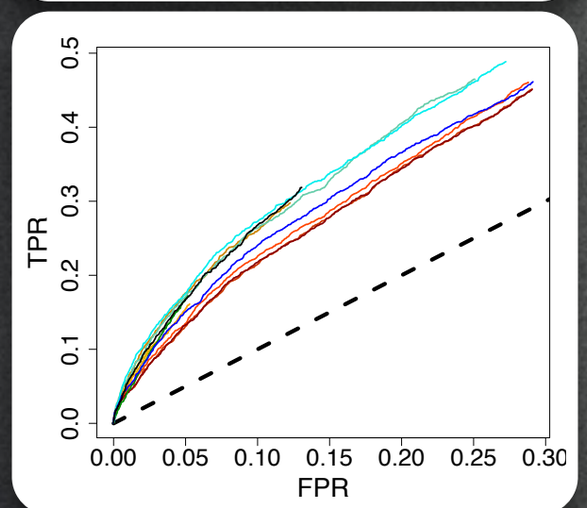


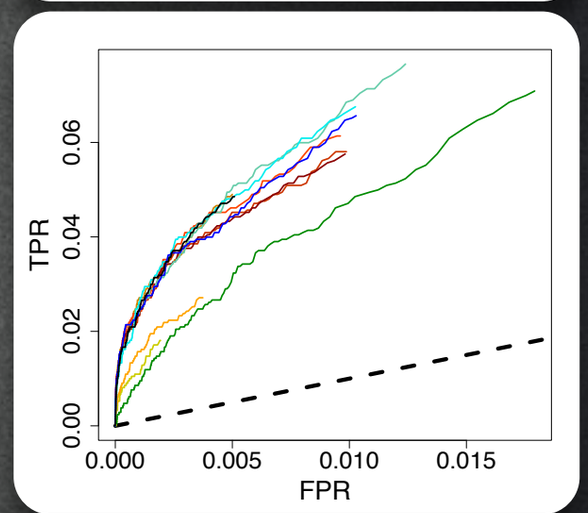


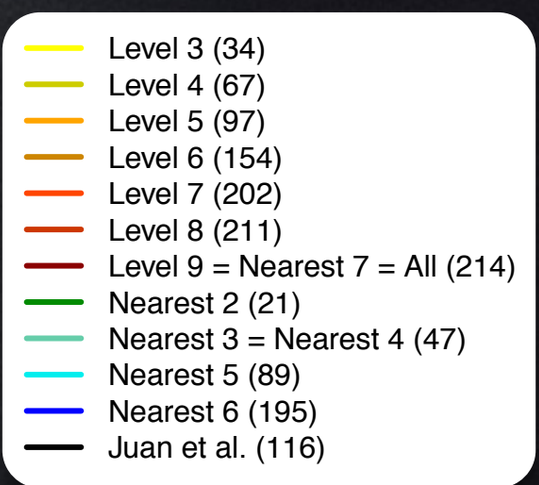


Binary Physical

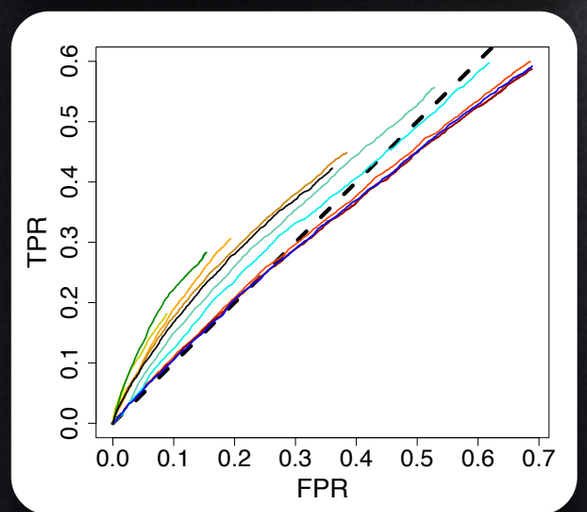


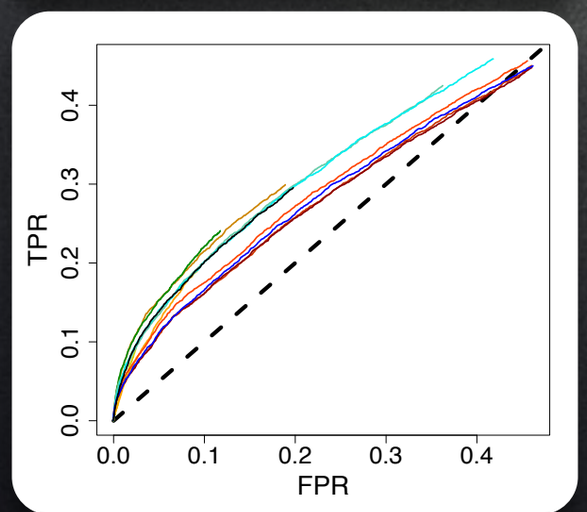


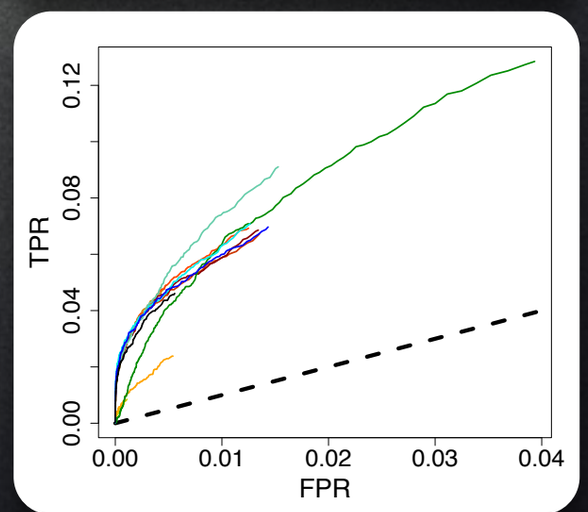




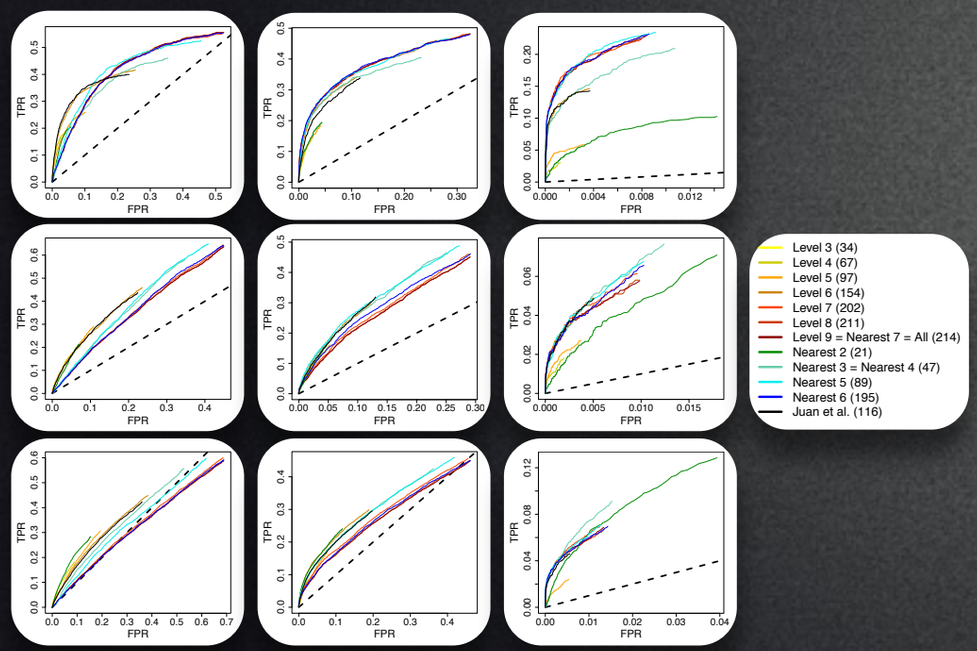
Pathways



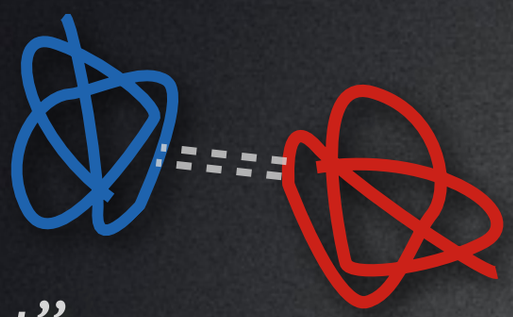




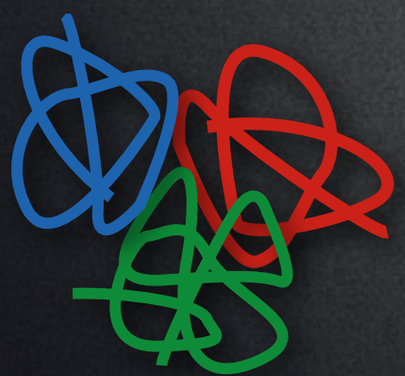
Conclusions



- Not always more organisms is better
- Redundancy negatively affect mirrortree predictions
- Sampling close/distant organisms influences the prediction of different types of interactions

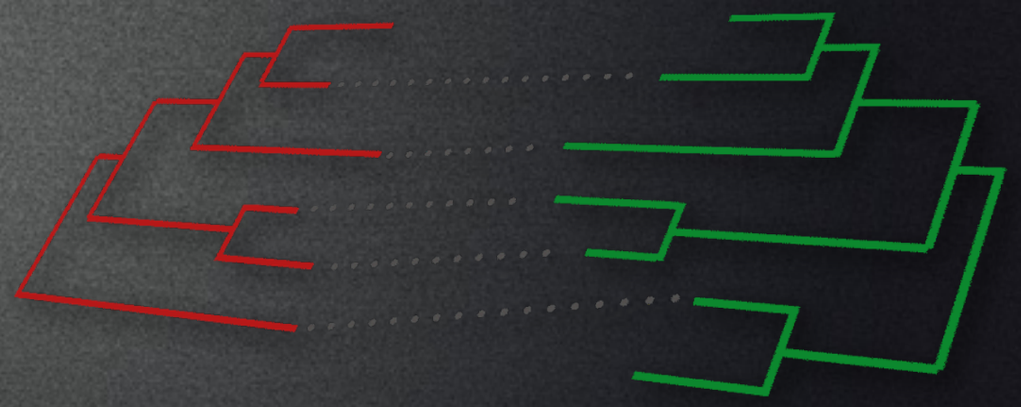


“recent”



“old”

	AUCs	
	Level9 (=all)	Nearest2
MINE_ECOLI	0.12	**0.83**
PABA_ECOLI	0.28	**0.96**
DHAS_ECOLI	0.17	**0.81**
GSHB_ECOLI	0.30	**0.93**
DPO3A_ECOLI	**0.70**	0.11
DPO3B_ECOLI	**0.64**	0.22
RPOB_ECOLI	**0.82**	0.48
RPOA_ECOLI	**0.81**	0.48
ZNUB_ECOLI	**1.00**	0.36
ZNUC_ECOLI	**0.99**	0.41
ZNUA_ECOLI	**0.98**	0.79



4. Co-evolution significance

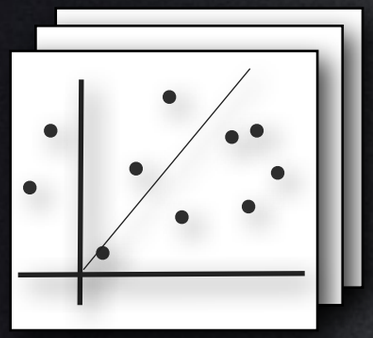
Confidence evaluation

Distances matrix A

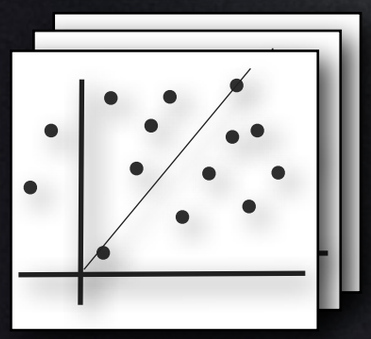
	R1	R2	R3	R4	R5	R6
R1						
R2						
R3						
R4						
R5						
R6						

Distances matrix B

	S2	S3	S4	S5	S6	S7	S8
S2							
S3							
S4							
S5							
S6							
S7							
S8							

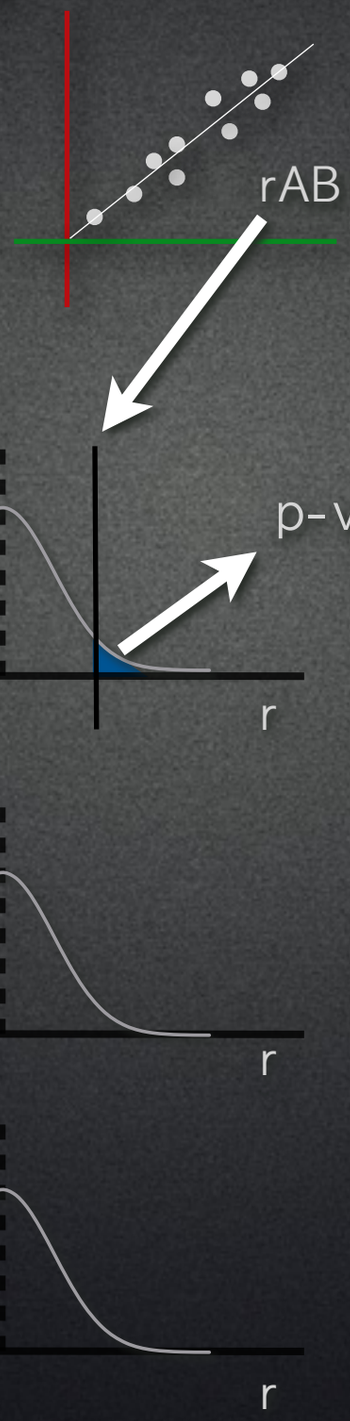


n=10

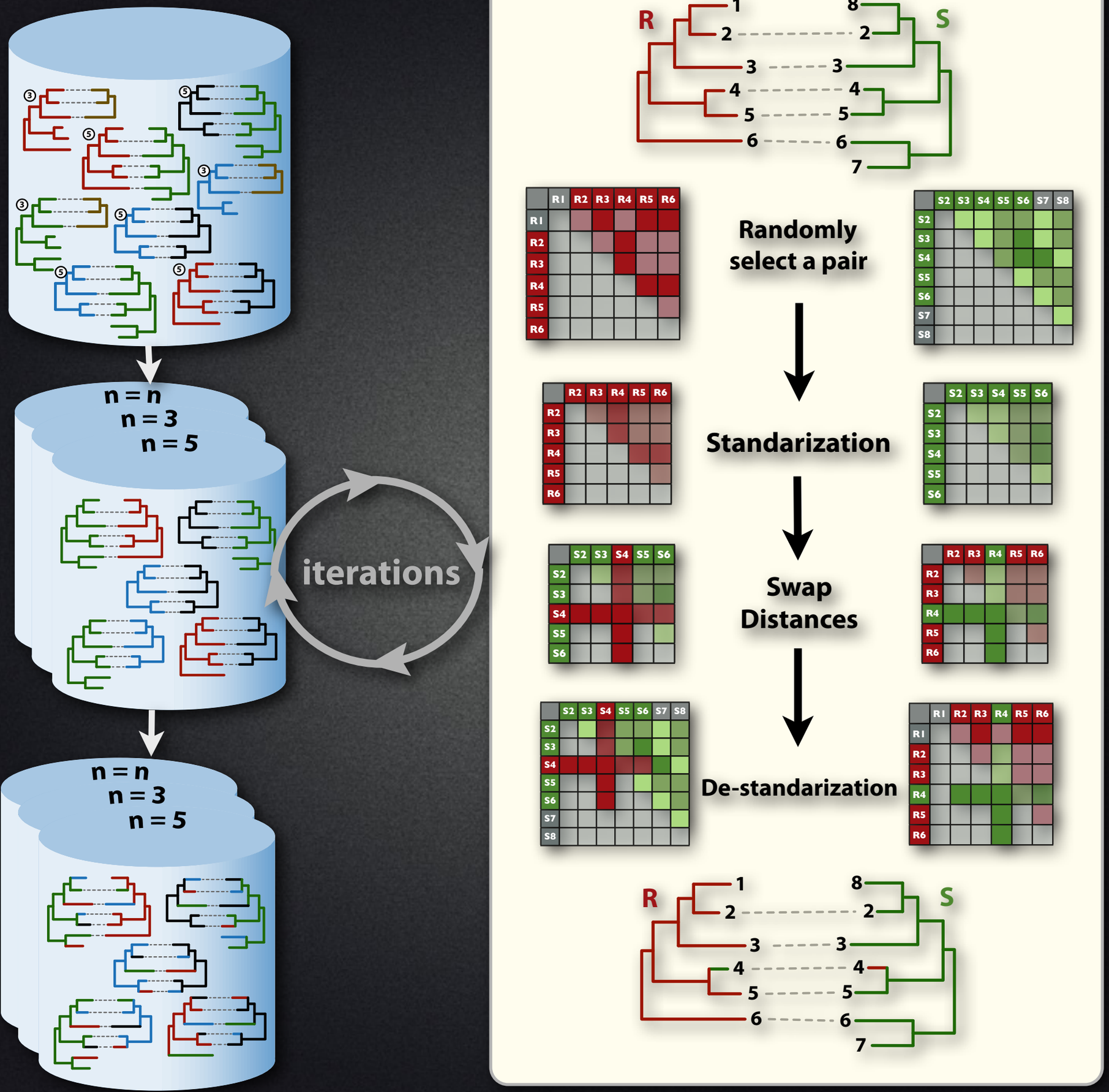


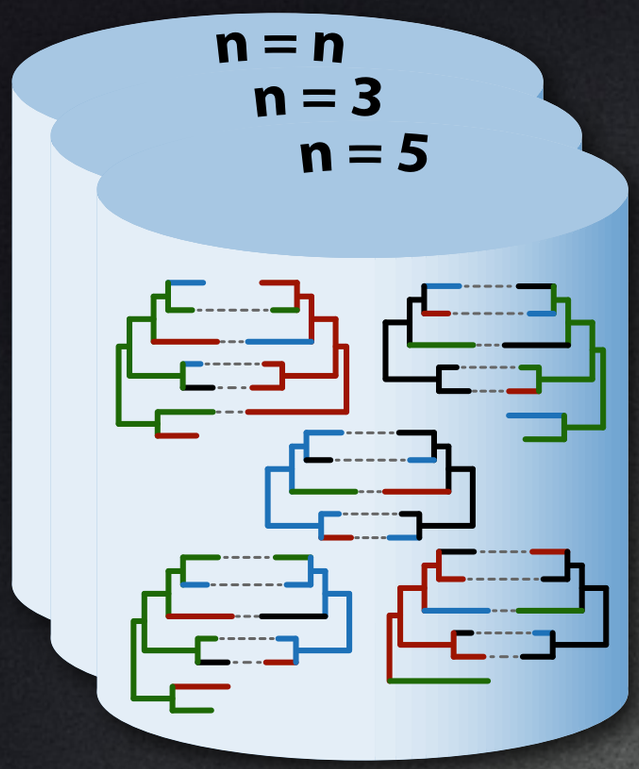
n=15

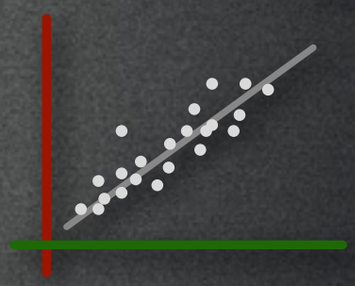
n=n ...



Non-specific null model

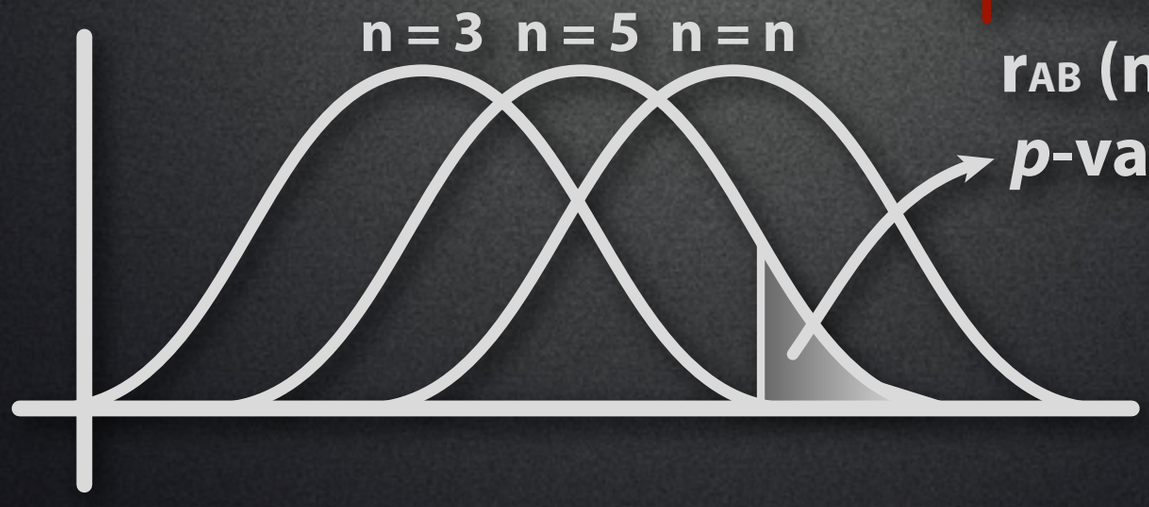

n = n
n = 3
n = 5
iterations
n = n
n = 3
n = 5
R
S
Randomly
select a pair
Standarization
Swap
Distances
De-standarization
R
S





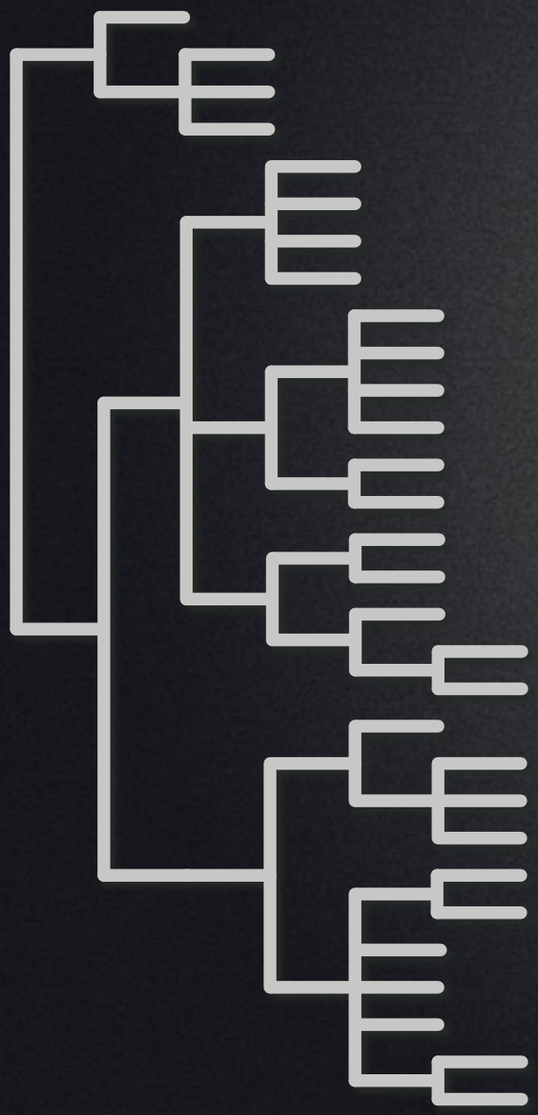
r_{AB} (n=5)

p-value

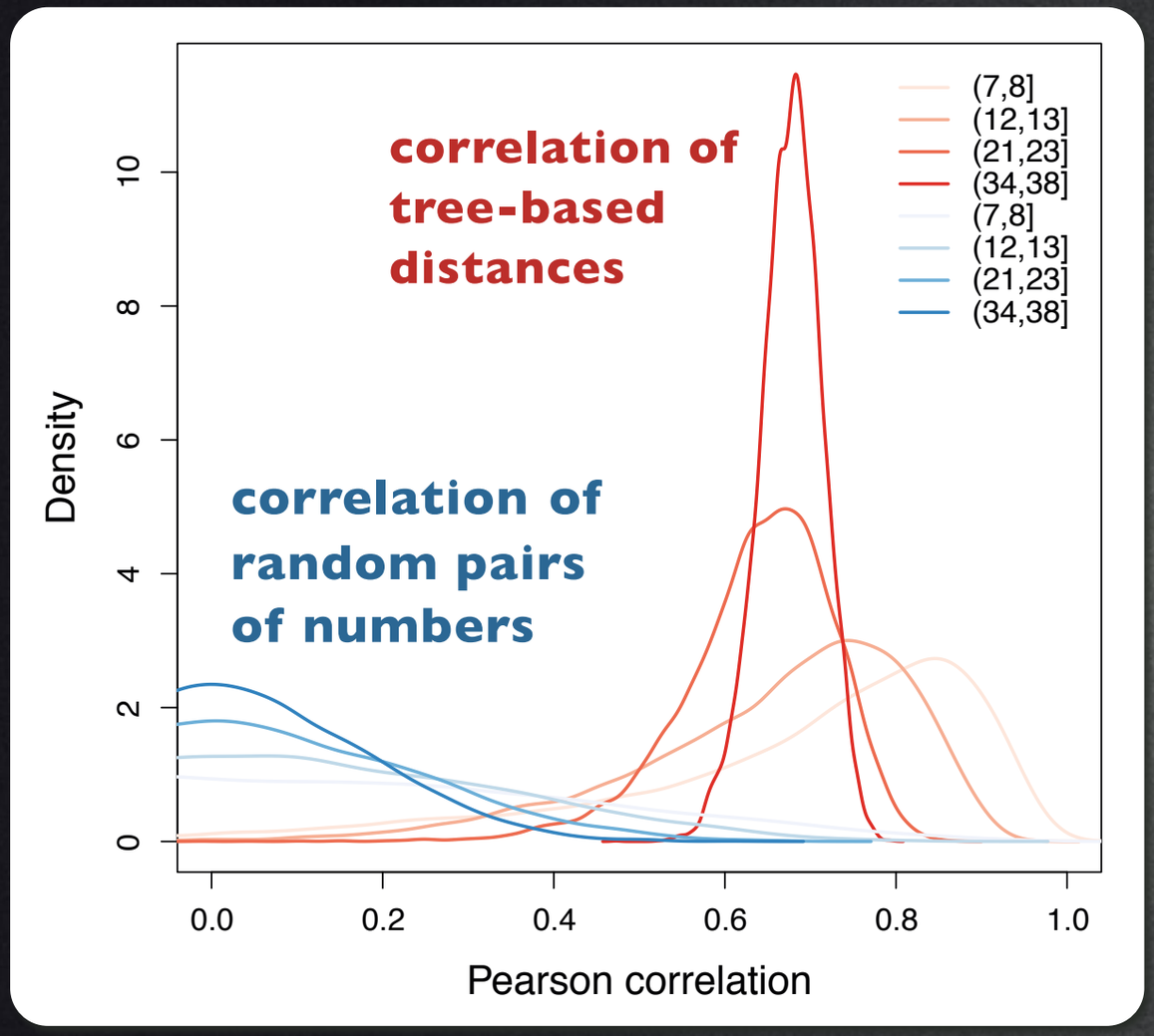


p-mirrortree

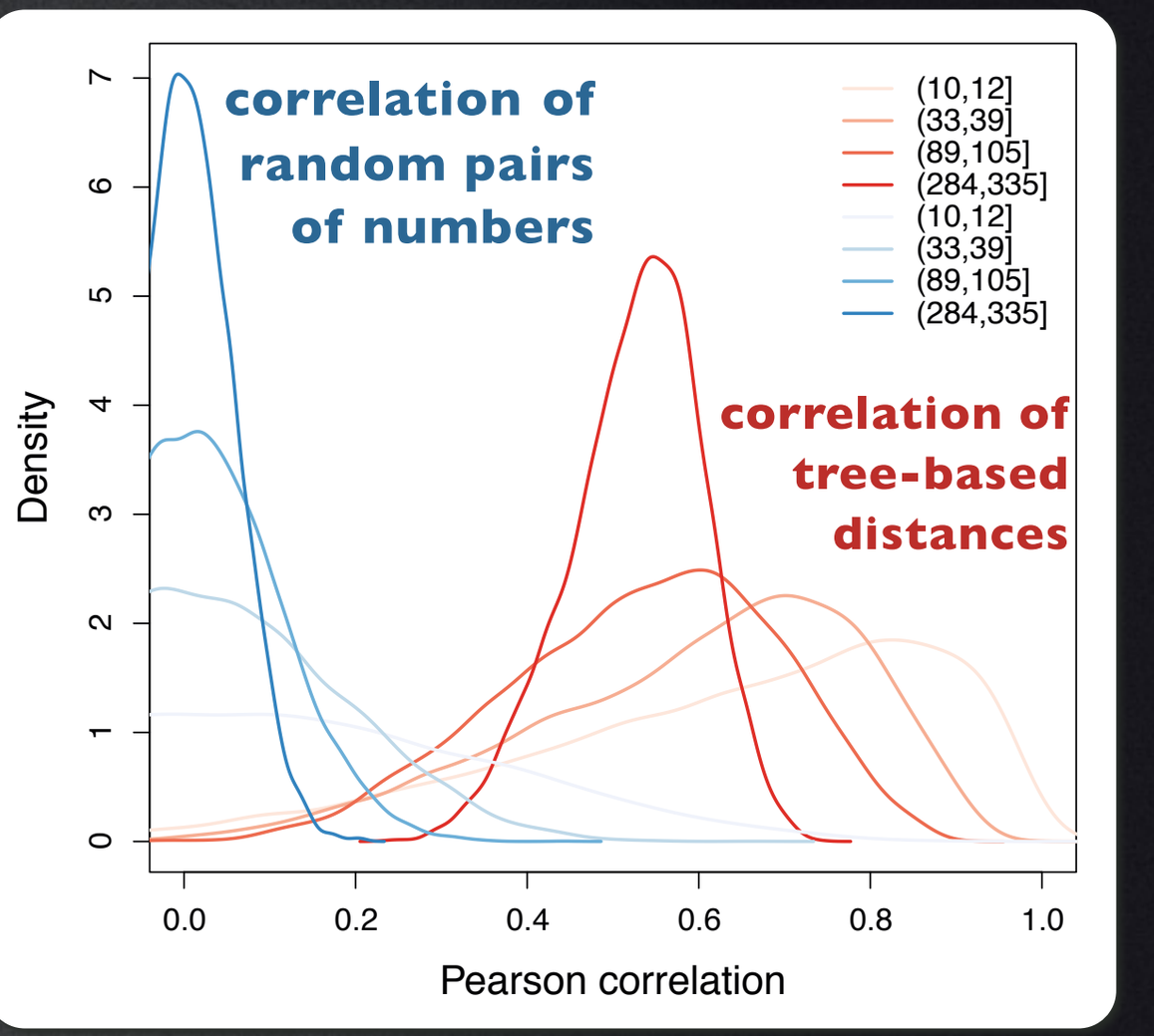
Reference set of organisms



- Prokaryotes in KEGG 2000-2010
- Redundant vs Non-redundant

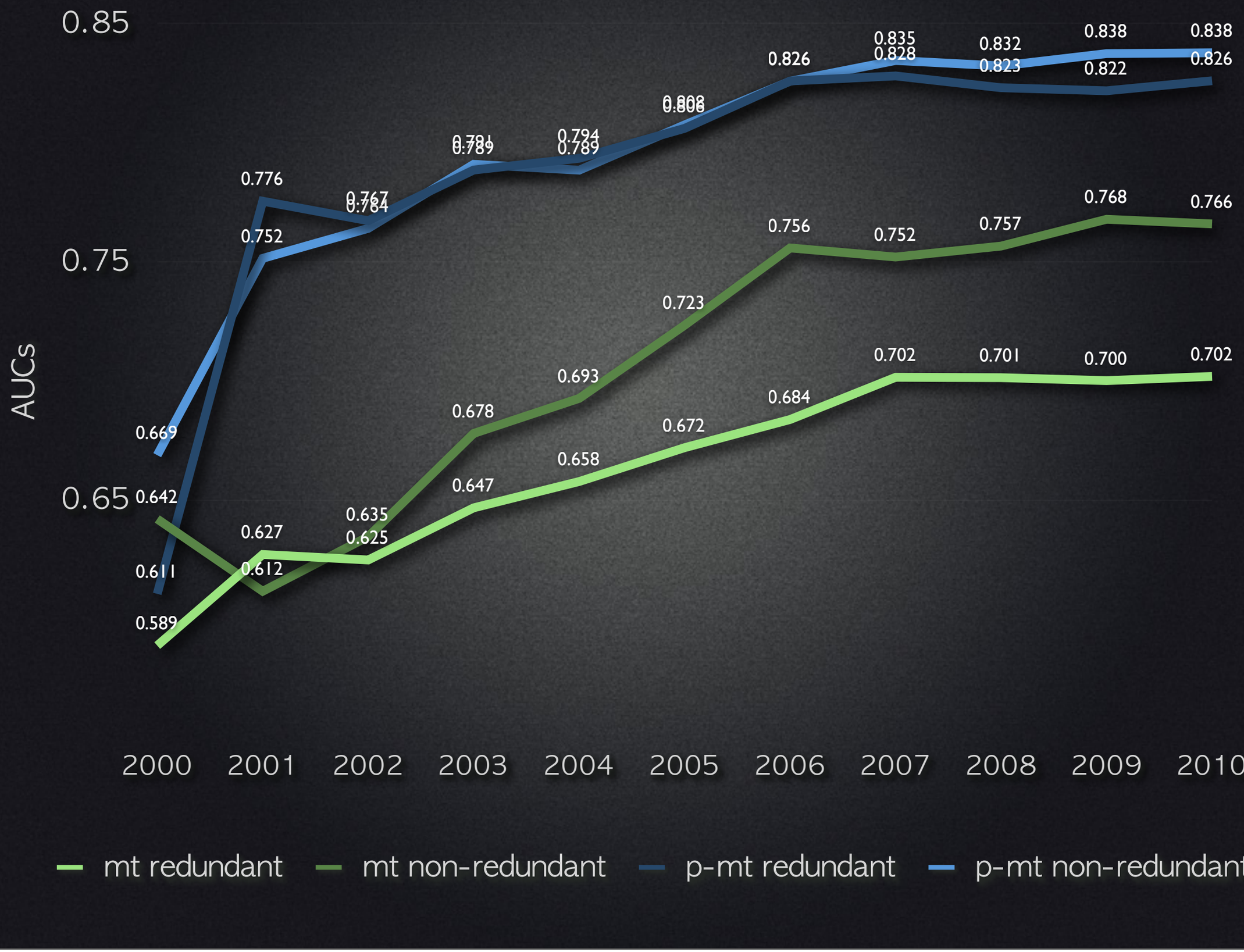

correlation of
tree-based
distances
correlation of
random pairs
of numbers
(7,8]
(12,13]
(21,23]
(34,38]
(7,8]
(12,13]
(21,23]
(34,38]
Density
0
2
4
6
8
10
0.0
0.2
0.4
0.6
0.8
1.0
Pearson correlation

2001


correlation of
random pairs
of numbers
correlation of
tree-based
distances
(10,12]
(33,39]
(89,105]
(284,335]
(10,12]
(33,39]
(89,105]
(284,335]
Density
0
1
2
3
4
5
6
7
0.0
0.2
0.4
0.6
0.8
1.0
Pearson correlation

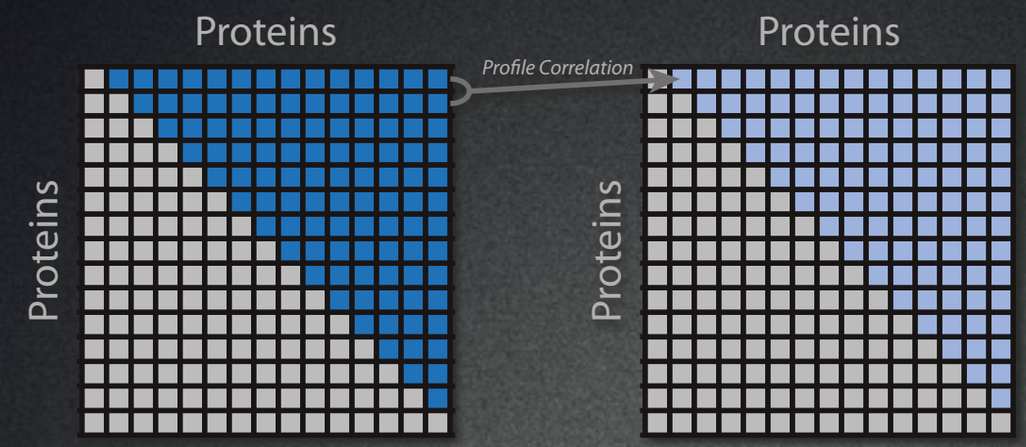
2010

Complexes

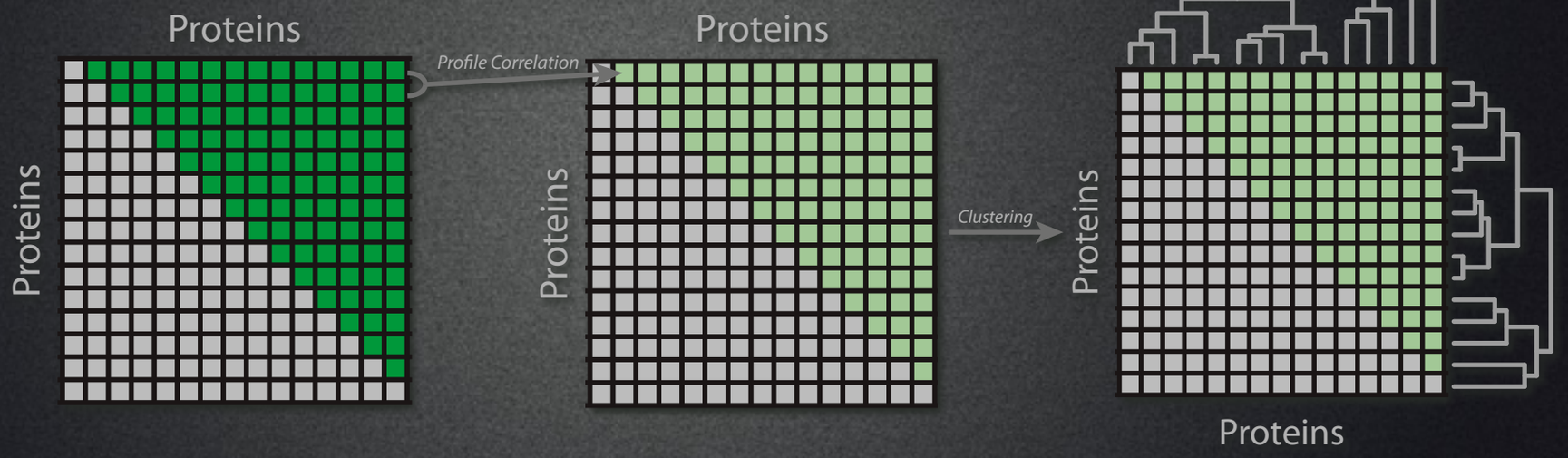

0.85
0.75
0.65
AUCs
0.776
0.752
0.669
0.642
0.611
0.589
0.767
0.784
0.627
0.612
0.781
0.789
0.635
0.625
0.794
0.789
0.678
0.693
0.723
0.647
0.658
0.672
0.684
0.808
0.806
0.826
0.828
0.835
0.832
0.823
0.838
0.822
0.838
0.826
0.702
0.701
0.700
0.702
0.768
0.766
0.756
0.752
0.757
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
mt redundant
mt non-redundant
p-mt redundant
p-mt non-redundant

Context methods using p-values

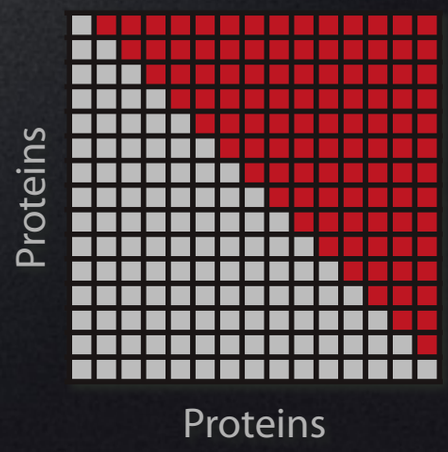
Profile Correlation mirrortree



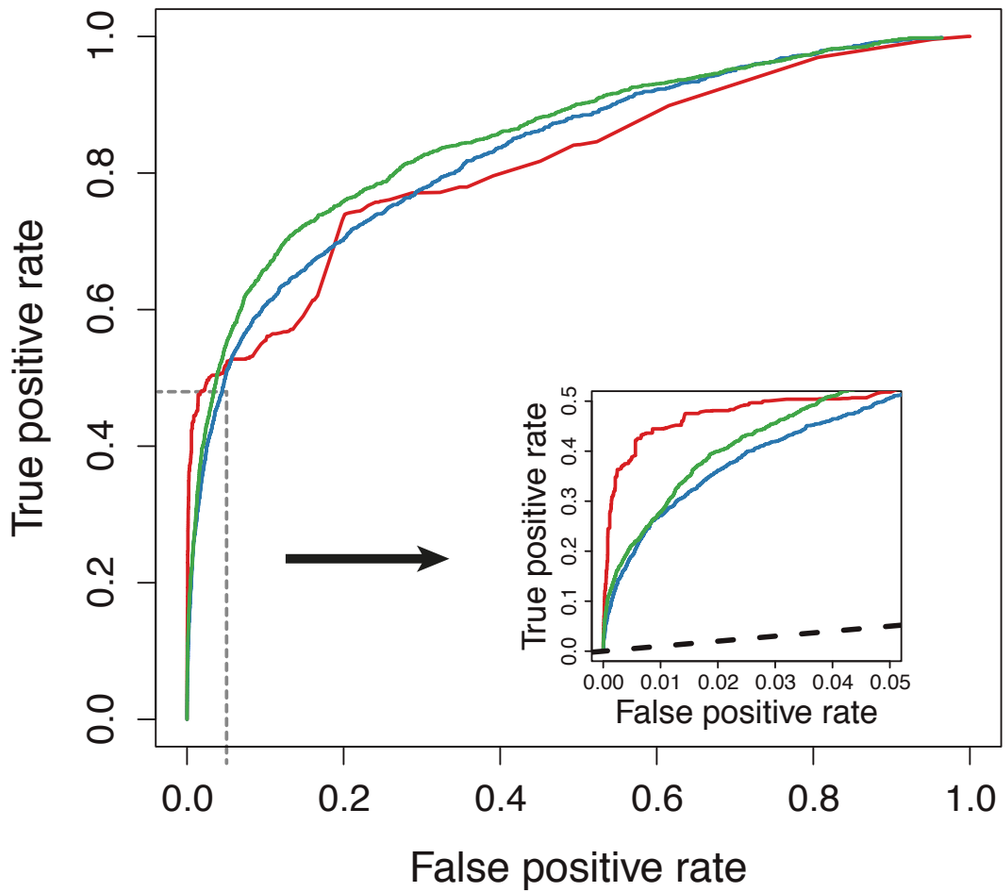
Profile Correlation p-mirrortree

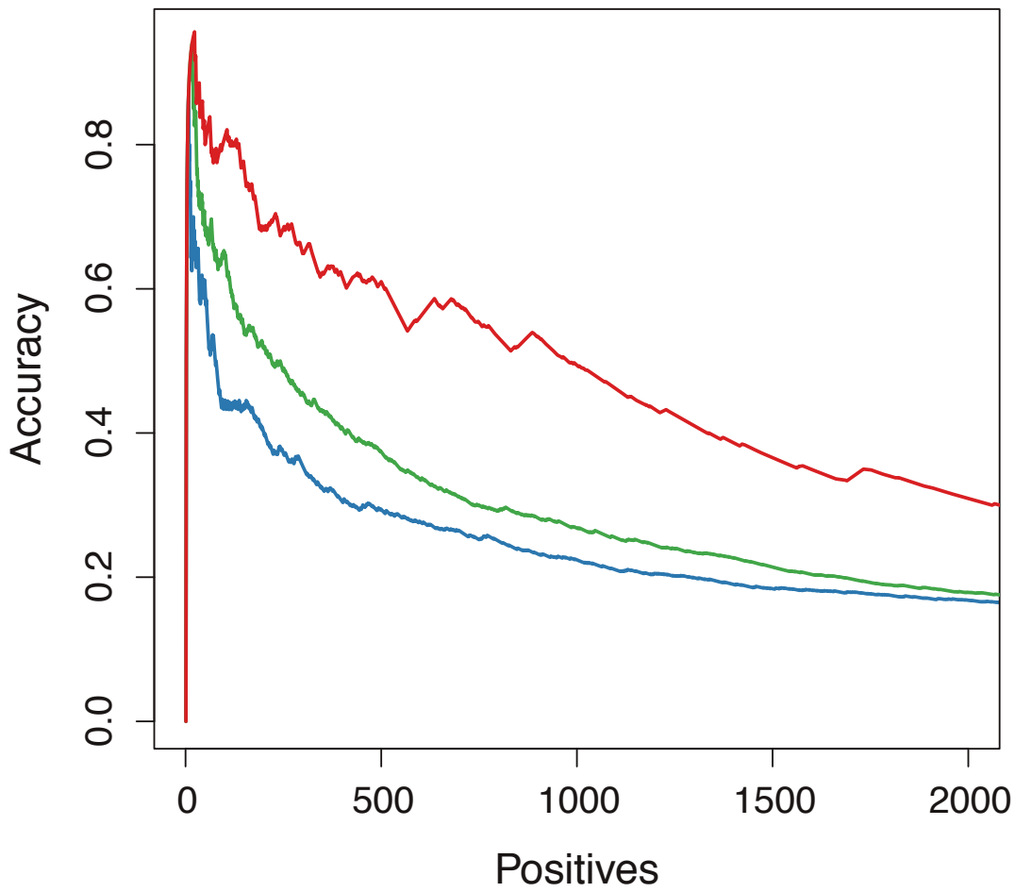


Hierarchical Clustering Analysis (HCA)



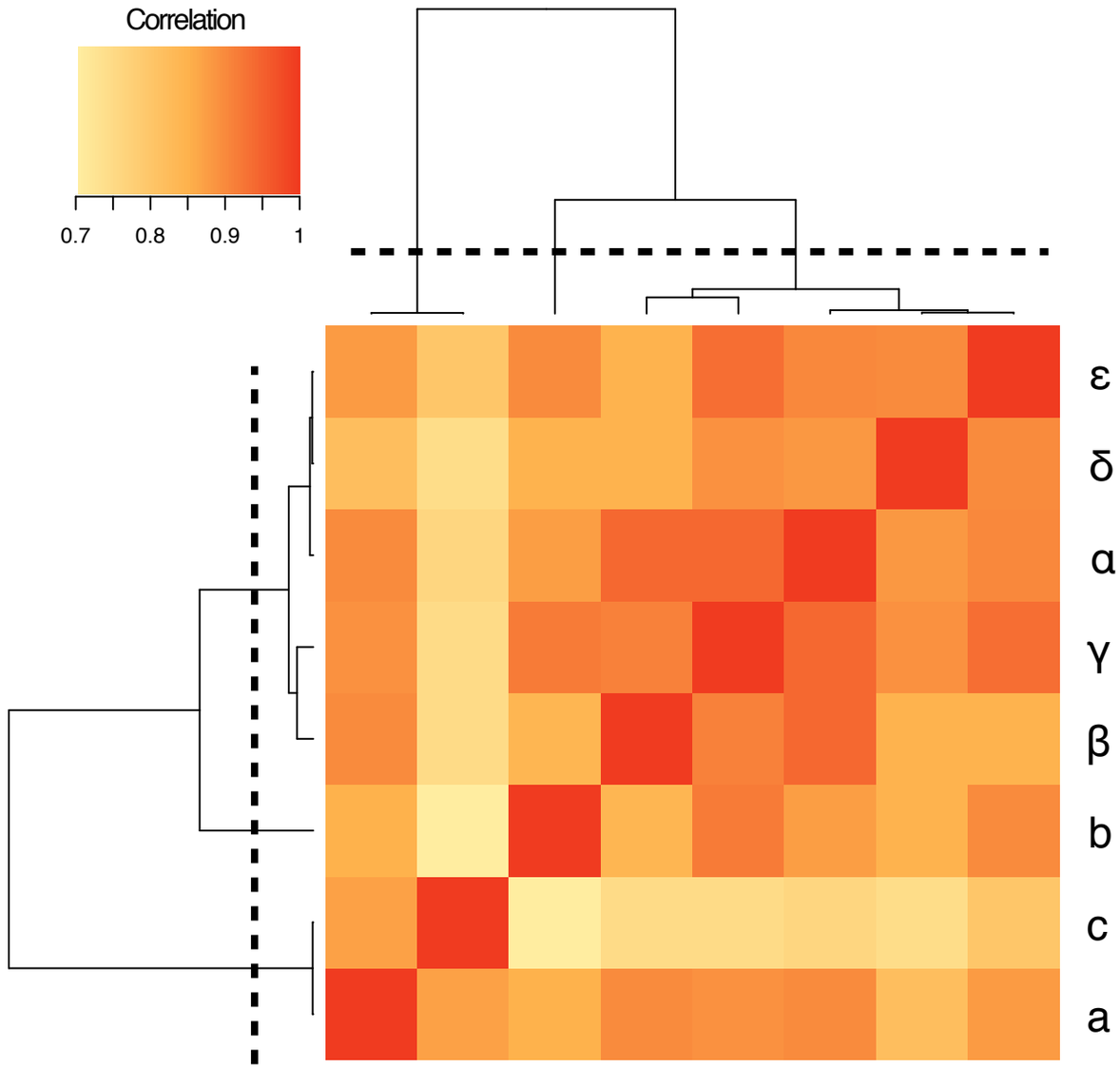
Context methods using p-values

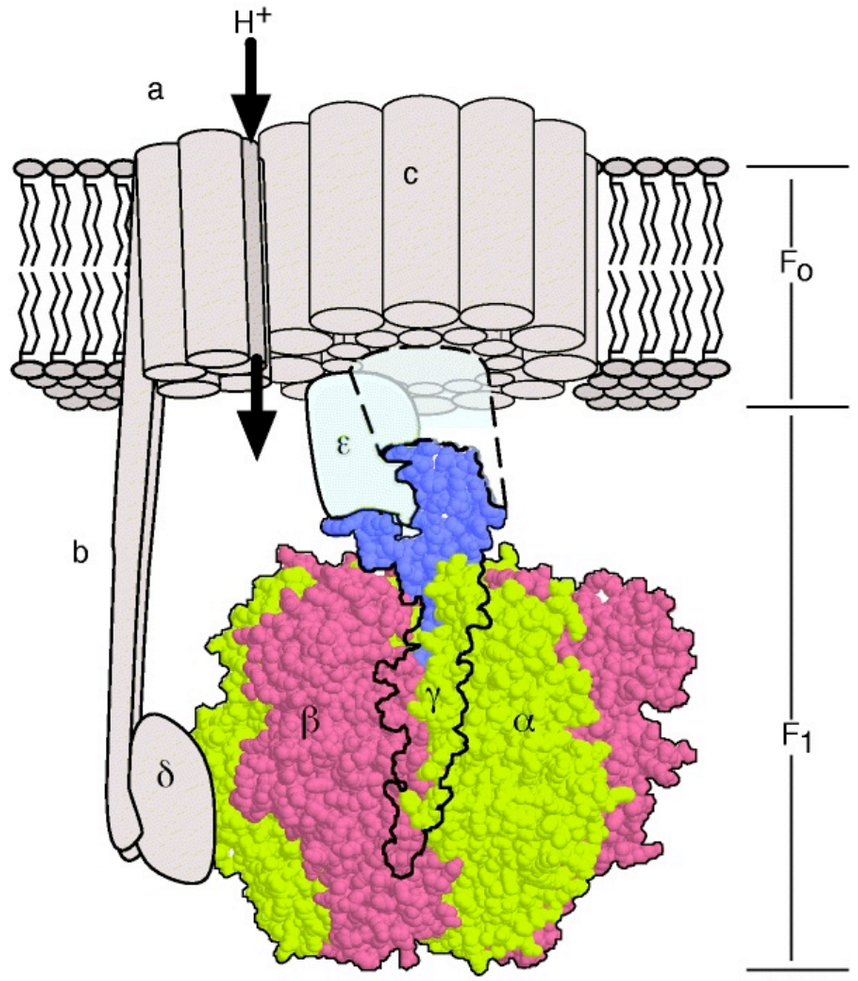




PC – correlations PC – pvalues HCA

ATPase coevolutionary map





Conclusions

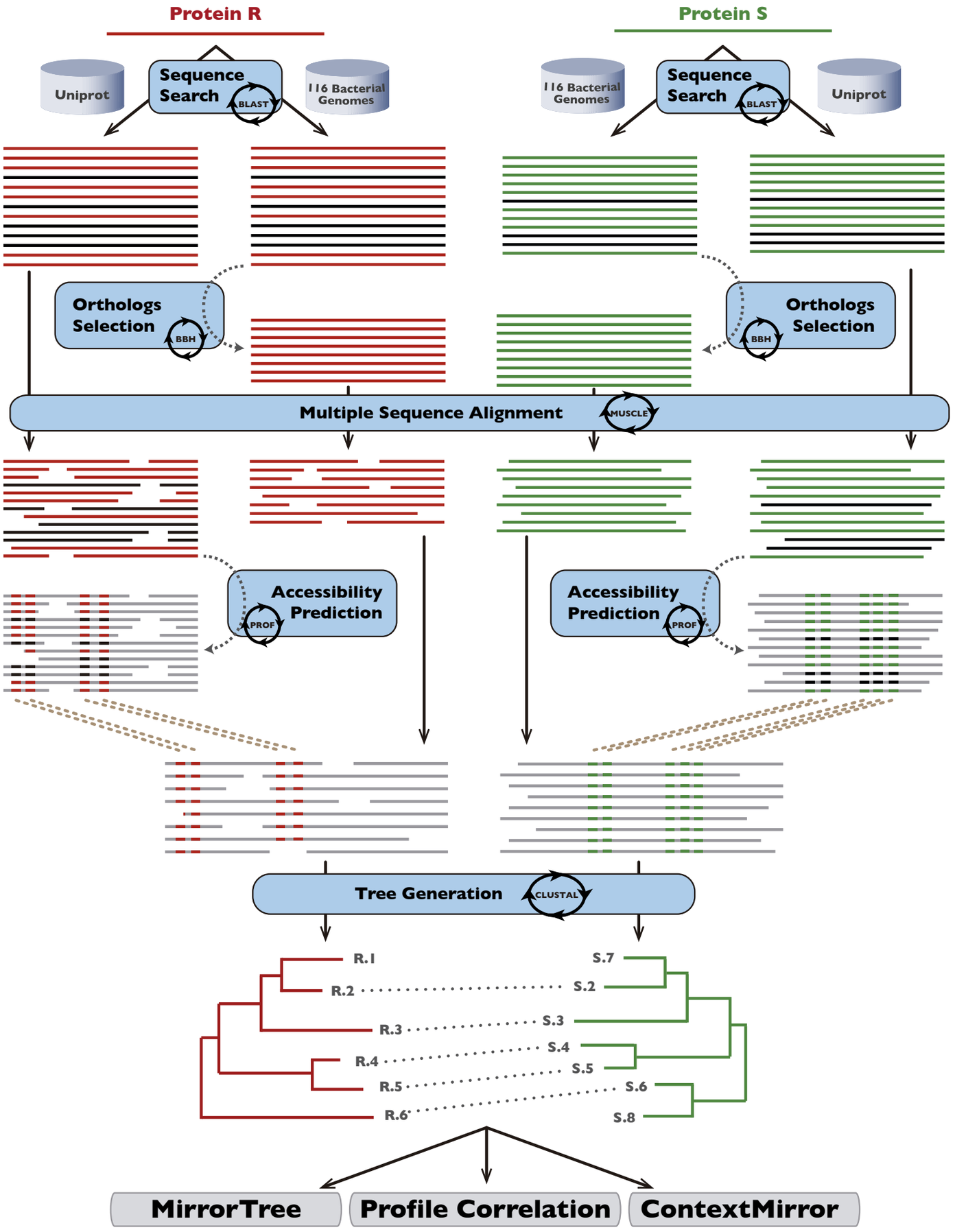
- MirrorTree Server allows to explore the co-evolution of protein families in a taxonomic context, independently of the user's expertise
- In agreement with previous observations, mirrortree family of methods proved being particularly accurate predicting different types of interactions at large scale
- Incorporation of predicted solvent accessibility helps the co-evolution-based prediction of binary physical interactions when context-based methodologies are applied
- The set of organisms used to generate the phylogenetic trees conditions the final performance and the type of interaction predicted by the methods
- The novel methodology, p-mirrortree, outperforms the existing mirrortree-based approaches and extends their range of applicability. The improvement is independent of the set of organisms and might help the input of context-based approaches.

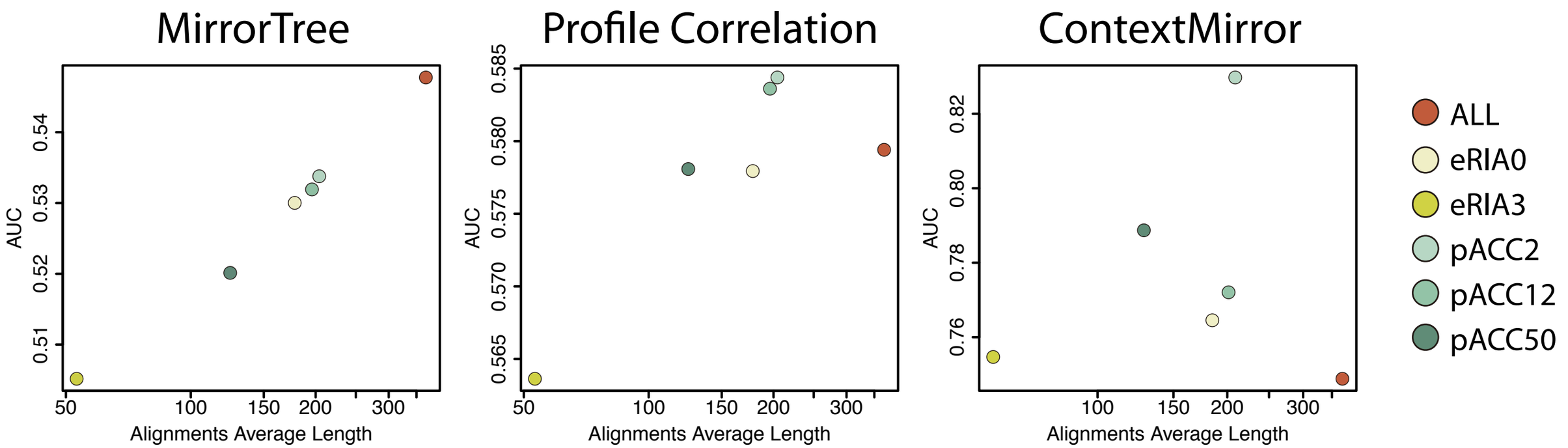
Tesis Doctoral

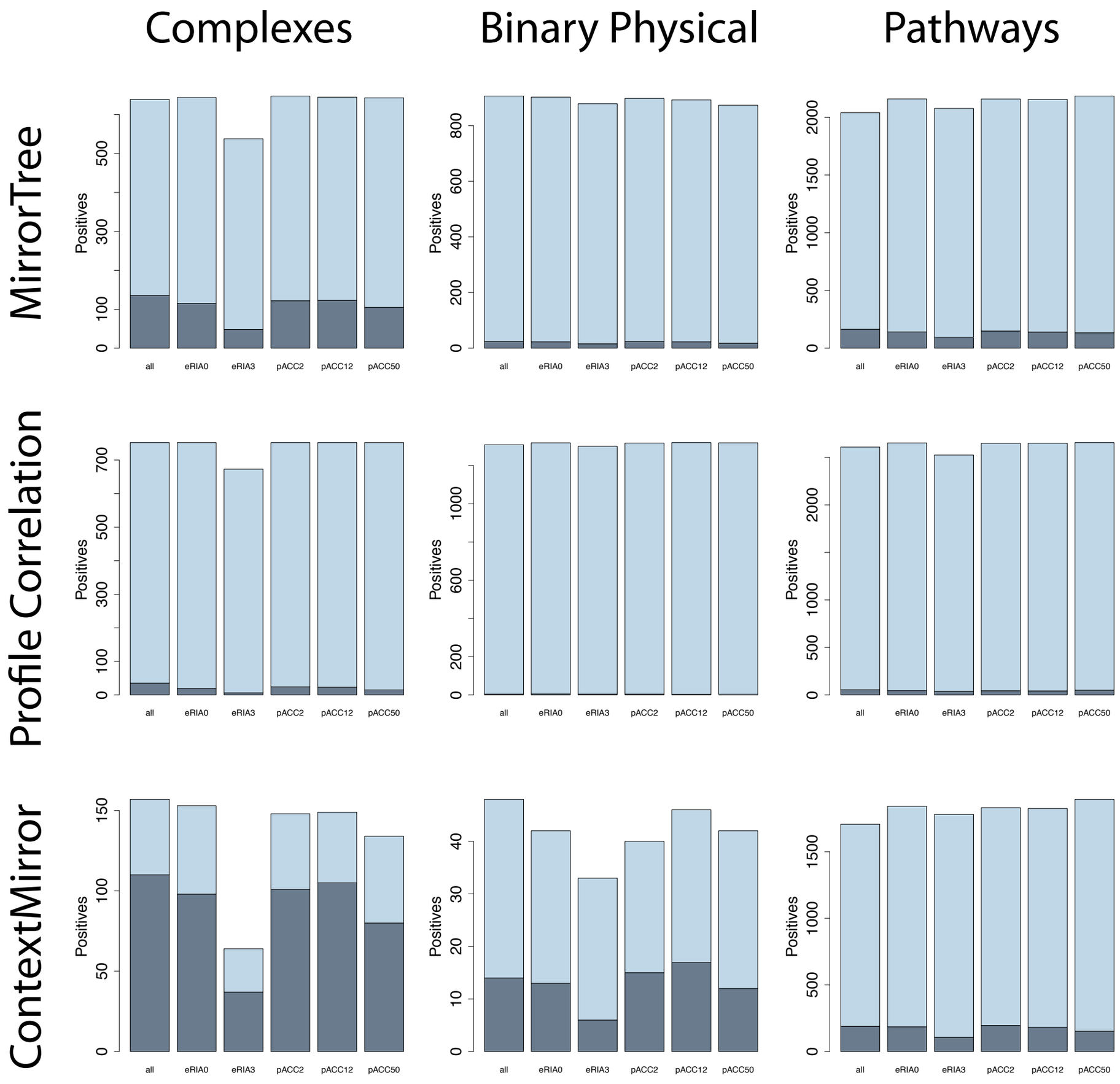
Improving Co-evolution Based Methods for Protein-Protein Interaction Prediction

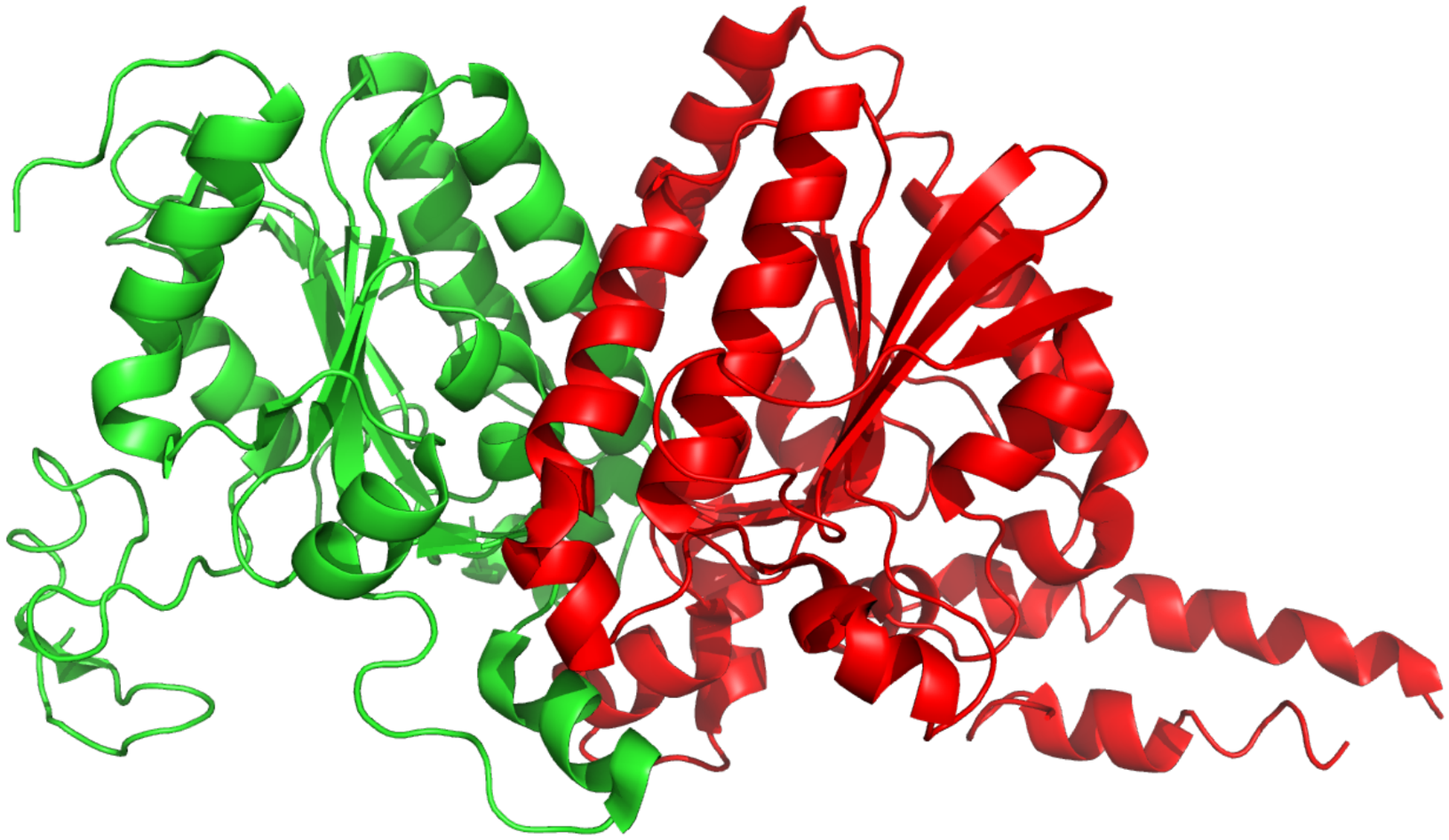
David Ochoa

Universidad Autónoma de Madrid

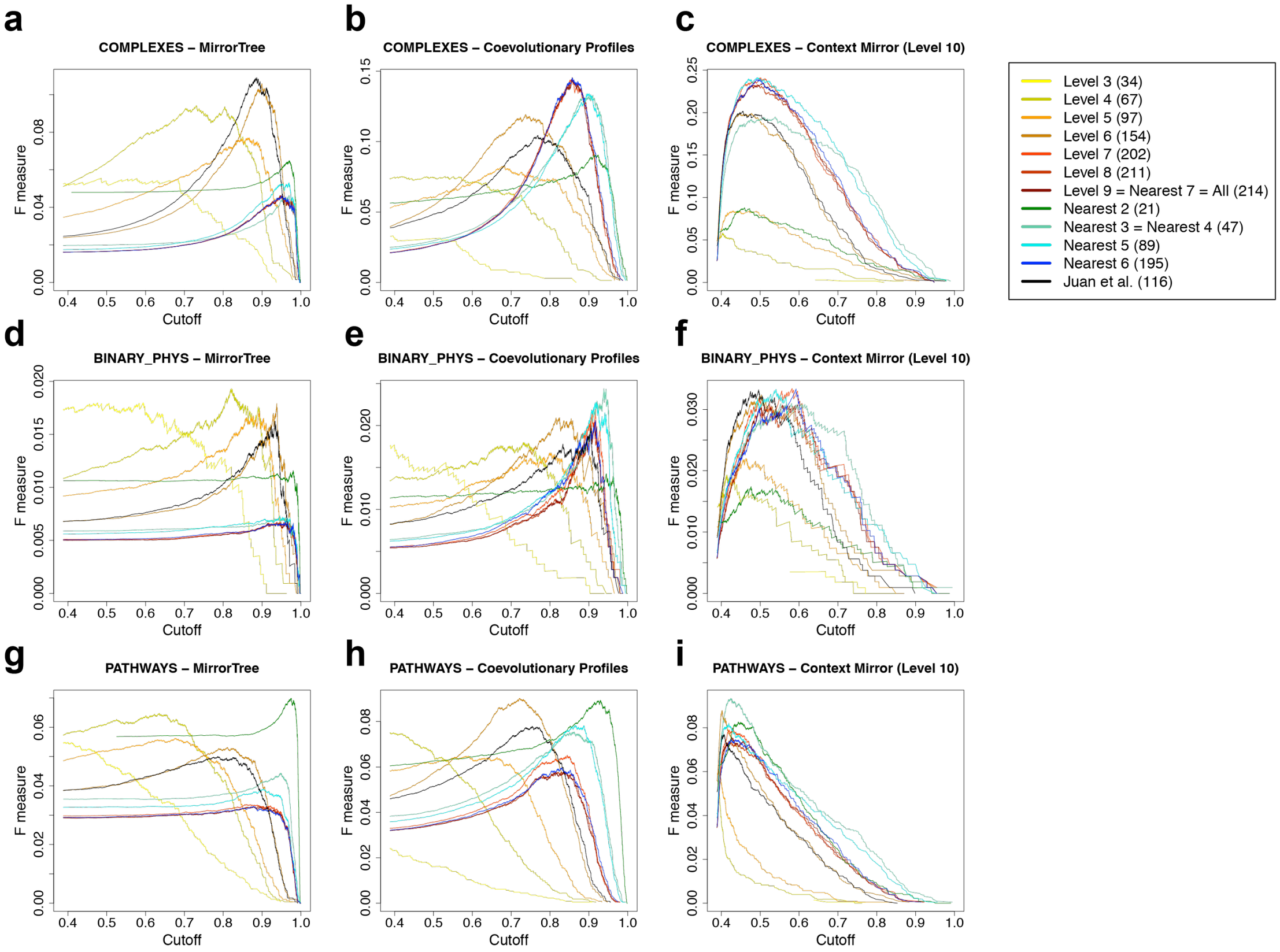

Protein R
Protein S
Uniprot
Sequence Search
BLAST
116 Bacterial Genomes
116 Bacterial Genomes
Sequence Search
BLAST
Uniprot
Orthologs Selection
BBH
Orthologs Selection
BBH
Multiple Sequence Alignment
MUSCLE
Accessibility Prediction
PROF
Accessibility Prediction
PROF
Tree Generation
CLUSTAL
R.1
R.2
R.3
R.4
R.5
R.6
S.7
S.2
S.3
S.4
S.5
S.6
S.8
MirrorTree
Profile Correlation
ContextMirror

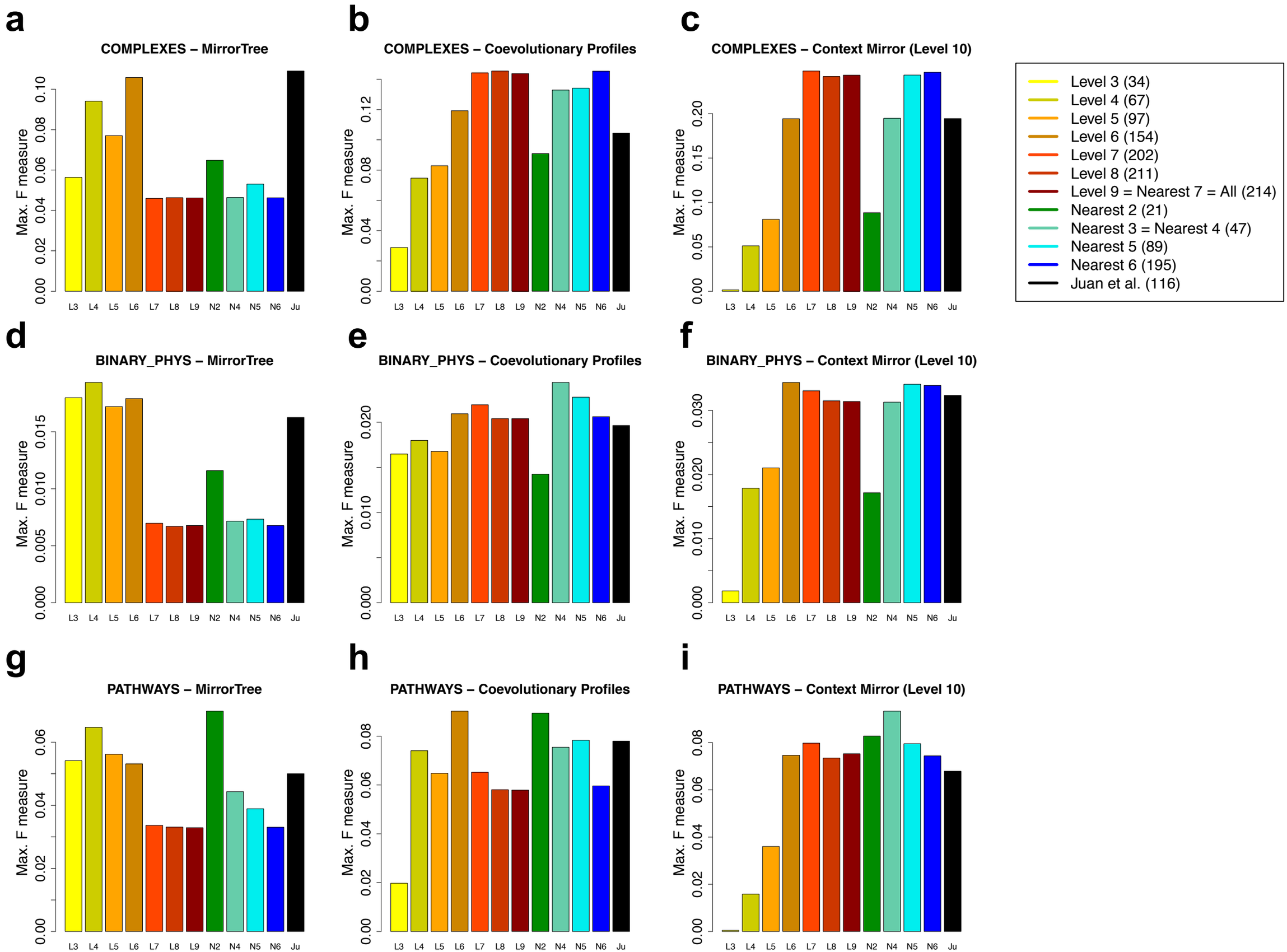

MirrorTree
Profile Correlation
ContextMirror
AUC
0.51
0.52
0.53
0.54
0.565
0.570
0.575
0.580
0.585
0.76
0.78
0.80
0.82
50
100
150
200
300
Alignments Average Length
ALL
eRIA0
eRIA3
pACC2
pACC12
pACC50

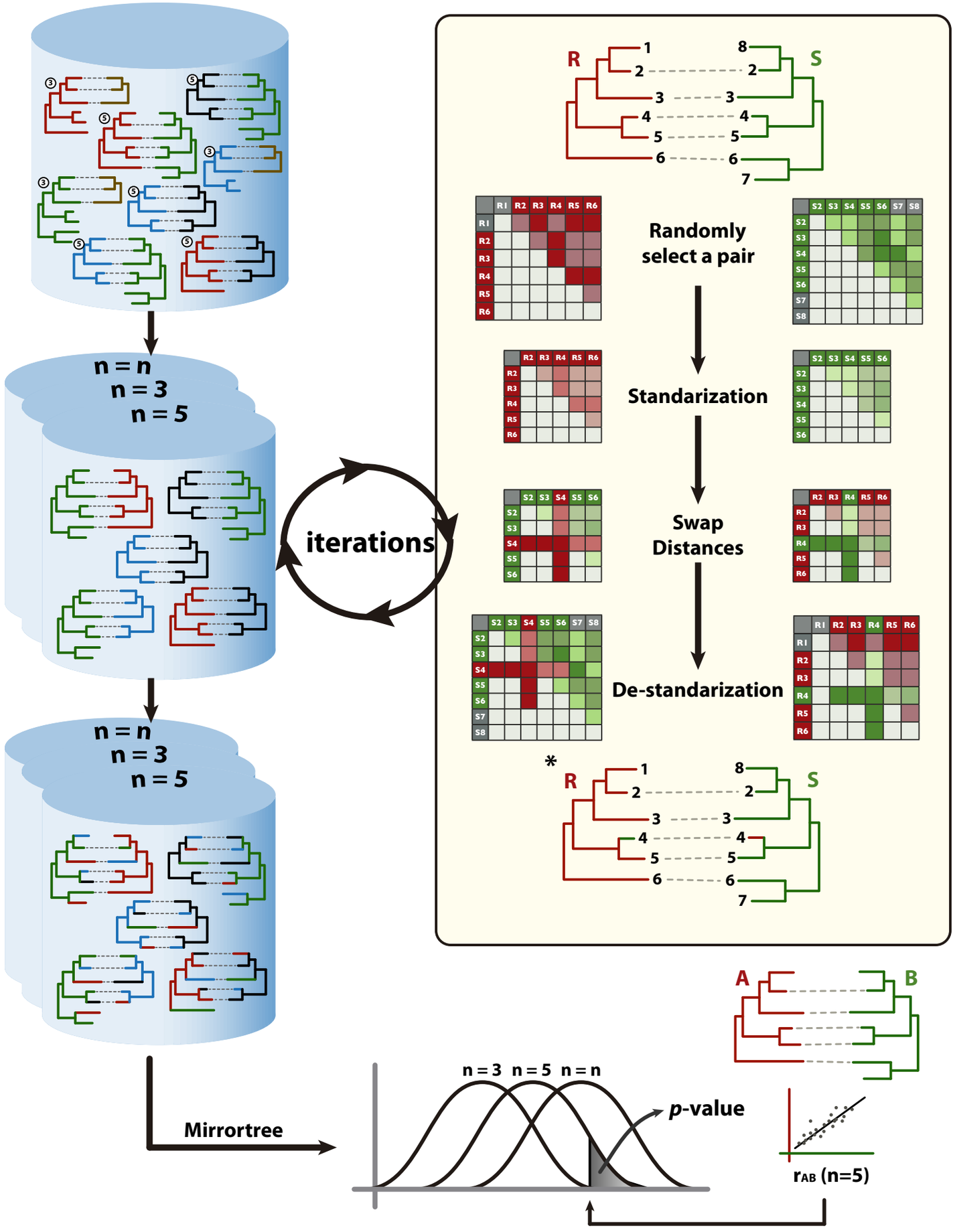

Complexes
Binary Physical
Pathways
MirrorTree
Profile Correlation
ContextMirror
Positives
all
eRIA0
eRIA3
pACC2
pACC12
pACC50



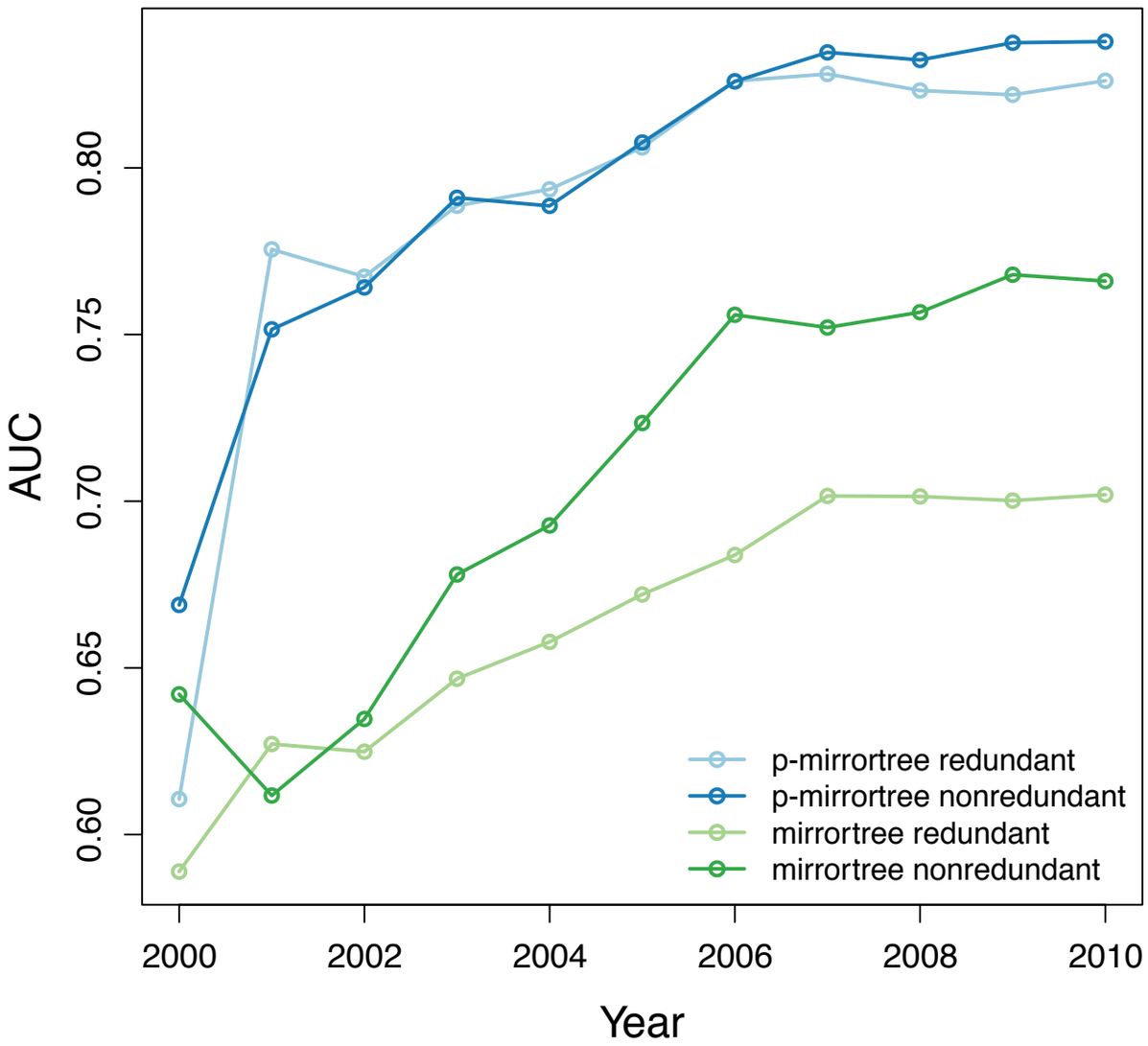
	ALL	eRIA0	eRIA3	pACC2	pACC12	pACC50
MirrorTree	0.9083	0.8982	0.8331	0.8998	0.9069	0.8924
Profile Correlation	0.9516	0.9531	0.9435	0.9605	0.9592	0.9328
ContextMirror	0.6068	0.6650	0.5410	0.6818	0.6828	0.5407


a
COMPLEXES – MirrorTree
b
COMPLEXES – Coevolutionary Profiles
c
COMPLEXES – Context Mirror (Level 10)
d
BINARY_PHYS – MirrorTree
e
BINARY_PHYS – Coevolutionary Profiles
f
BINARY_PHYS – Context Mirror (Level 10)
g
PATHWAYS – MirrorTree
h
PATHWAYS – Coevolutionary Profiles
i
PATHWAYS – Context Mirror (Level 10)
F measure
Cutoff
Level 3 (34)
Level 4 (67)
Level 5 (97)
Level 6 (154)
Level 7 (202)
Level 8 (211)
Level 9 = Nearest 7 = All (214)
Nearest 2 (21)
Nearest 3 = Nearest 4 (47)
Nearest 5 (89)
Nearest 6 (195)
Juan et al. (116)

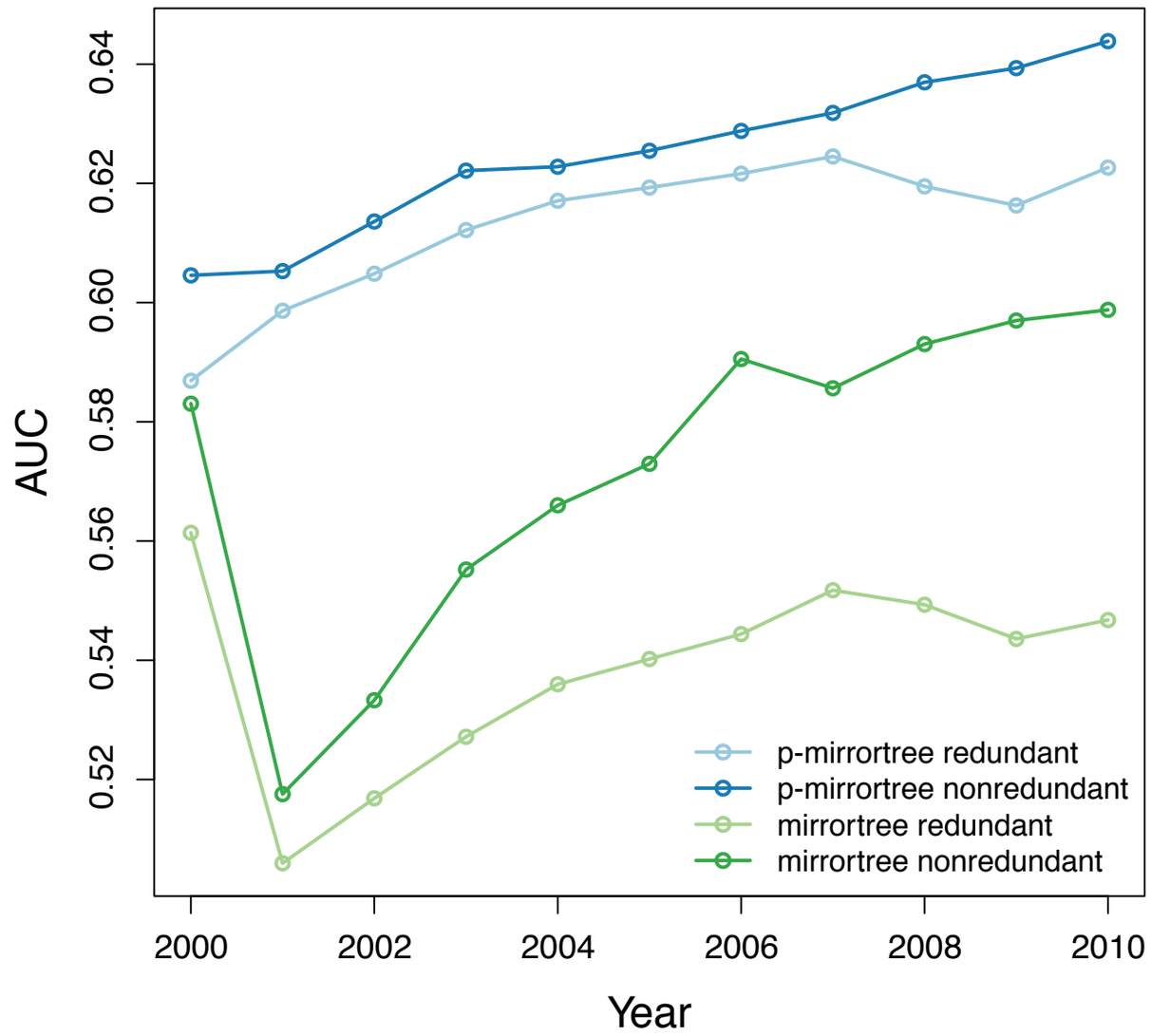

a
COMPLEXES – MirrorTree
b
COMPLEXES – Coevolutionary Profiles
c
COMPLEXES – Context Mirror (Level 10)
d
BINARY_PHYS – MirrorTree
e
BINARY_PHYS – Coevolutionary Profiles
f
BINARY_PHYS – Context Mirror (Level 10)
g
PATHWAYS – MirrorTree
h
PATHWAYS – Coevolutionary Profiles
i
PATHWAYS – Context Mirror (Level 10)
Max. F measure
L3 L4 L5 L6 L7 L8 L9 N2 N4 N5 N6 Ju
Level 3 (34)
Level 4 (67)
Level 5 (97)
Level 6 (154)
Level 7 (202)
Level 8 (211)
Level 9 = Nearest 7 = All (214)
Nearest 2 (21)
Nearest 3 = Nearest 4 (47)
Nearest 5 (89)
Nearest 6 (195)
Juan et al. (116)


n = n
n = 3
n = 5
iterations
n = n
n = 3
n = 5
Mirrortree
R
S
Randomly
select a pair
Standarization
Swap
Distances
De-standarization
*
R
S
A
B
n = 3 n = 5 n = n
p-value
rAB (n=5)

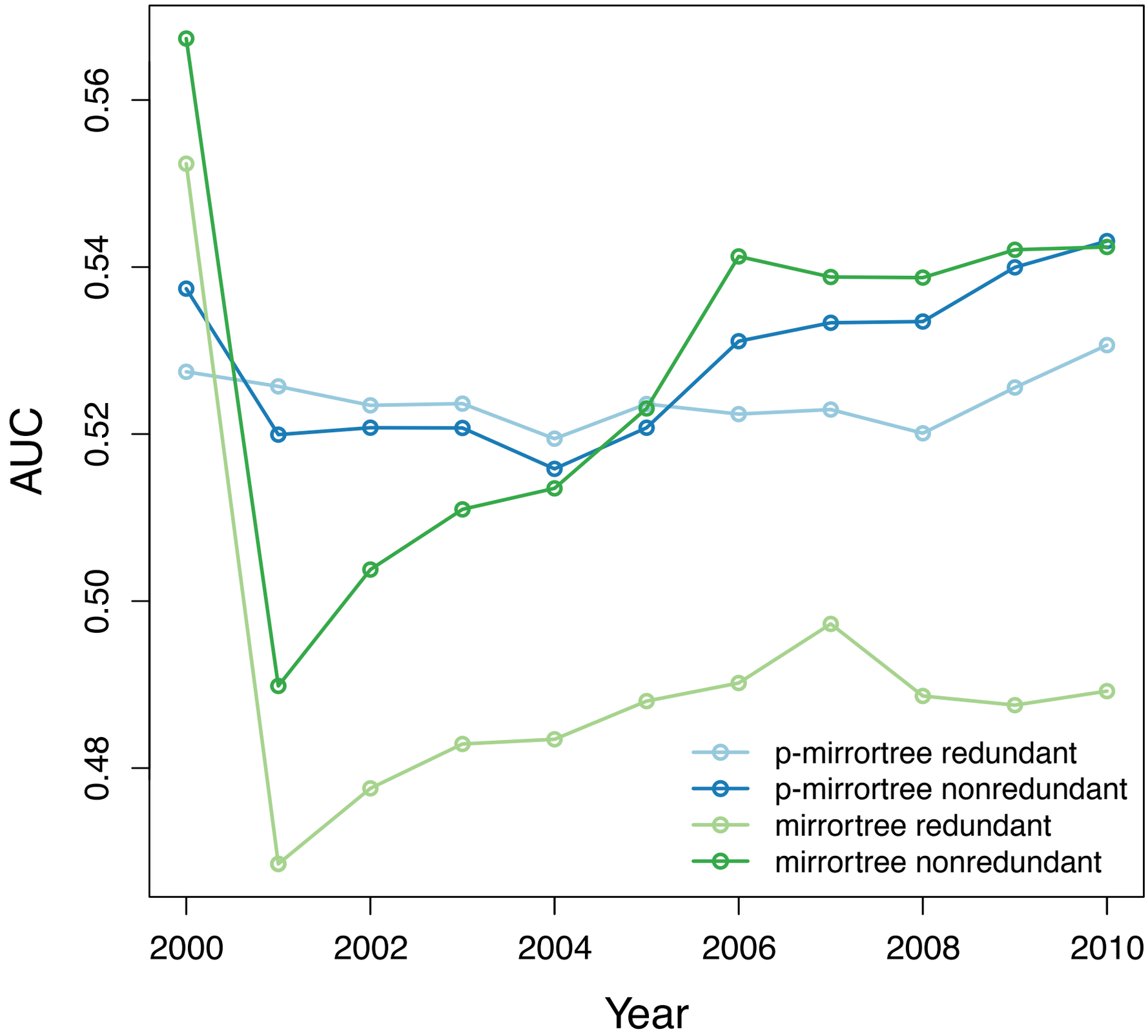
Complexes



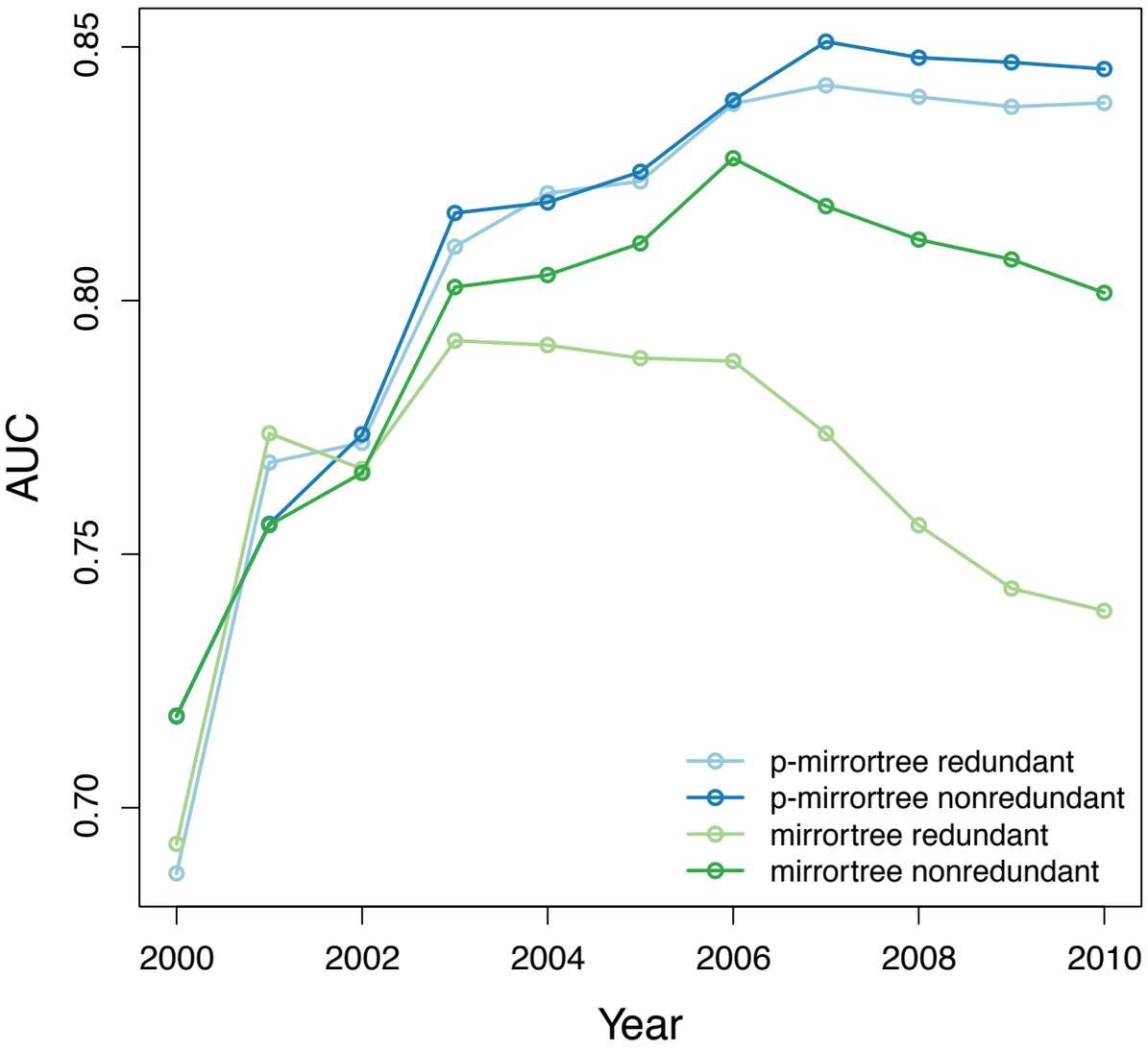
Binary Physical



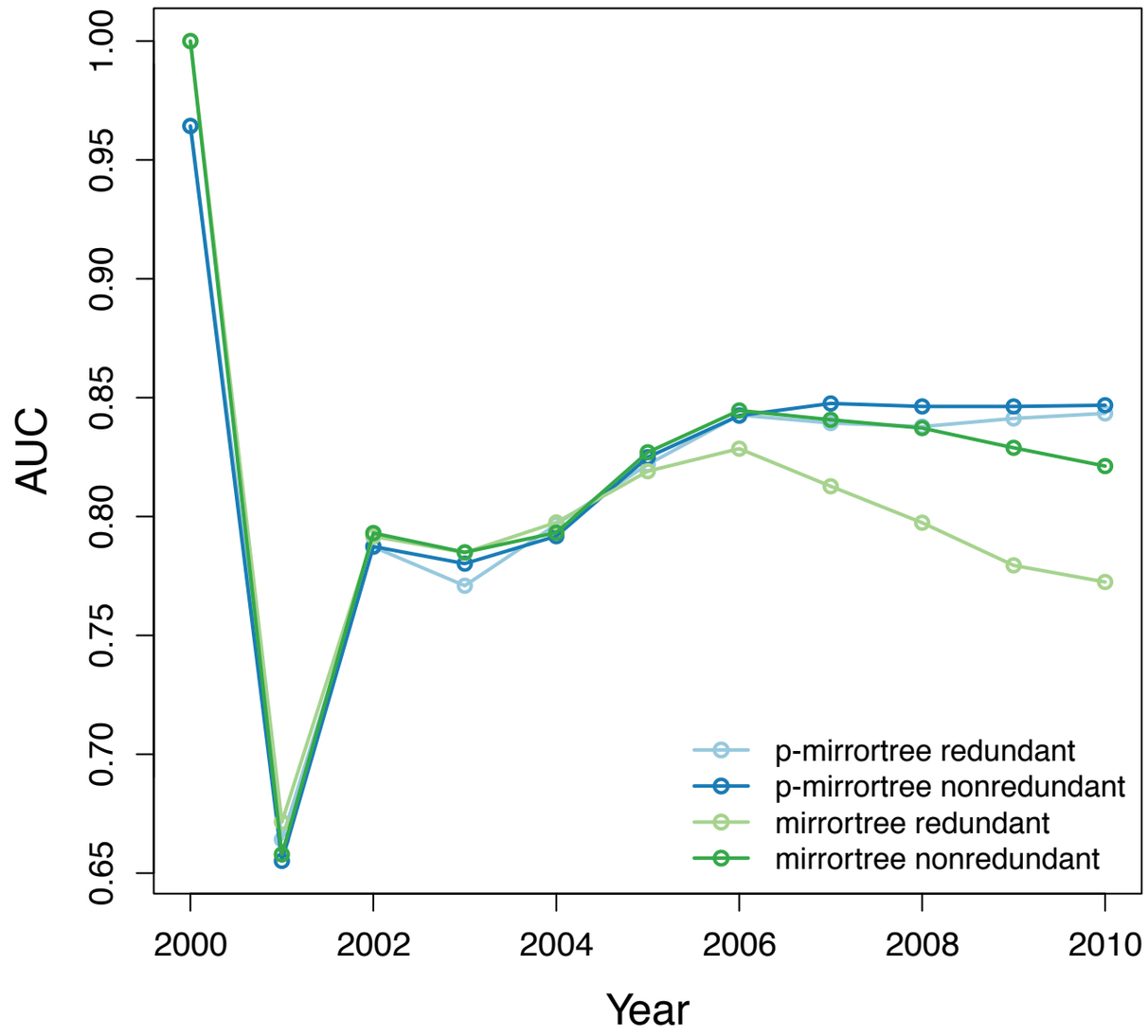
Pathways

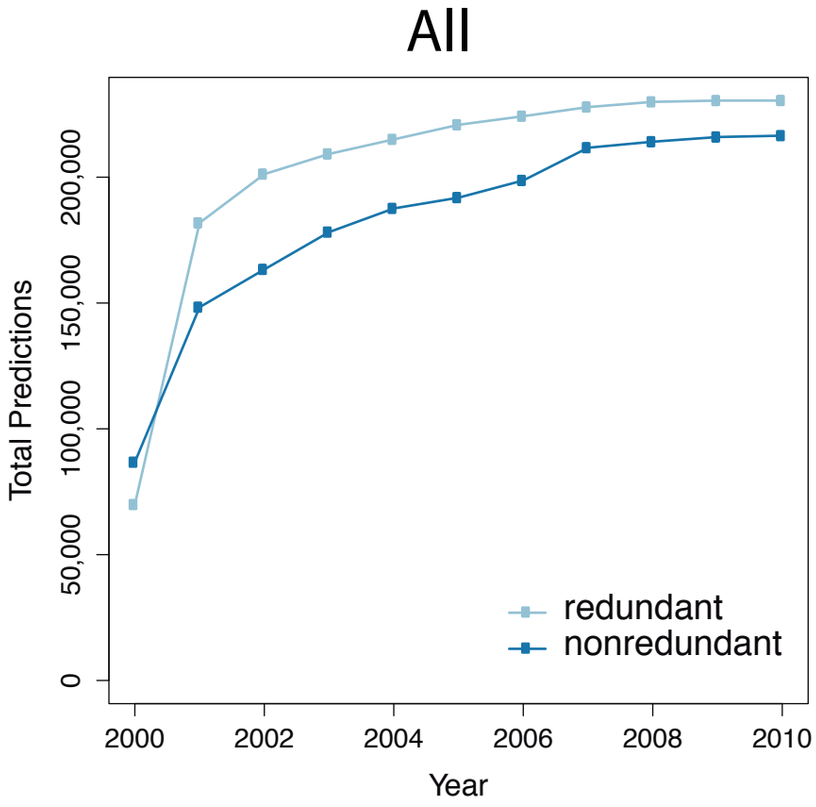

AUC
0.48
0.50
0.52
0.54
0.56
2000
2002
2004
2006
2008
2010
Year
p-mirrortree redundant
p-mirrortree nonredundant
mirrortree redundant
mirrortree nonredundant

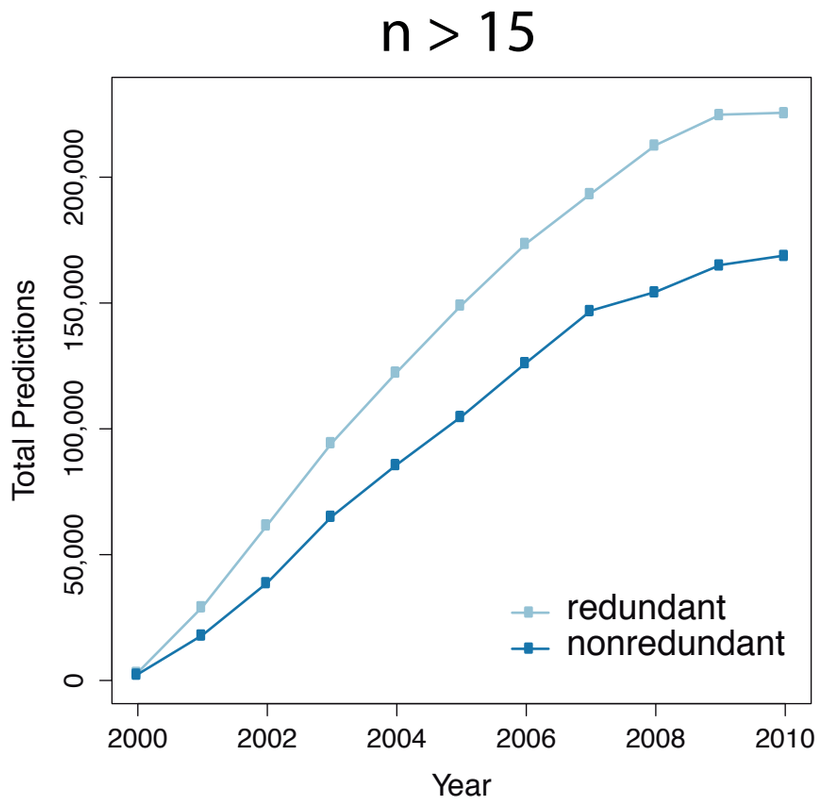
n > 15

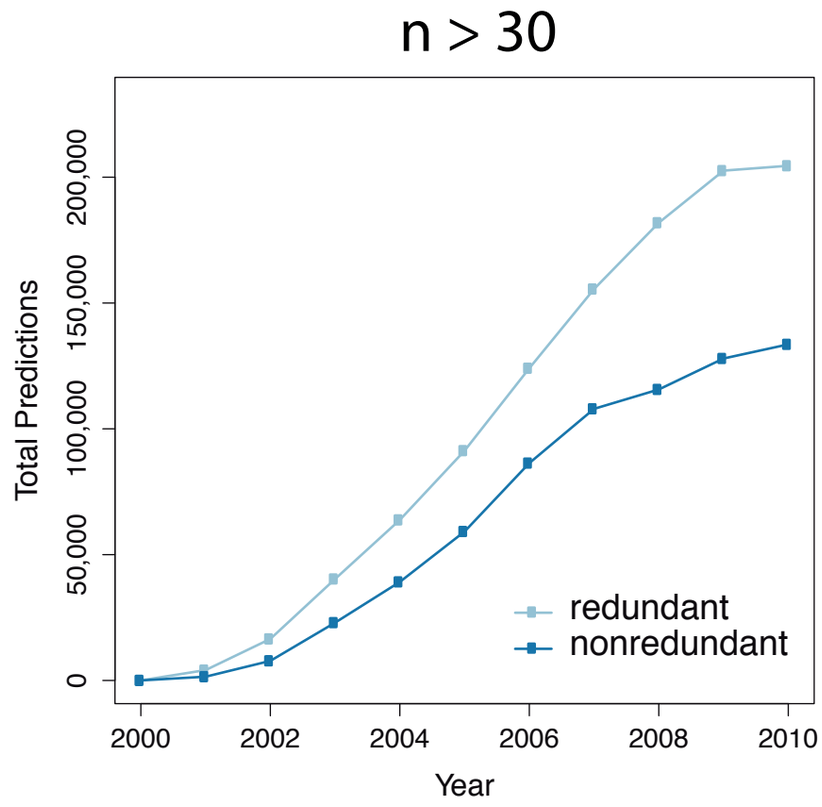

AUC
0.85
0.80
0.75
0.70
2000
2002
2004
2006
2008
2010
Year
p-mirrortree redundant
p-mirrortree nonredundant
mirrortree redundant
mirrortree nonredundant

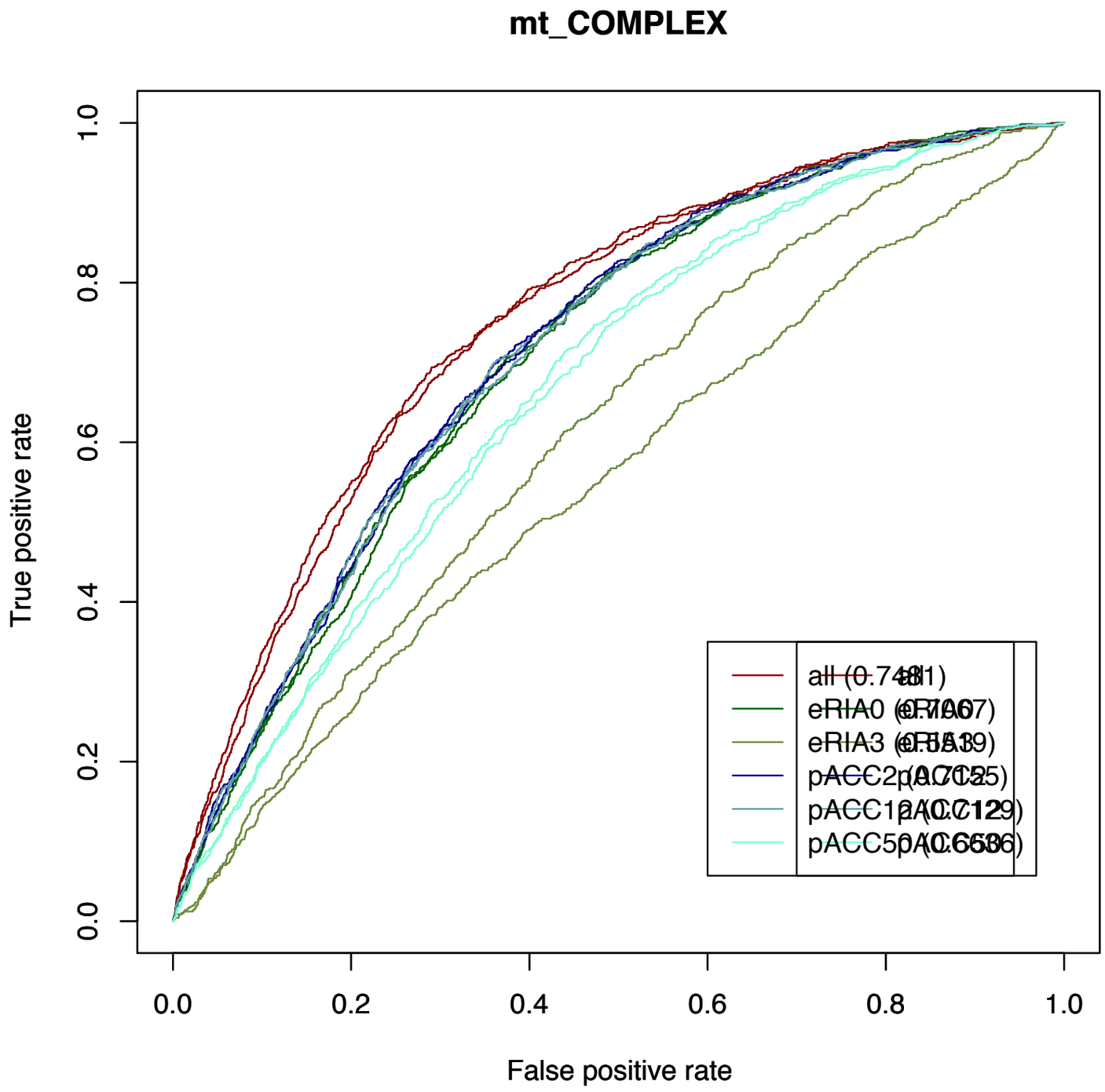
n > 30

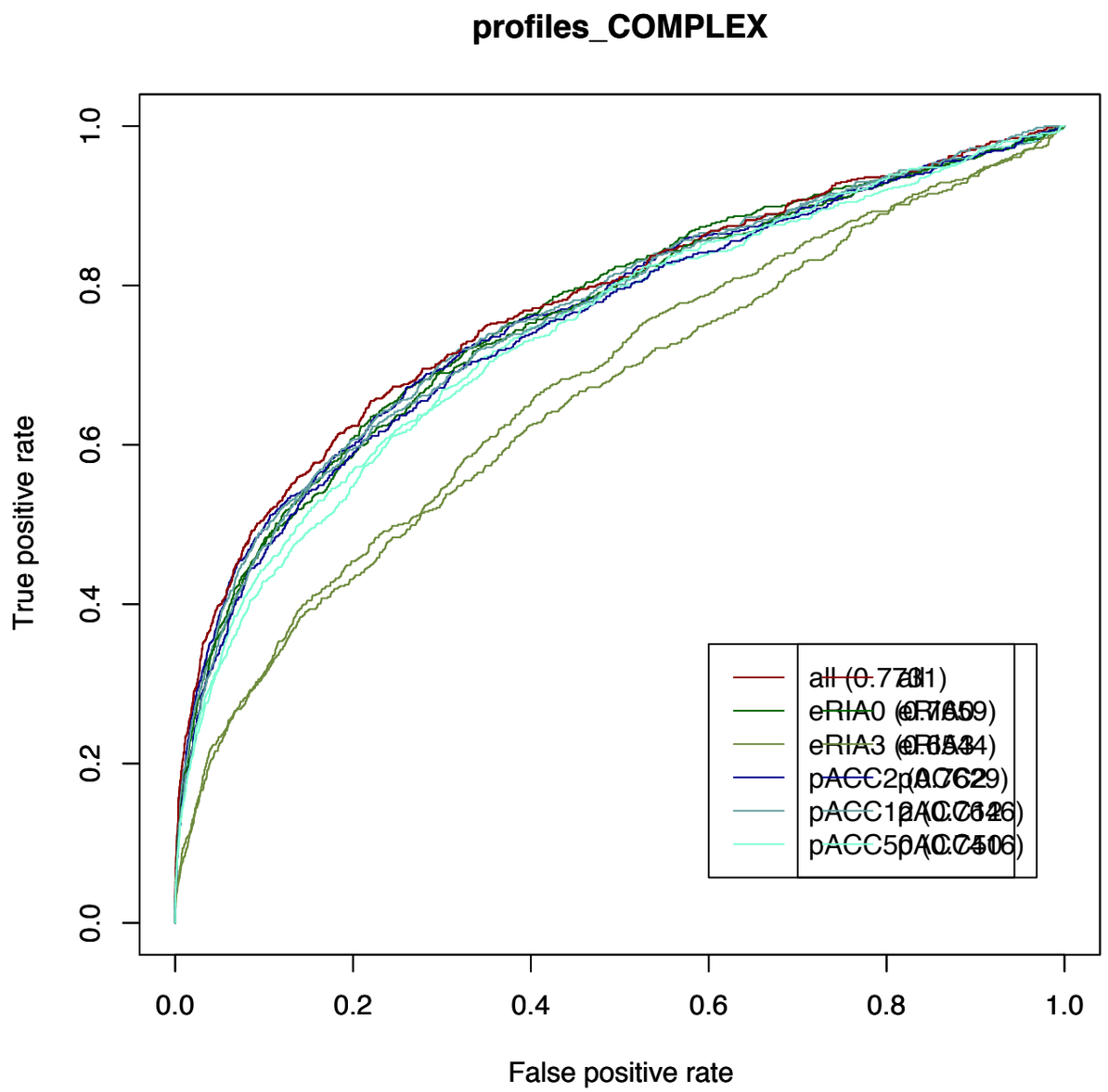

AUC
1.00
0.95
0.90
0.85
0.80
0.75
0.70
0.65
2000
2002
2004
2006
2008
2010
Year
p-mirrortree redundant
p-mirrortree nonredundant
mirrortree redundant
mirrortree nonredundant


All
Total Predictions
0
50,000
100,000
150,000
200,000
2000
2002
2004
2006
2008
2010
Year
redundant
nonredundant

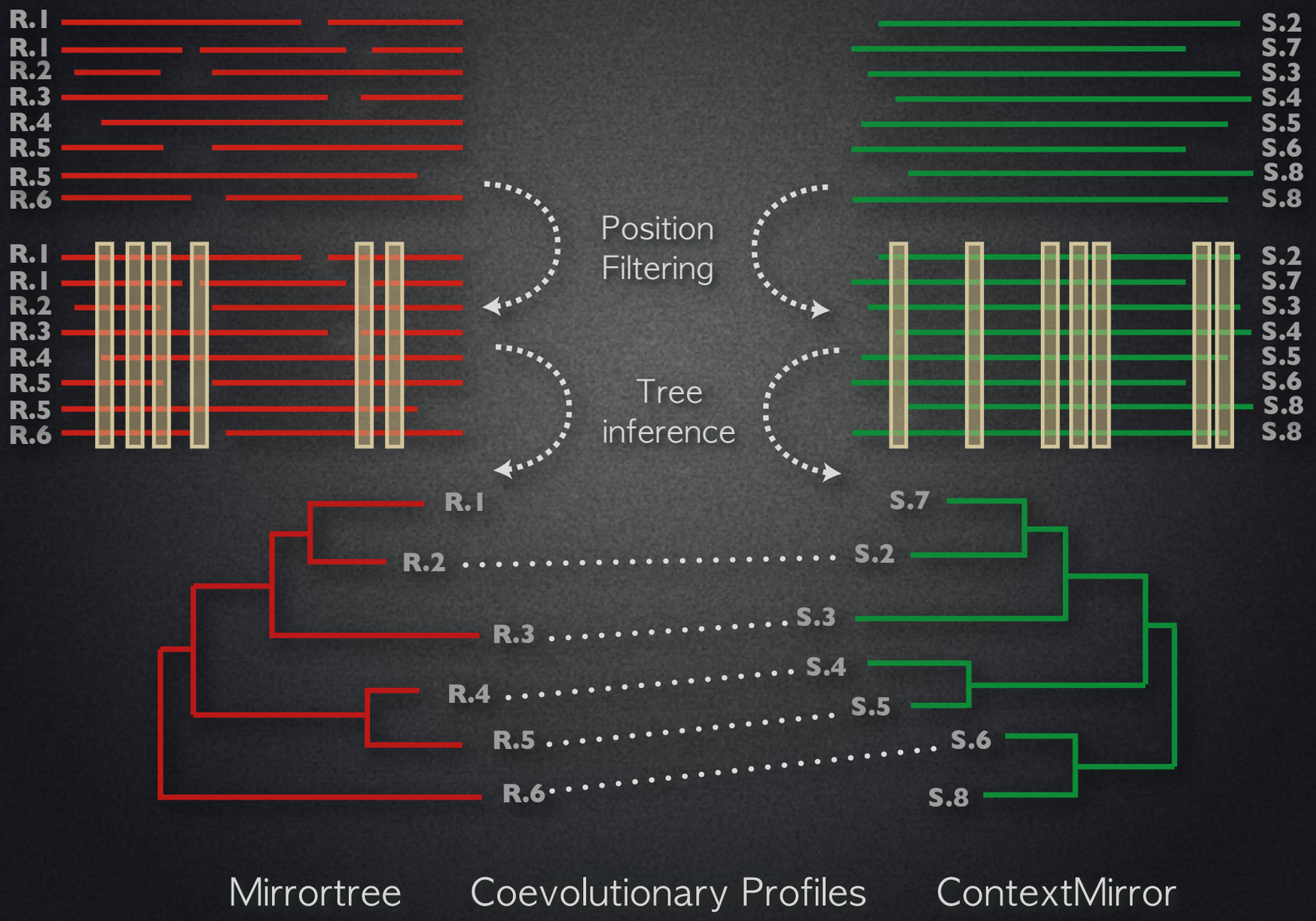

n > 15
Total Predictions
0
50,000
100,000
150,000
200,000
2000
2002
2004
2006
2008
2010
Year
redundant
nonredundant


n > 30
Total Predictions
0
50,000
100,000
150,000
200,000
2000
2002
2004
2006
2008
2010
Year
redundant
nonredundant

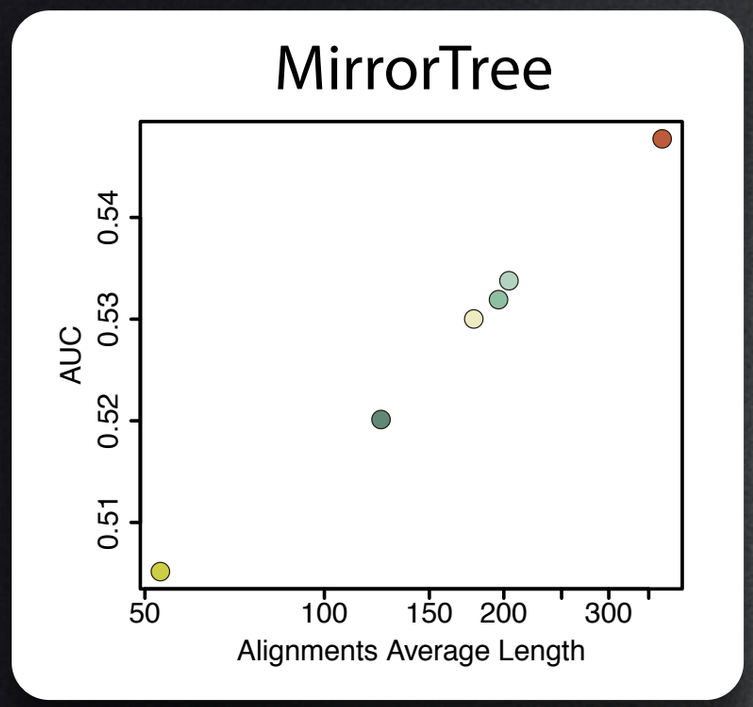

mt_COMPLEX
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
all (0.7481)
eRIA0 (0.7067)
eRIA3 (0.5513)
pACC2 (0.7025)
pACC1 (0.7129)
pACC5 (0.6536)

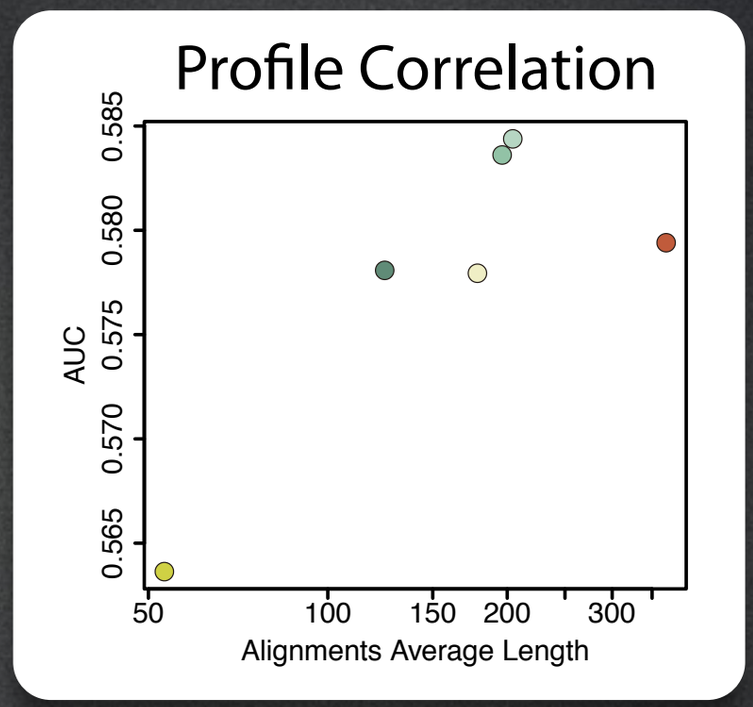

profiles_COMPLEX
True positive rate
False positive rate
0.0
0.2
0.4
0.6
0.8
1.0
all (0.7731)
eRIA0 (0.7659)
eRIA3 (0.6534)
pACC2 (0.7629)
pACC1 (0.7526)
pACC5 (0.7406)

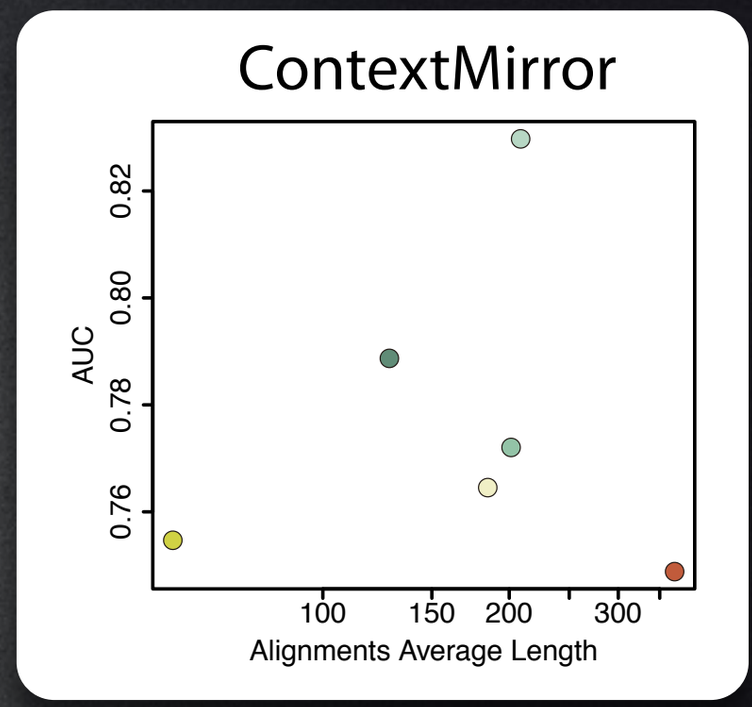
Adapted workflow

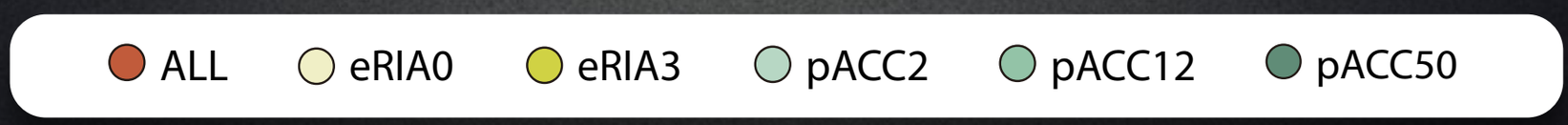


Complexes

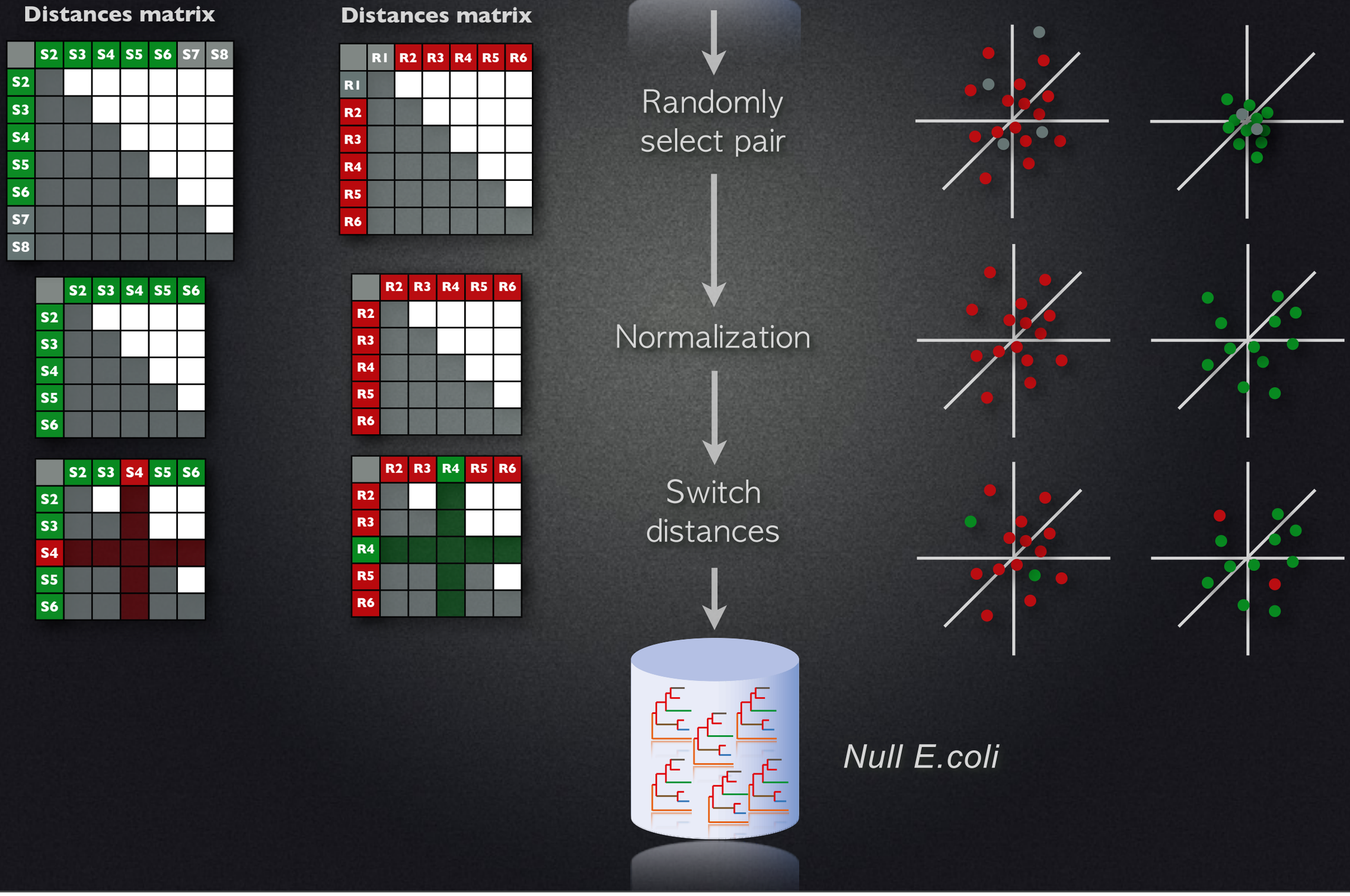


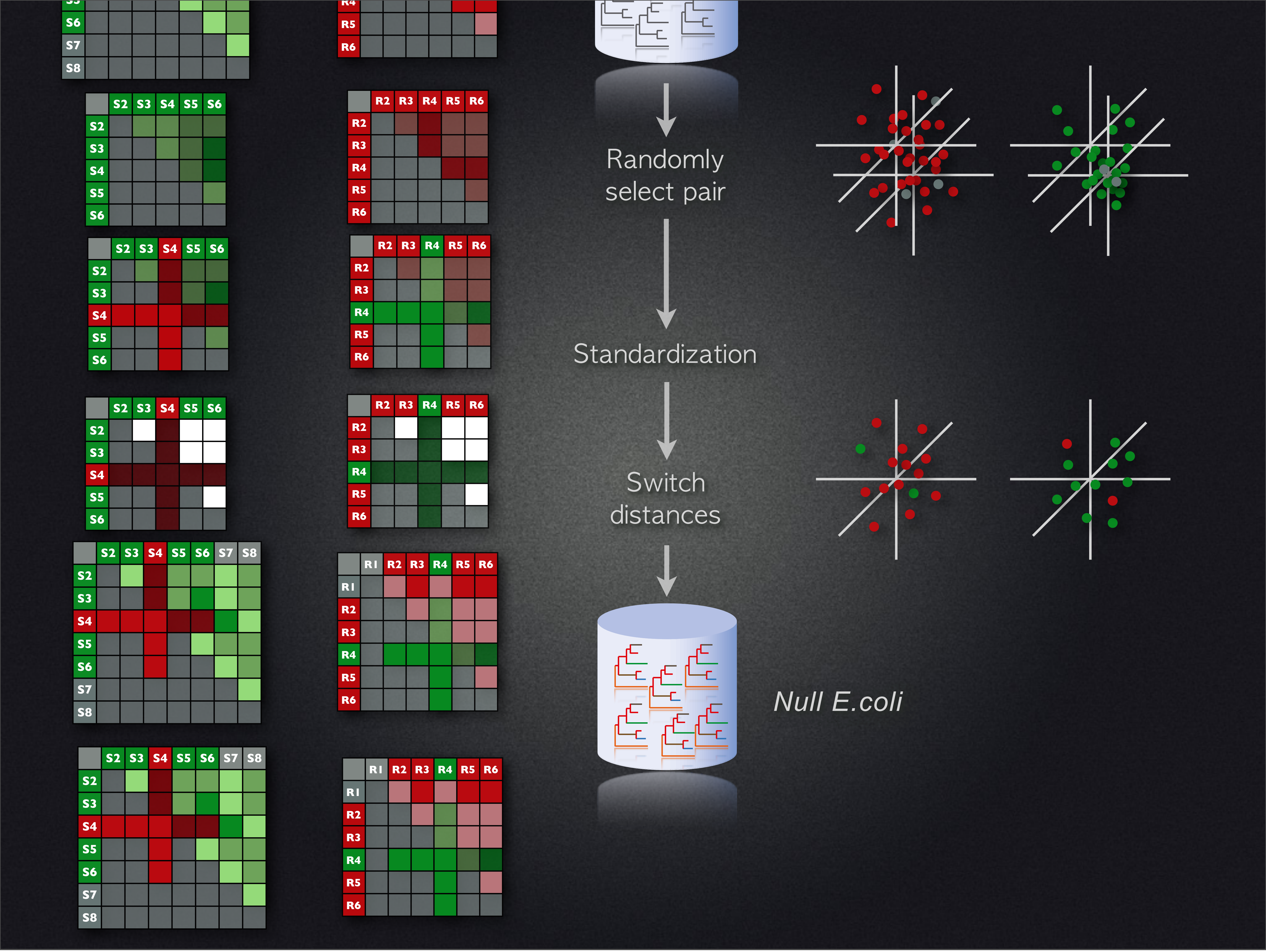




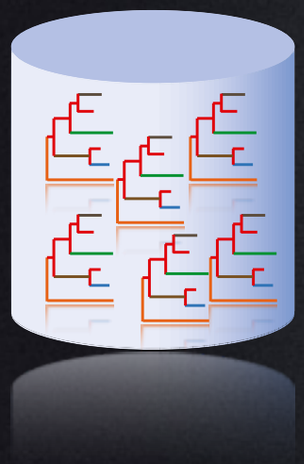


Ochoa, D., García-Gutiérrez, P., Juan, D., Valencia, A. & Pazos, F. Incorporating information on predicted solvent accessibility to the co-evolution-based study of protein interactions. Molecular bioSystems 9, 70–76 (2013).


Distances matrix
S2 S3 S4 S5 S6 S7 S8
S2
S3
S4
S5
S6
S7
S8
S2 S3 S4 S5 S6
S2
S3
S4
S5
S6
S2 S3 S4 S5 S6
S2
S3
S4
S5
S6
Distances matrix
R1 R2 R3 R4 R5 R6
R1
R2
R3
R4
R5
R6
R2 R3 R4 R5 R6
R2
R3
R4
R5
R6
R2 R3 R4 R5 R6
R2
R3
R4
R5
R6
E.coli
Randomly select pair
Normalization
Switch distances
Null E.coli

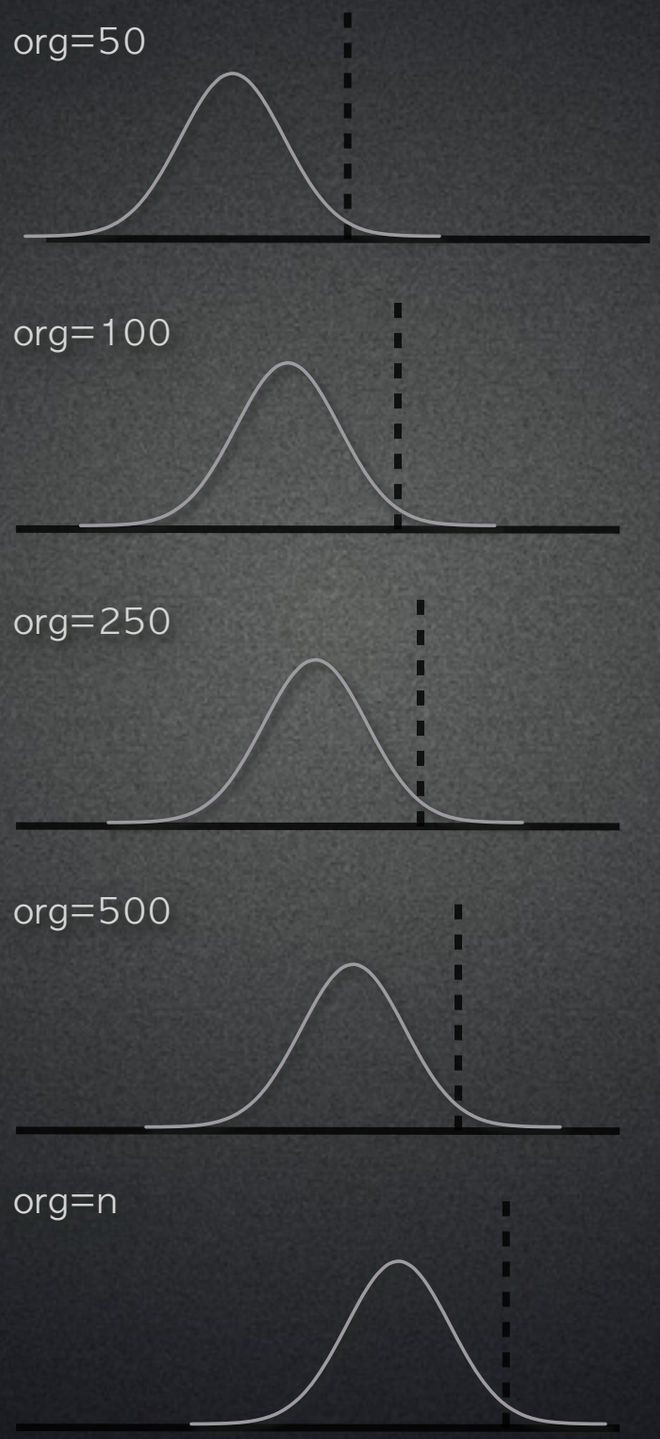

Randomly select pair
Standardization
Switch distances
Null E.coli

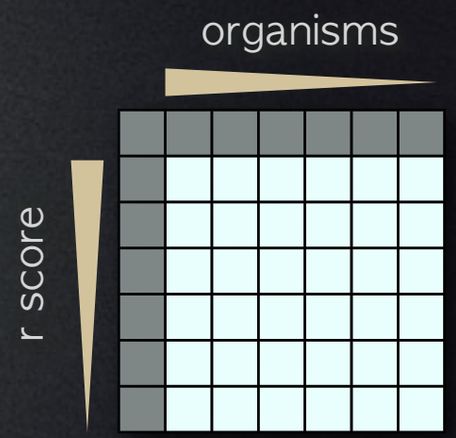
Corrected by interaction age



mirrortree

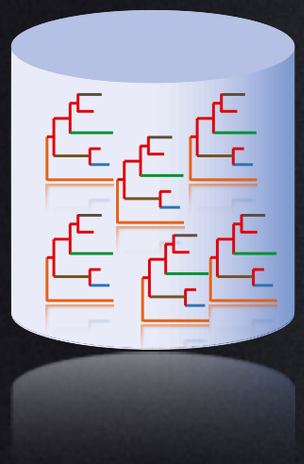
all vs. all





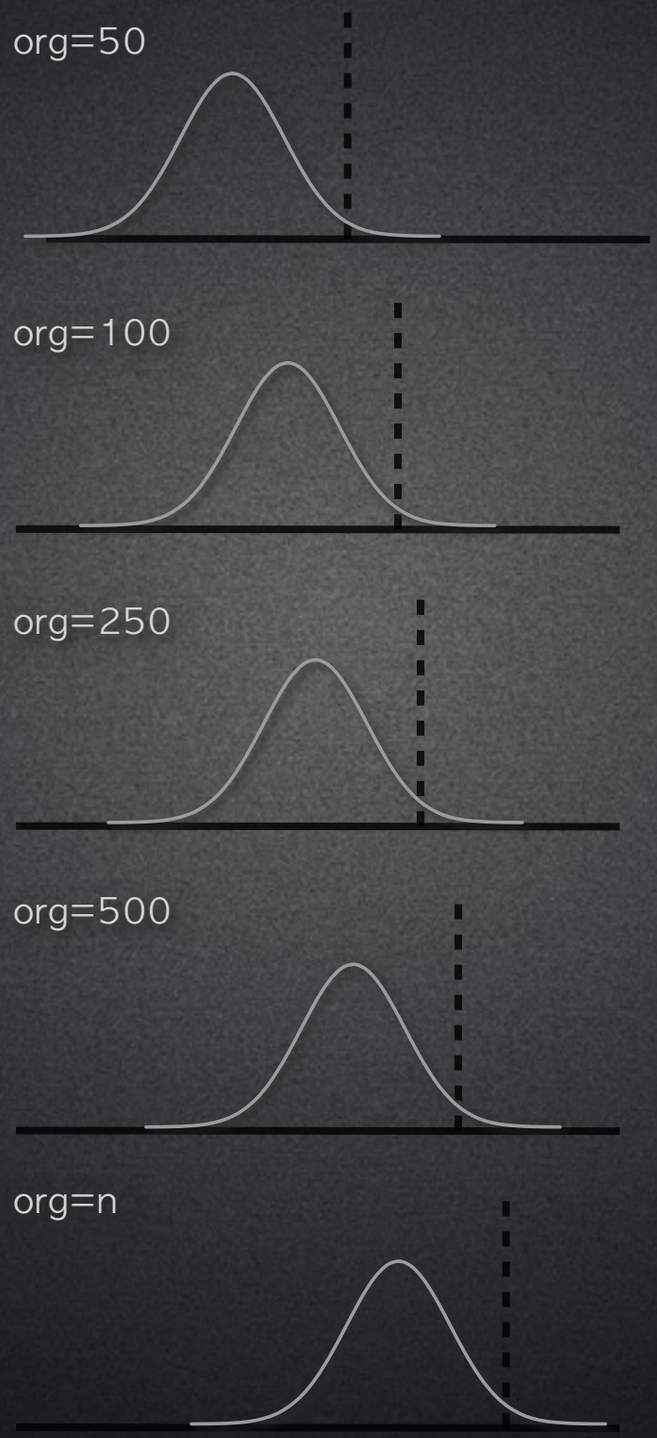
New *p-values*

null distribution



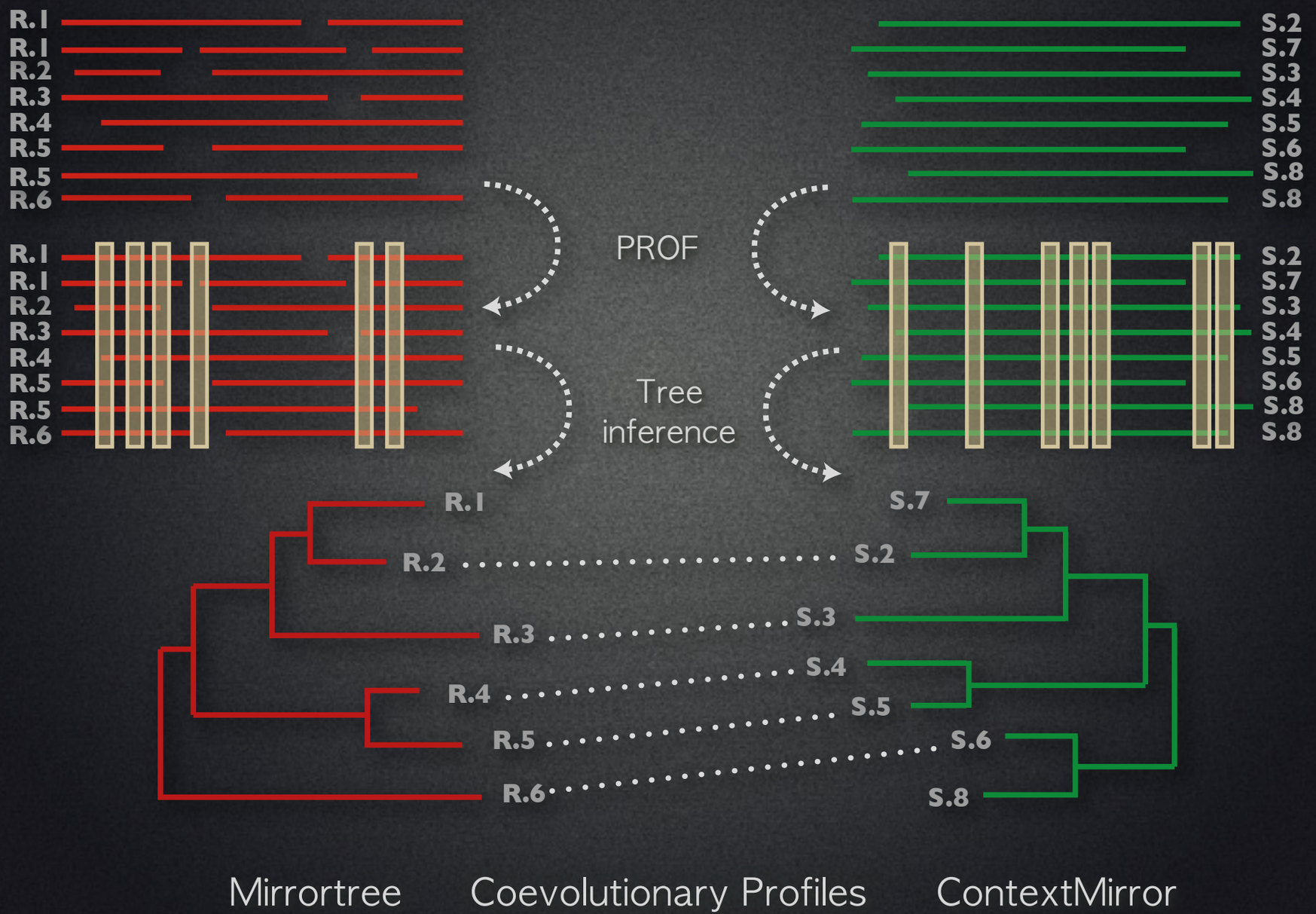
mirrortree

all vs. all



New *p-values*

Adapted workflow



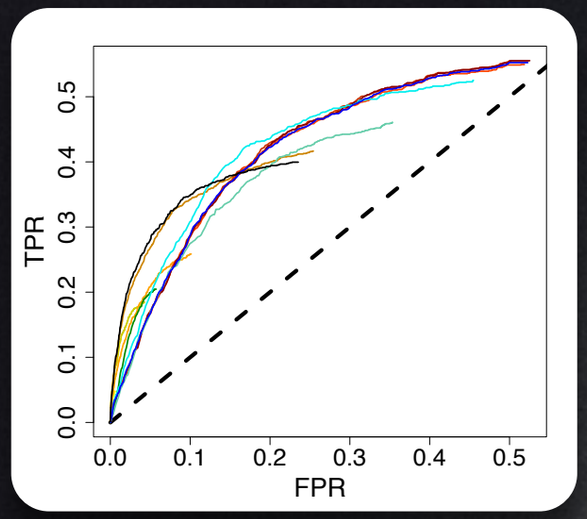
Rost, B. & Sander, C. Conservation and prediction of solvent accessibility in protein families. Proteins 20, 216–226 (1994).

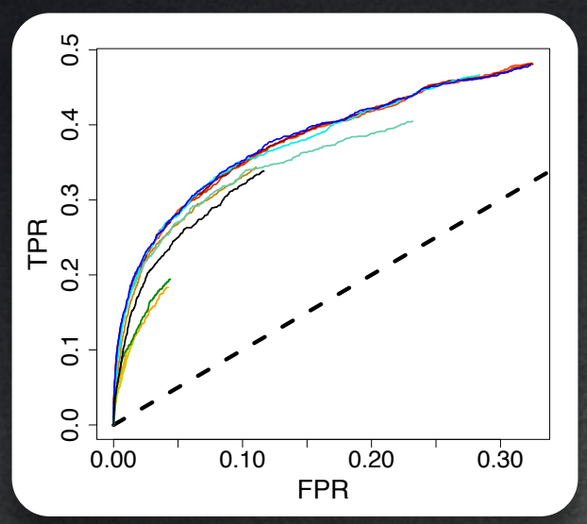
Mirrortree

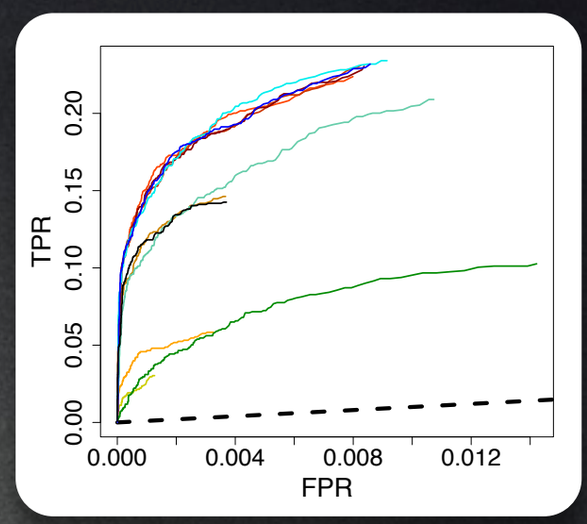
Profile Correlation

ContextMirror

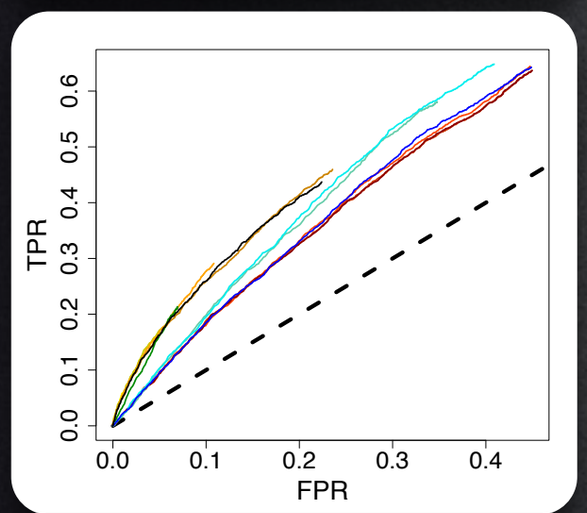
Complexes

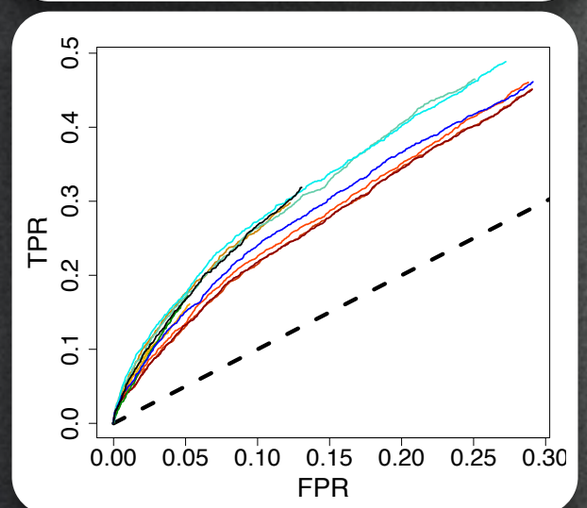


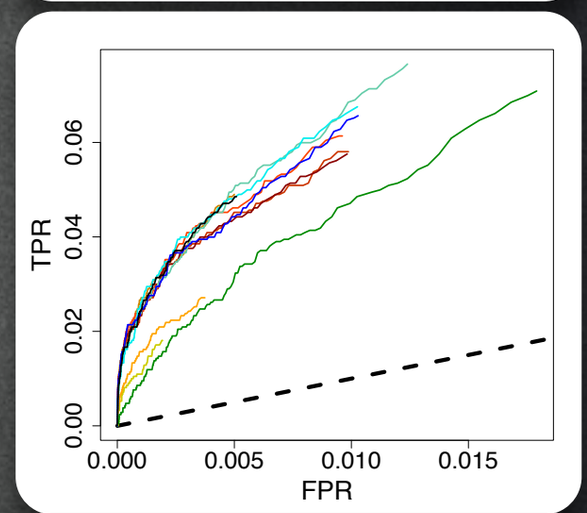


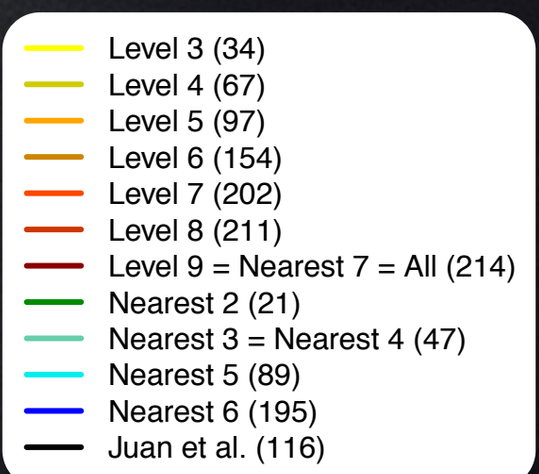


Binary Physical

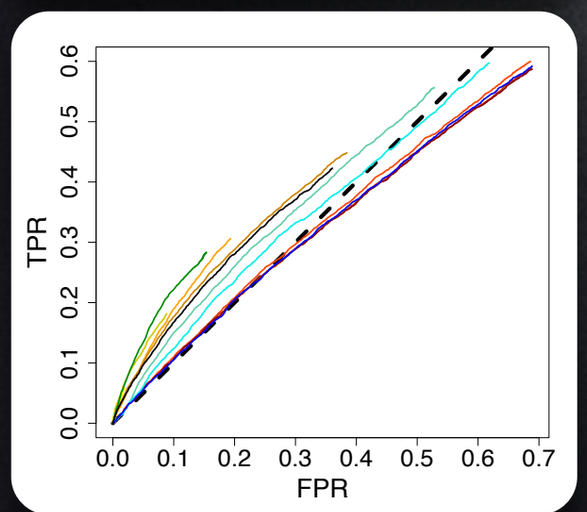


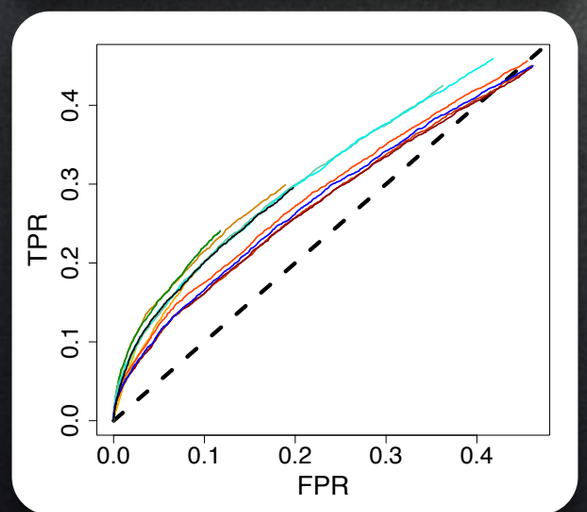


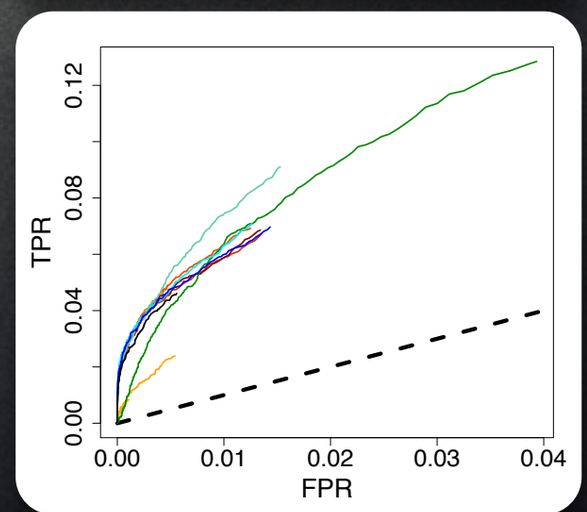




Pathways

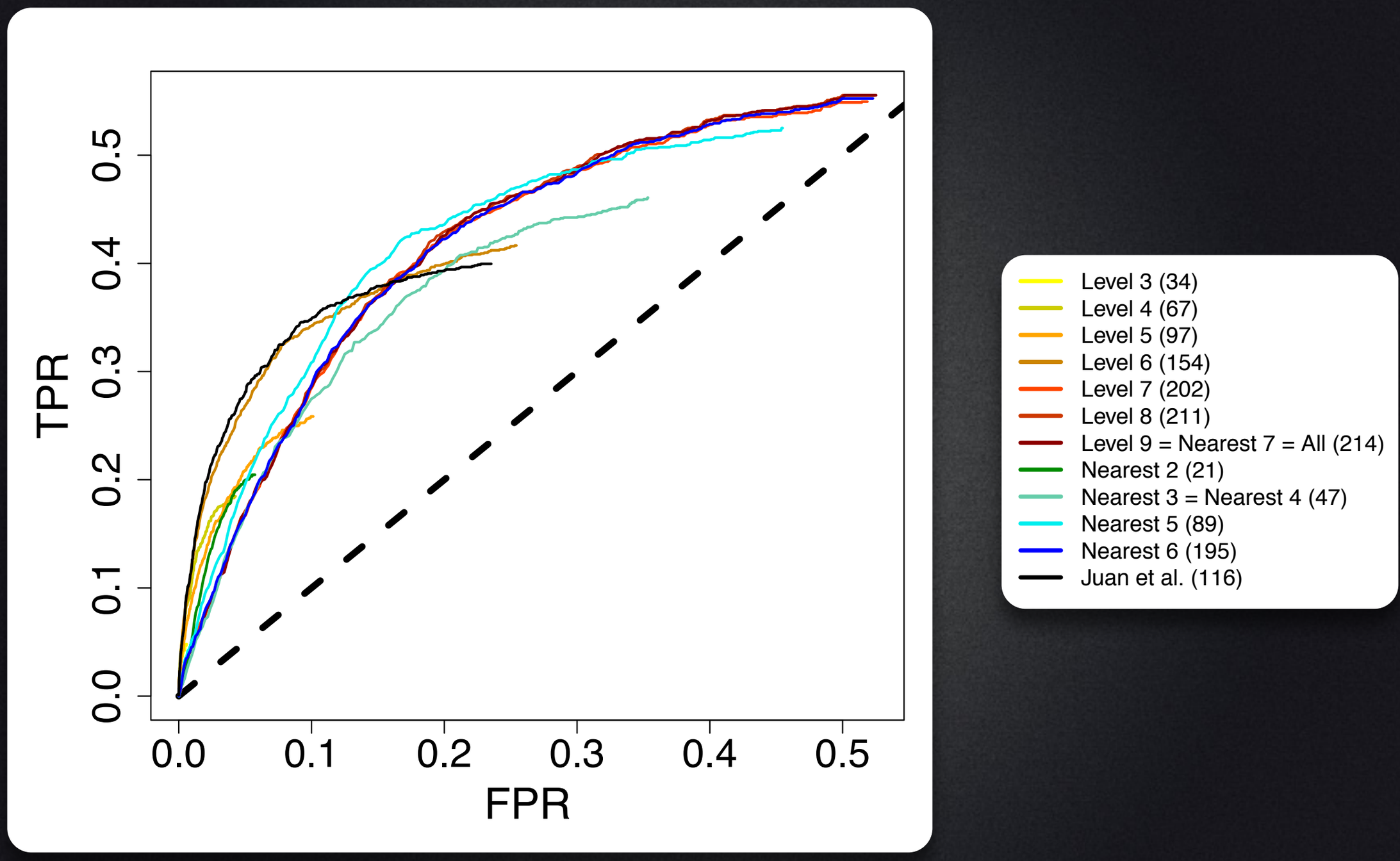






Mirrortree

Complexes

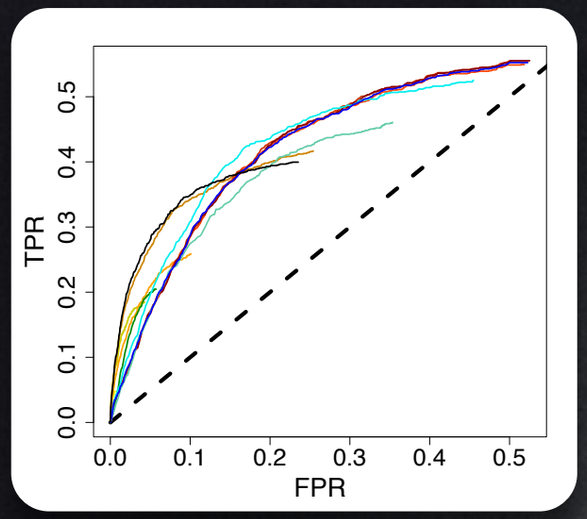


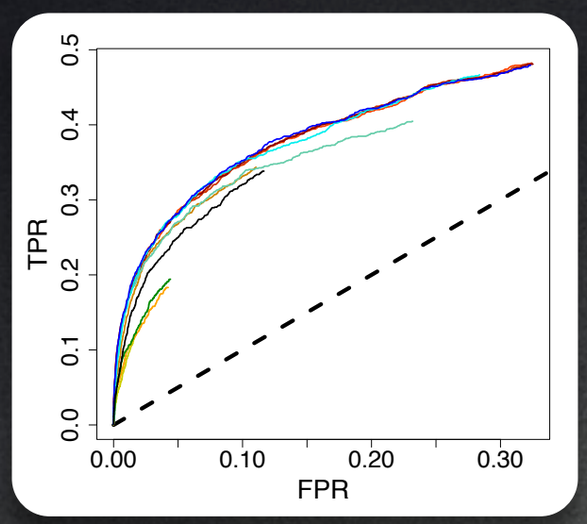
Mirrortree

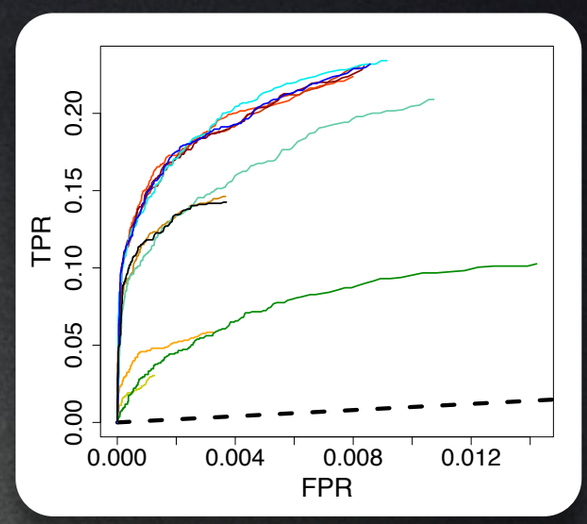
Profile Correlation

ContextMirror

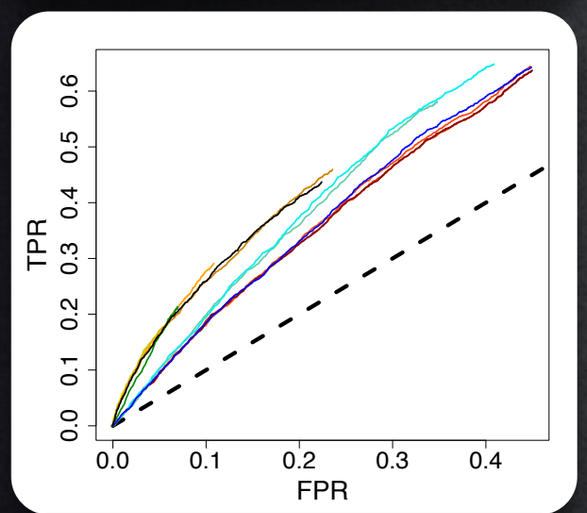
Complexes

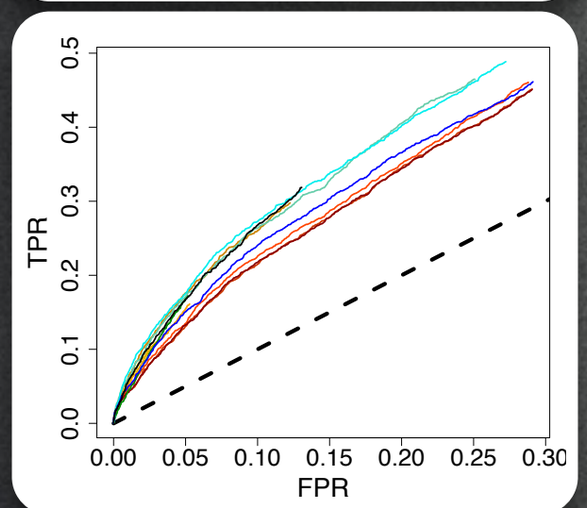


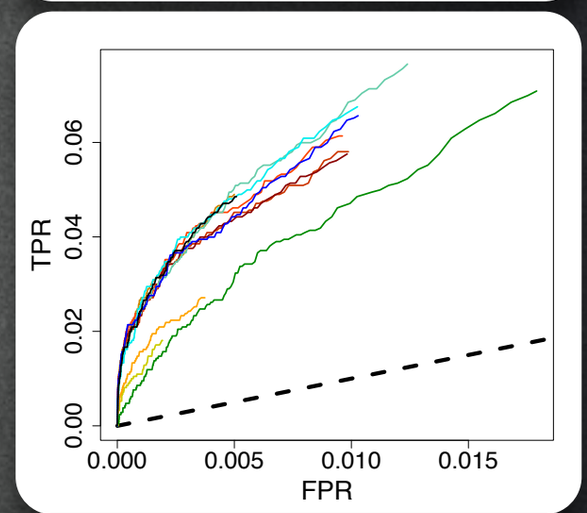


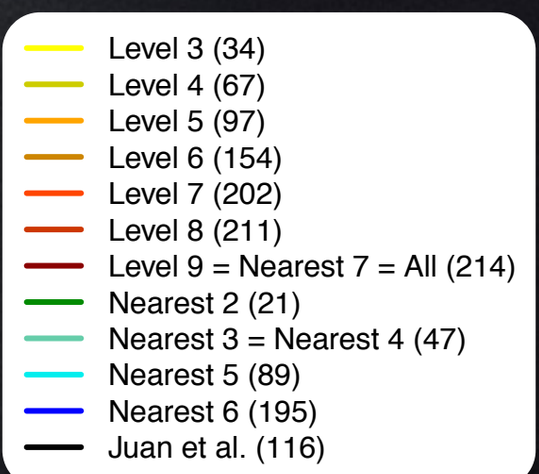


Binary Physical

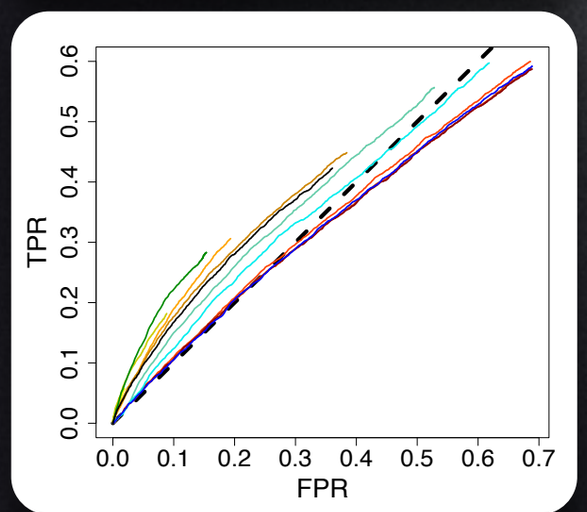


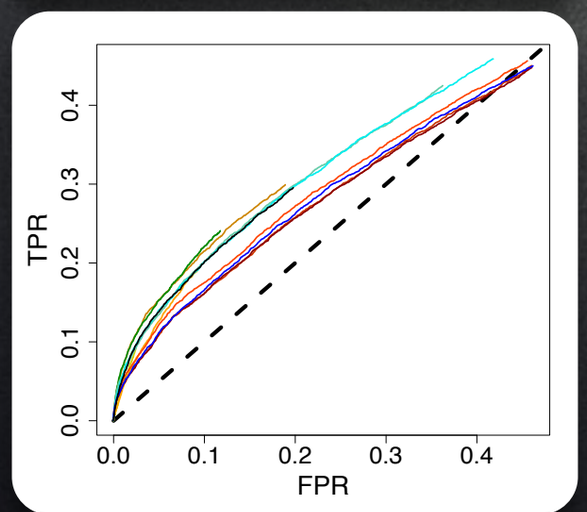


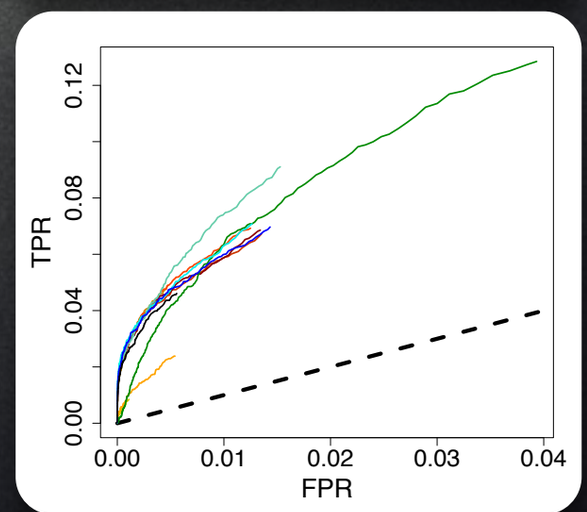




Pathways

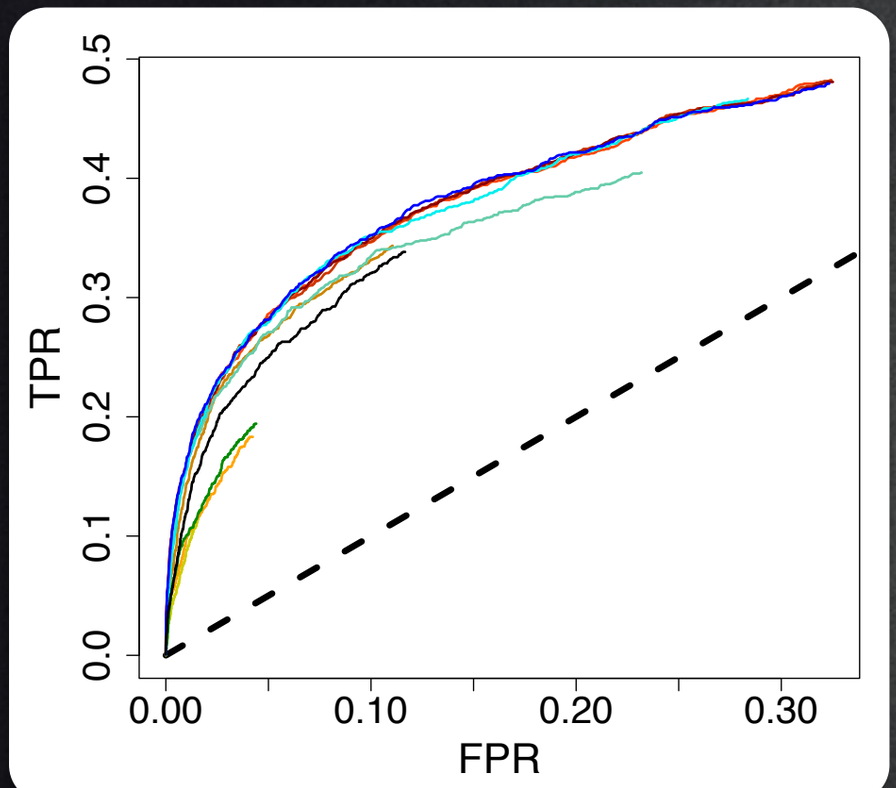




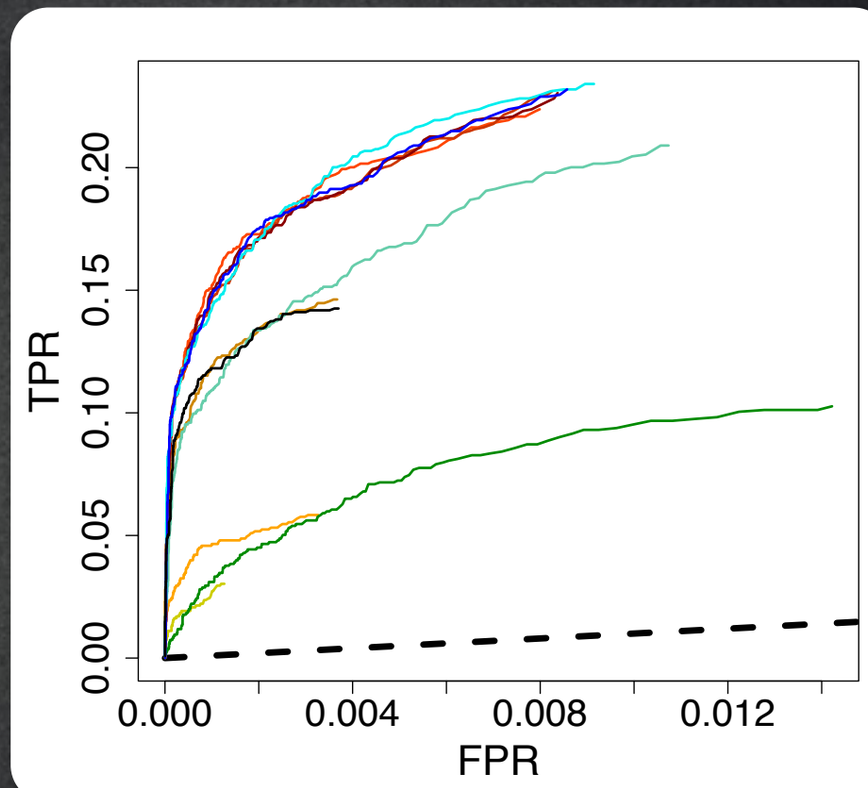


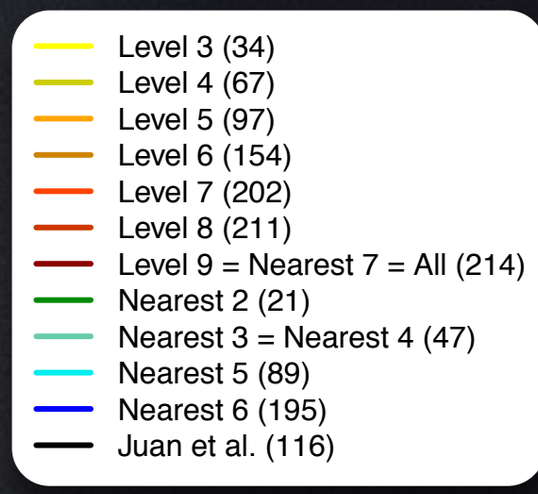
Com

Profile Correlation



ContextMirror



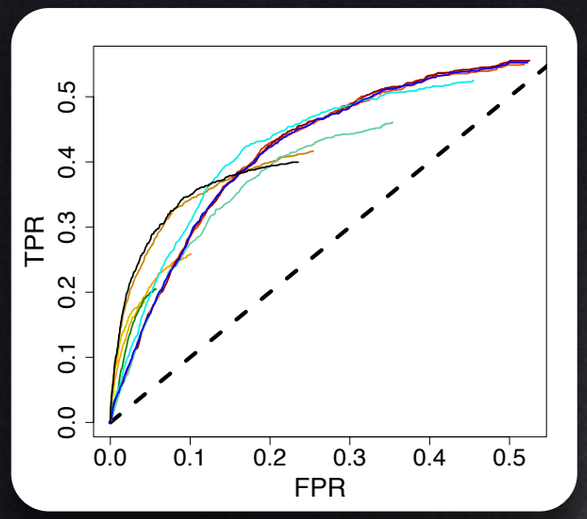


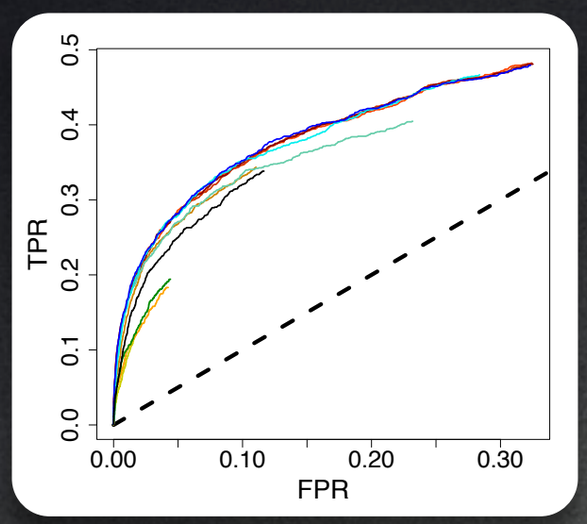
Mirrortree

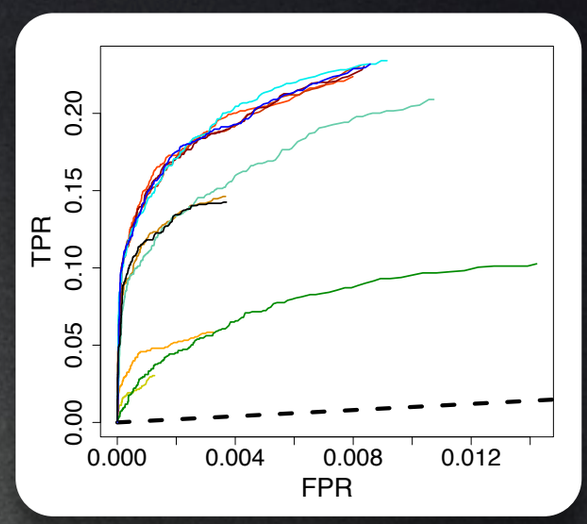
Profile Correlation

ContextMirror

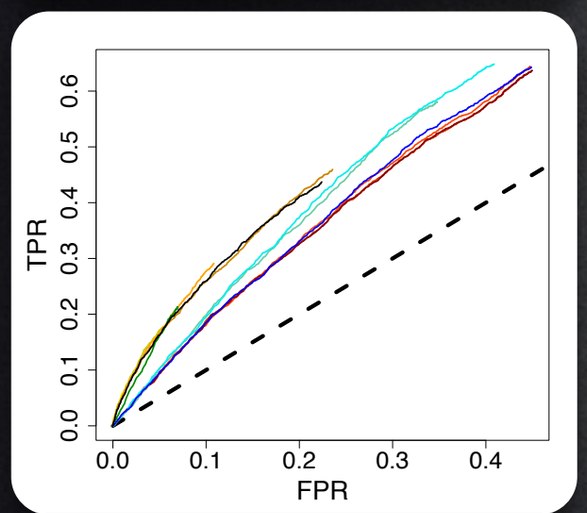
Complexes

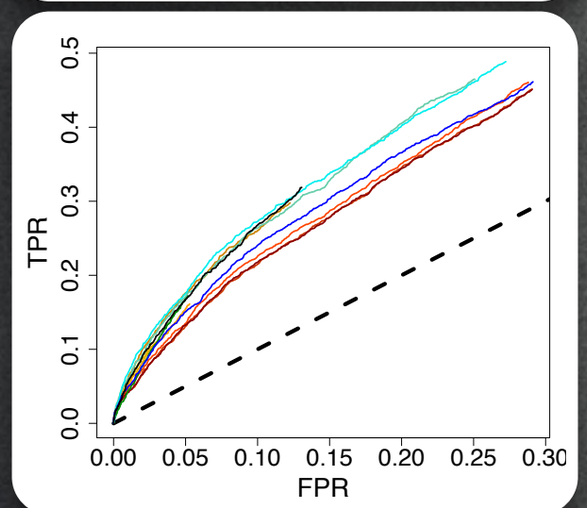


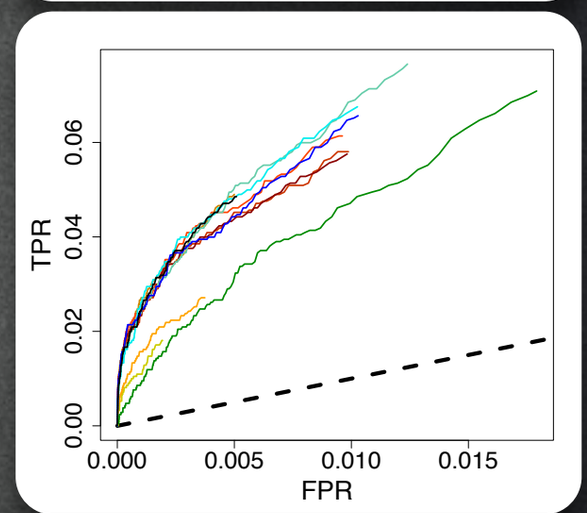


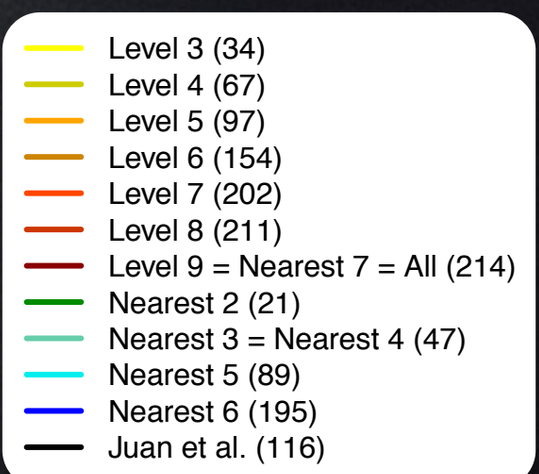


Binary Physical

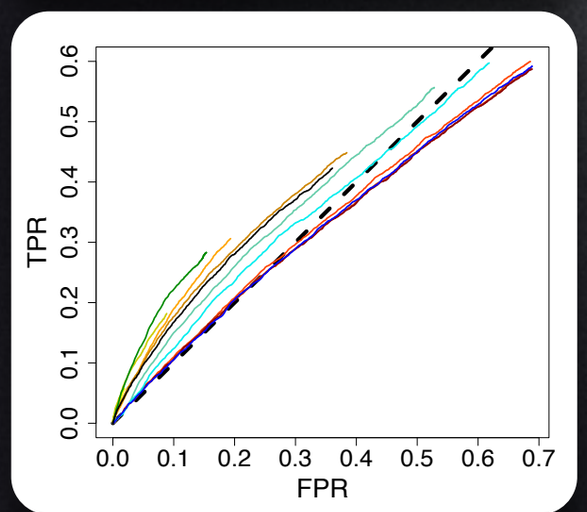


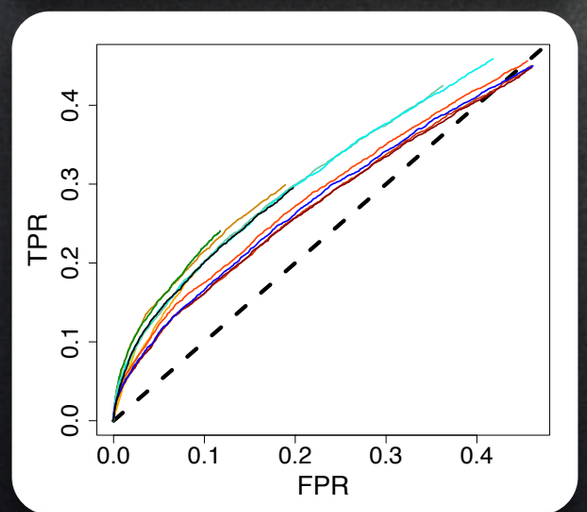


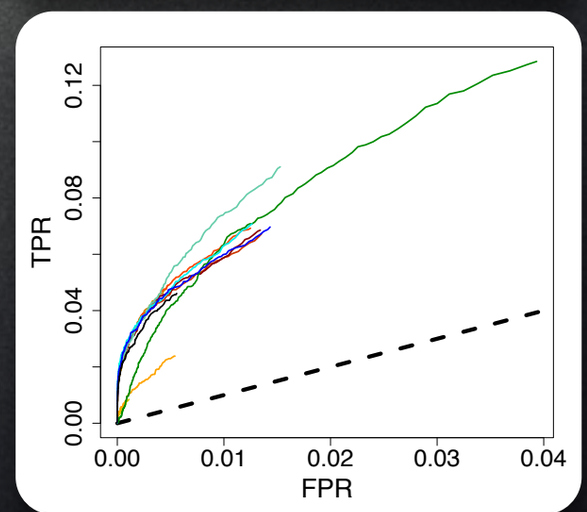




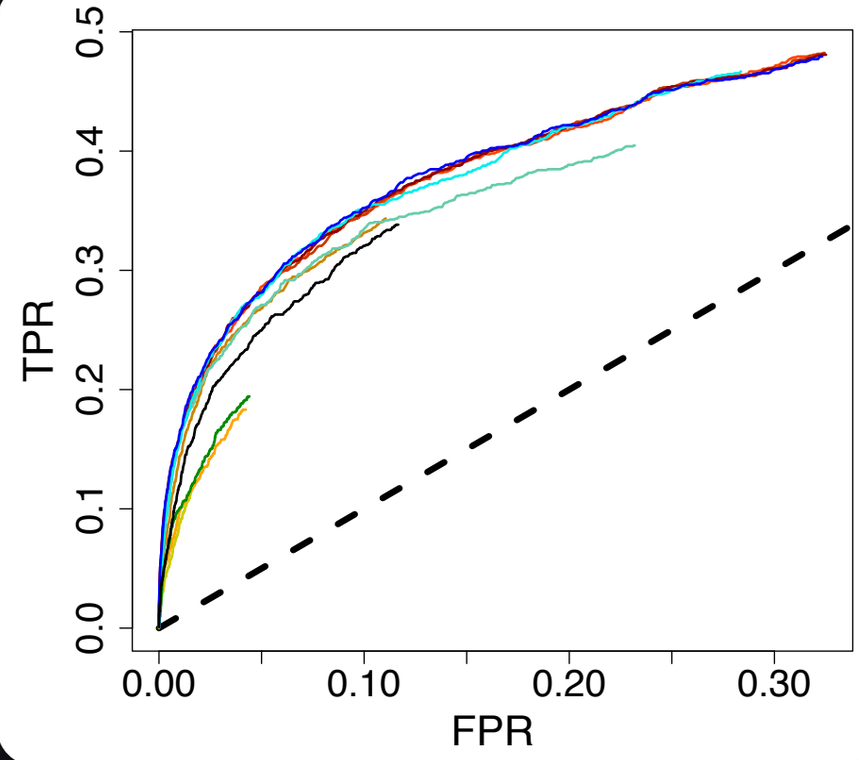
Pathways



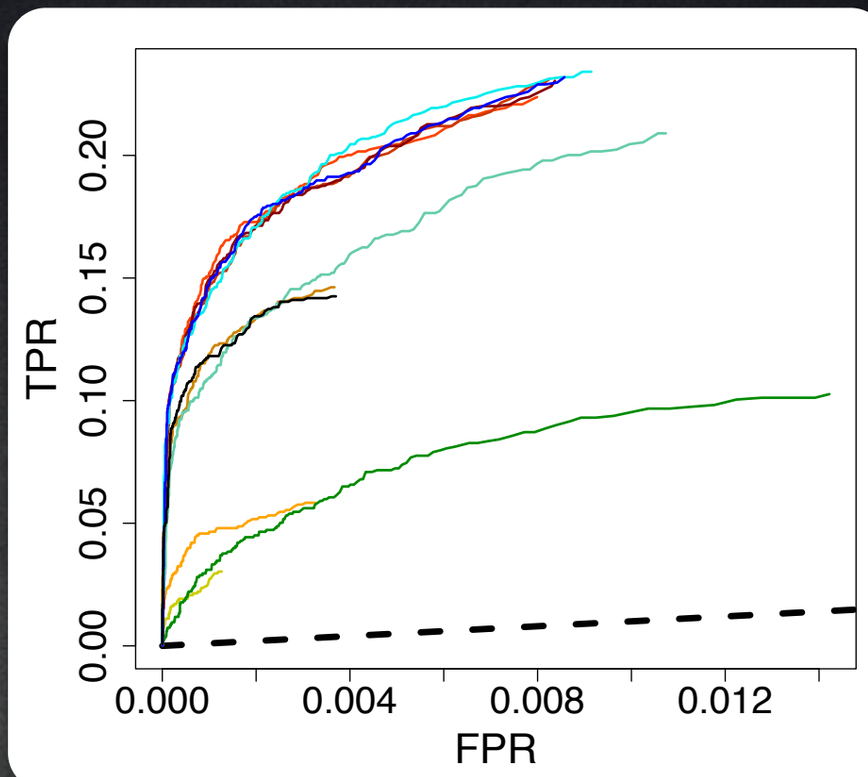




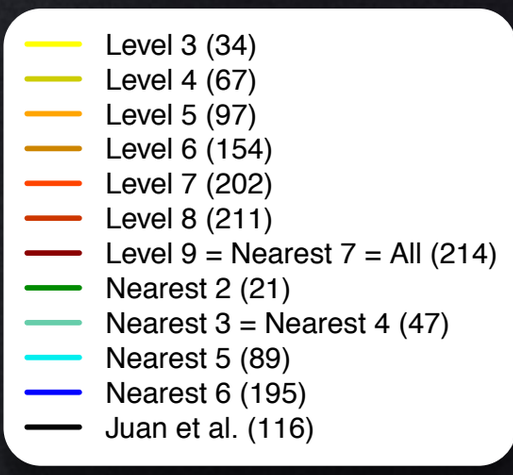
Profile Correlation

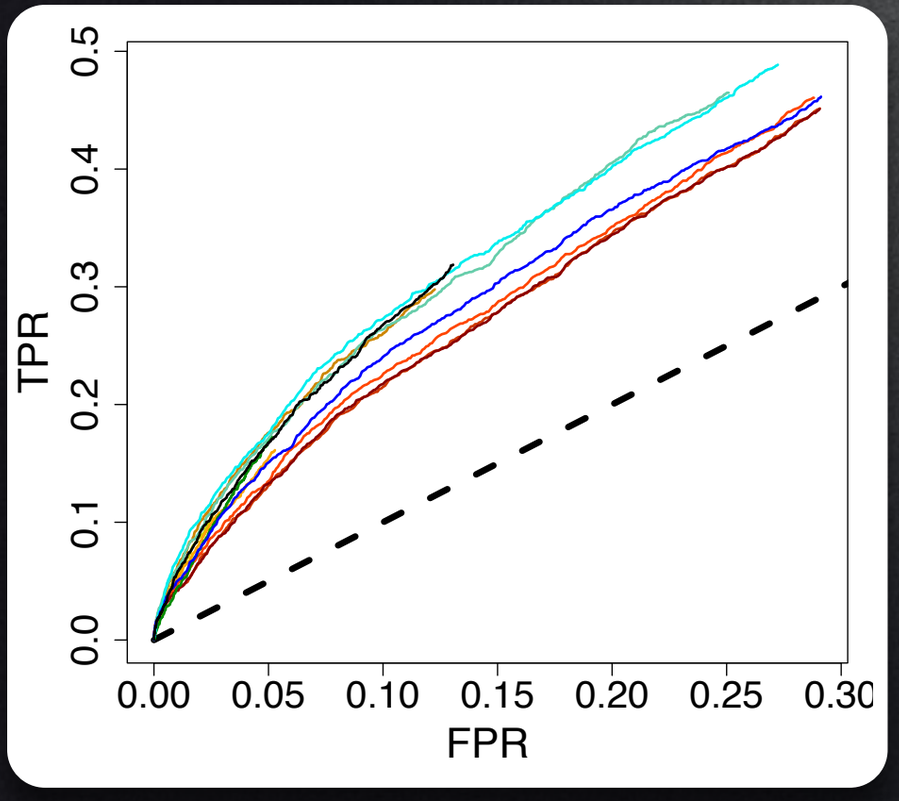


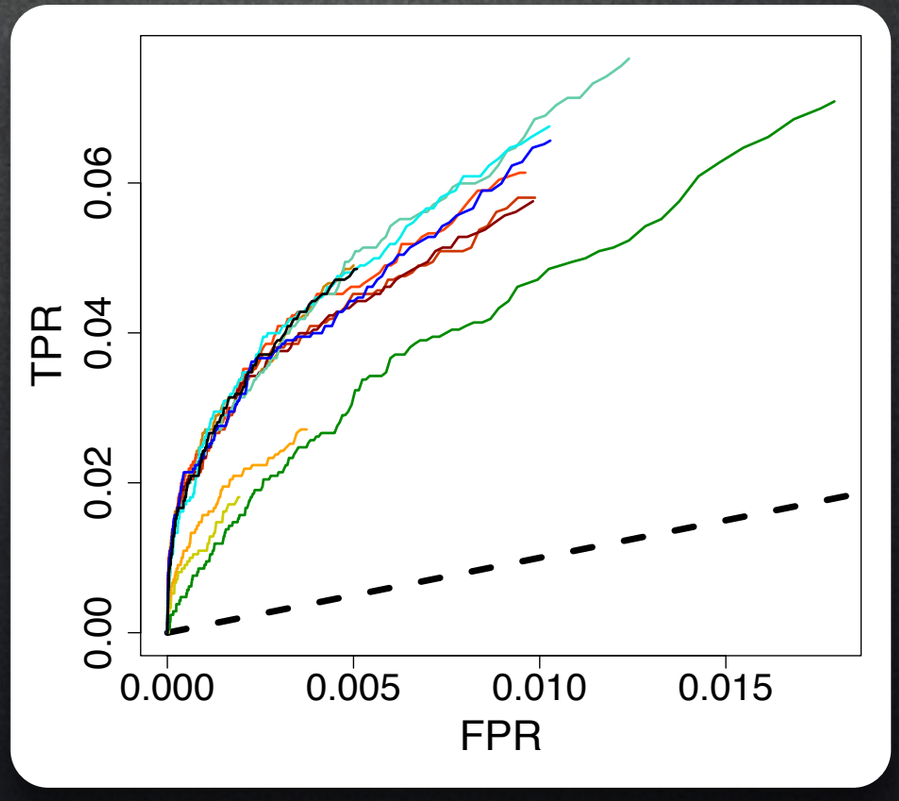
ContextMirror



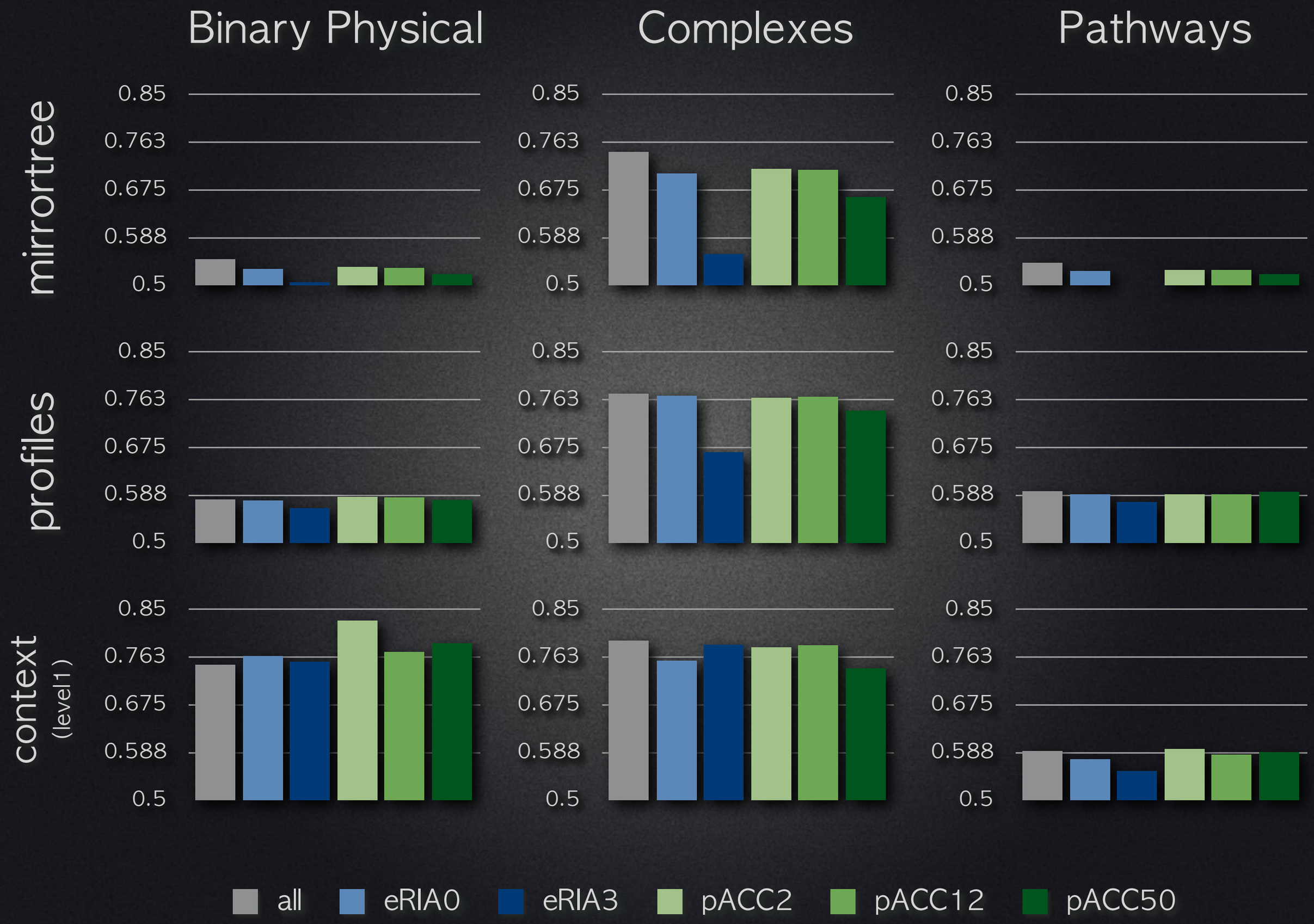
Complexes







Binary Physical


Binary Physical
Complexes
Pathways
mirrortree
profiles
context (level1)
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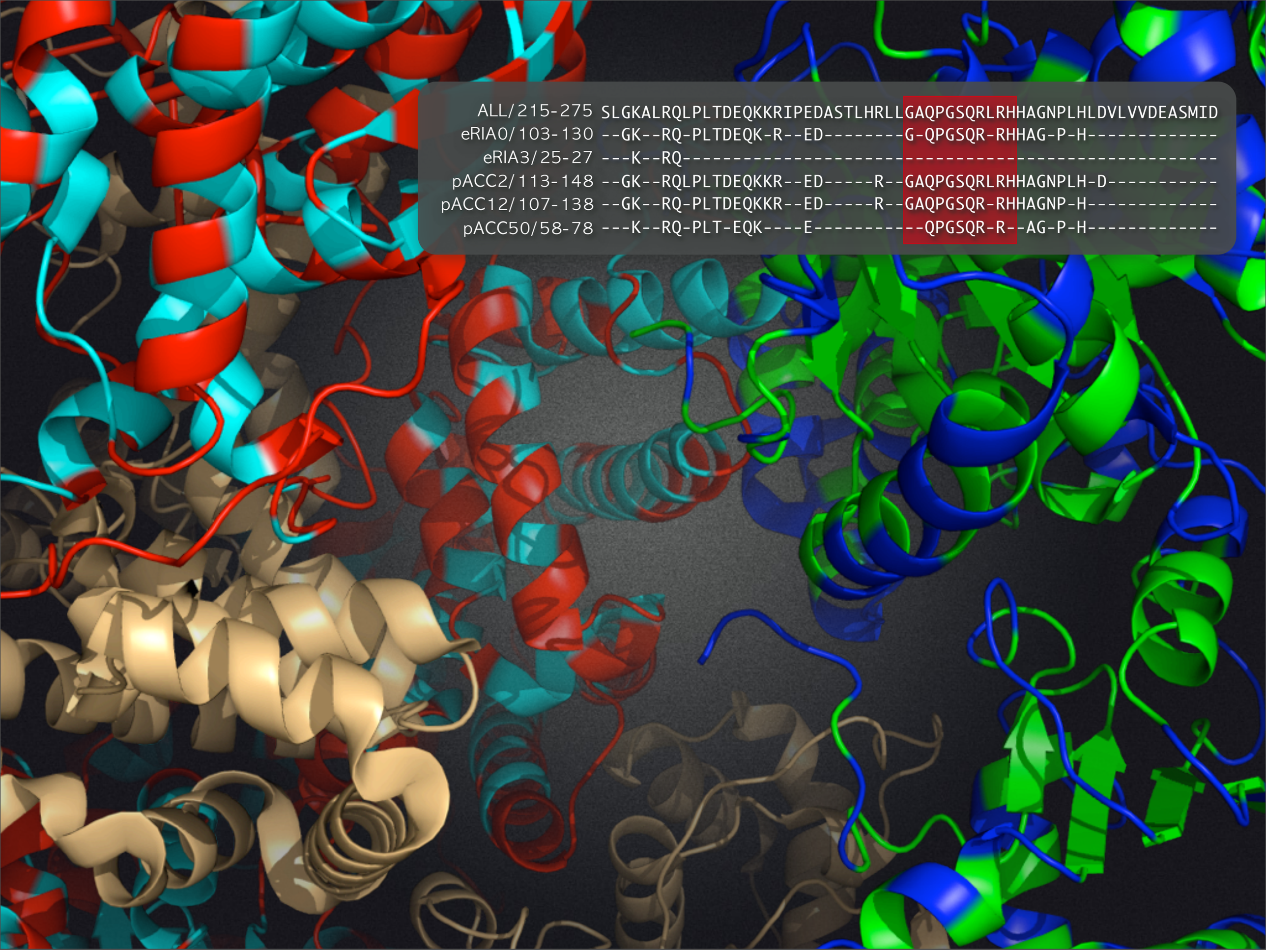
0.763
0.675
0.588
0.5
all
eRIA0
eRIA3
pACC2
pACC12
pACC50


Binary Physical
Complexes
Pathways
mirrortree
profiles
context
(level1)
1500
1125
750
375
0
800
600
400
200
3000
2250
1500
1000
700
525
350
175
50
37.5
25
12.5
200
150
100
50
2000
500
all
eRIA0
eRIA3
pACC2
pACC12
pACC50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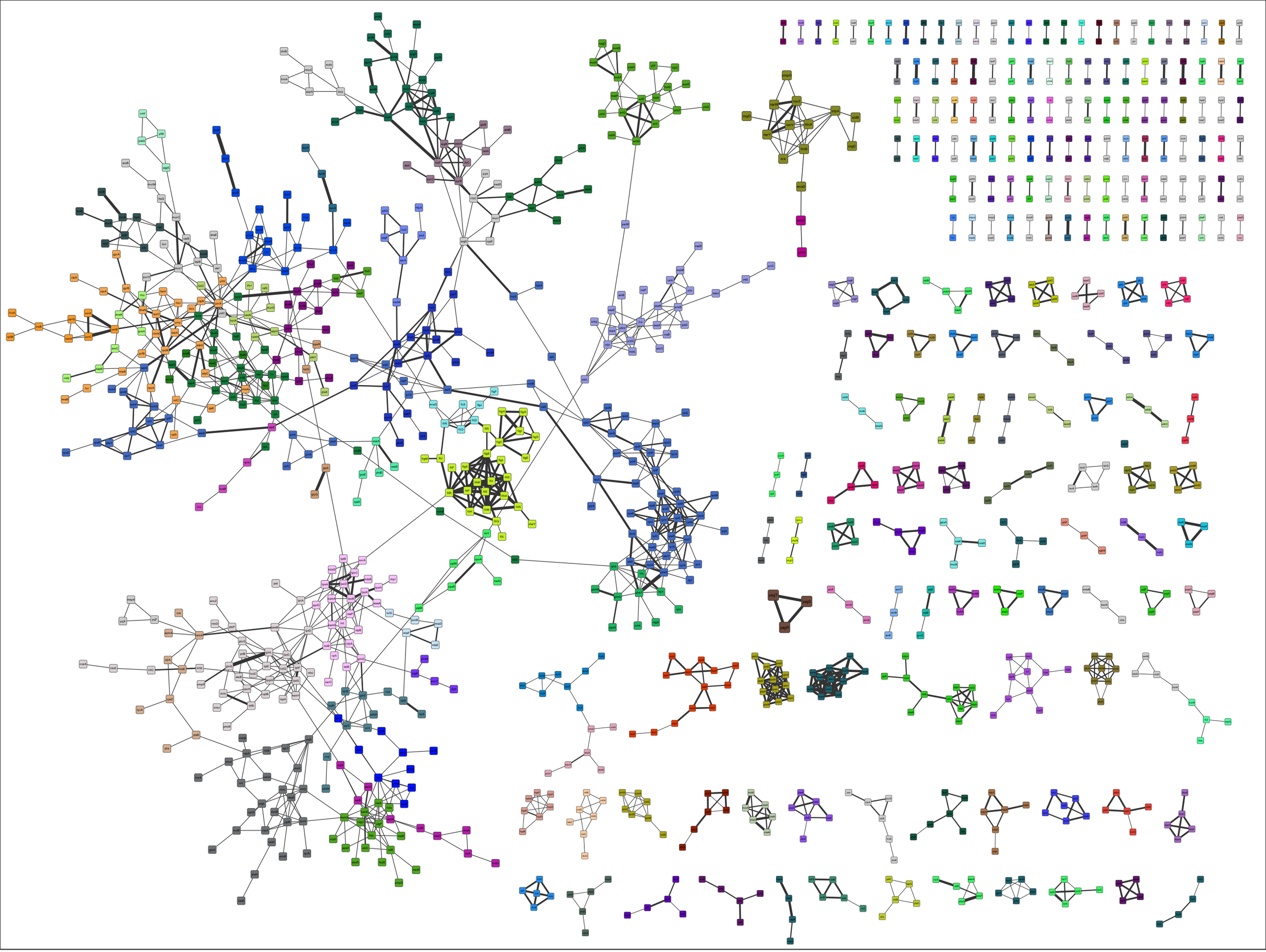
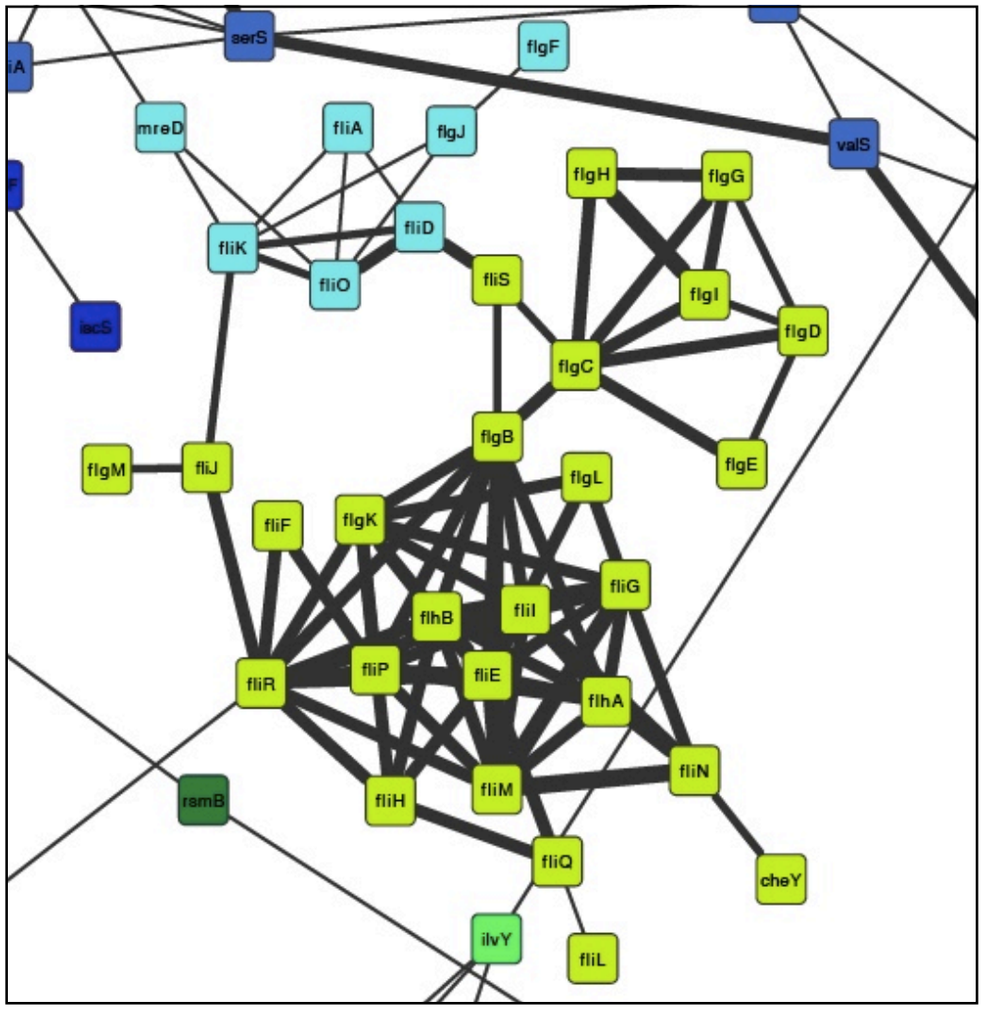
eRIA0/103-130 --GK--RQ-PLTDEQK-R--ED--------G-QPGSQR-RHHAG-P-H----------
eRIA3/25-27 ---K--RQ----------
pACC2/113-148 --GK--RQLPLTDEQKKR--ED-----R--GAQPGSQRLRHHAGNPLH-D----------
pACC12/107-138 --GK--RQ-PLTDEQKKR--ED-----R--GAQPGSQR-RHHAGNP-H----------
pACC50/58-78 ---K--RQ-PLT-EQK----E----------QPGSQR-R--AG-P-H----------

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flgF
mreD
fliA
flgJ
valS
flgH
flgG
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fliD
fliO
fliS
flgI
flgD
iscS
flgC
flgB
flgM
fliJ
flgL
flgE
fliF
flgK
fliG
flhB
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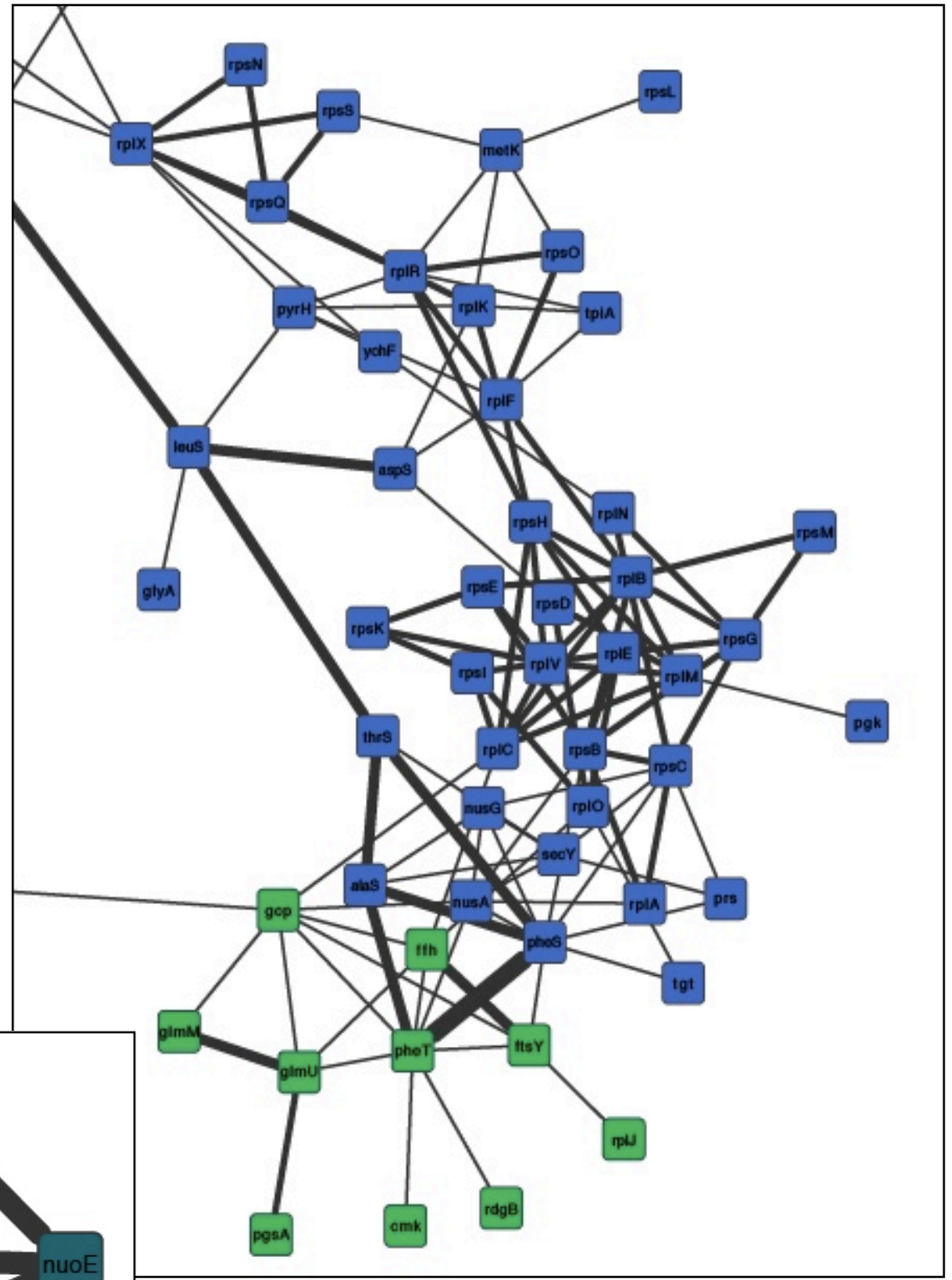
cheY
ilvY
fliL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rpsL
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leuS
aspS
rpsH
rplN
rpsM
glyA
rpsE
rpsD
rplB
rpsK
rpsG
rpsI
rplV
rplE
rplM
pgk
thrS
rplC
rpsB
rpsC
nusG
rplO
secY
alaS
nusA
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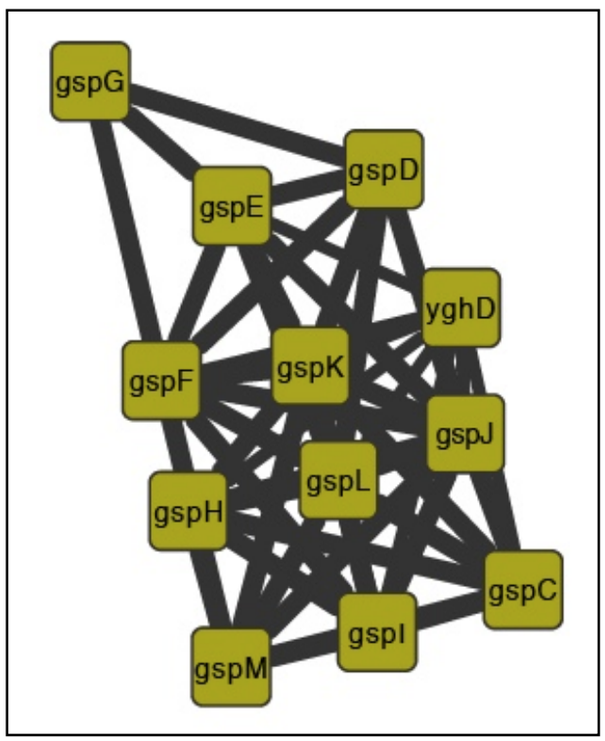
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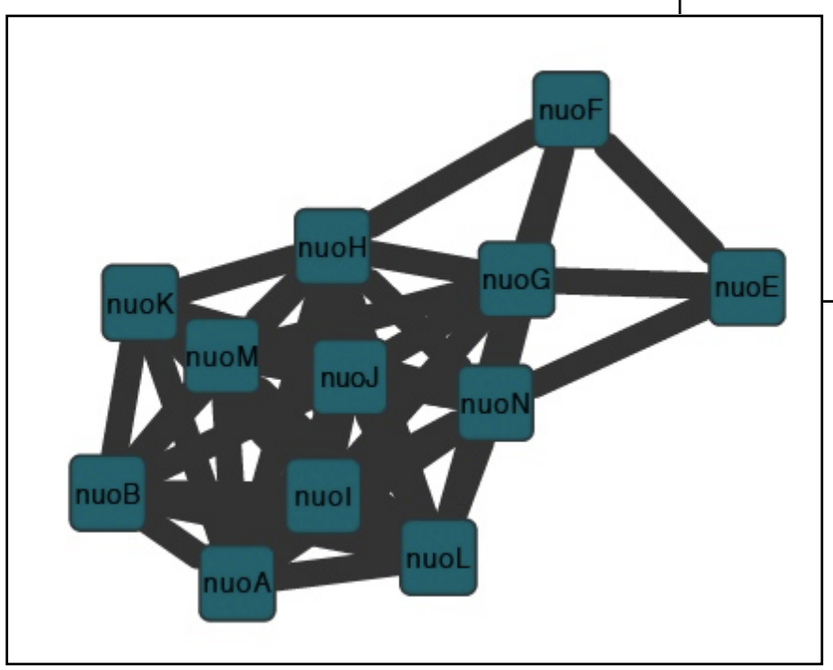
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