

STRINGdb Package Vignette

Andrea Franceschini and Damian Szklarczyk

1 INTRODUCTION

STRING (<https://www.string-db.org>) is a database of known and predicted protein-protein interactions. The interactions include direct (physical) and indirect (functional) associations. The database contains information from numerous sources, including experimental repositories, computational prediction methods and public text collections. Each interaction is associated with a combined confidence score that integrates the various evidences. STRING v12.0 covers 59.3 million proteins from 12,535 organisms and more than 20 billion interactions.

As you will learn in this guide, the STRING database can be useful to add meaning to lists of genes, for example the best hits coming out from a screen or the most differentially expressed genes coming out from a microarray or RNA-seq experiment.

We provide the STRINGdb R package in order to facilitate our users in accessing the STRING database from R. In this guide we explain, with examples, most of the package's features and functionalities.

In the STRINGdb R package we use the new ReferenceClasses of R (search for "ReferenceClasses" in the R documentation.). Besides we make use of the iGraph package (<http://igraph.sourceforge.net>) as a data structure to represent our protein-protein interaction network.

To begin, you should first know the NCBI taxonomy identifiers of the organism on which you have performed the experiment (e.g. 9606 for Human, 10090 for mouse). If you don't know that, you can search the NCBI Taxonomy (<http://www.ncbi.nlm.nih.gov/taxonomy>) or start looking at our species table (that you can also use to verify that your organism is represented in the STRING database). Hence, if your species is not Human (i.e. our default species), you can find it and their taxonomy identifiers on STRING webpage under the 'organisms' section (https://string-db.org/cgi/input.pl?input_page_active_form=org) or download the full list in the download section of STRING website.

```
> library(STRINGdb)
> string_db <- STRINGdb$new( version="12.0", species=9606,
+                             score_threshold=400, network_type="full", link_data="detailed", input_di
```

As it has been shown in the above commands, you start instantiating the STRINGdb reference class. In the constructor of the class you can also define the STRING version to be used and a threshold for the combined scores of the interactions, such that any interaction below that threshold is not loaded in the object (by default the score threshold is set to 400).

You can also specify the network type "functional" for full functional STRING network or "physical"

for physical subnetwork, which link only the proteins which share a physical complex. Besides, if you specify a local directory to the parameter input-directory, the database files will be downloaded into this directory and most of the methods can be used off-line. Otherwise, the database files will be saved and cached in a temporary directory that will be cleaned automatically when the R session is closed. By setting `link_data="detailed"` we also load the evidence score columns, such as the experimental score, in addition to the combined score.

For a better understanding of the package two other commands can be useful:

```
> STRINGdb$methods()           # To list all the methods available.

[1] ".objectPackage"           ".objectParent"
[3] "add_diff_exp_color"       "add_proteins_description"
[5] "benchmark_ppi"           "benchmark_ppi_pathway_view"
[7] "callSuper"               "copy"
[9] "enrichment_heatmap"       "export"
[11] "field"                   "getClass"
[13] "getRefClass"             "get_aliases"
[15] "get_annotations"         "get_bioc_graph"
[17] "get_clusters"            "get_enrichment"
[19] "get_enrichment_figure"    "get_graph"
[21] "get_homologs"            "get_homologs_besthits"
[23] "get_homology_graph"       "get_interaction_partners"
[25] "get_interactions"         "get_link"
[27] "get_neighbors"           "get_paralogs"
[29] "get_pathways_benchmarking_blackList" "get_png"
[31] "get_ppi_enrichment"       "get_ppi_enrichment_full"
[33] "get_proteins"            "get_pubmed"
[35] "get_pubmed_interaction"   "get_subnetwork"
[37] "get_summary"             "get_term_proteins"
[39] "import"                  "initFields"
[41] "initialize"              "load"
[43] "load_all"                "map"
[45] "mp"                      "plot_network"
[47] "plot_ppi_enrichment"     "post_payload"
[49] "ppi_enrichment"          "remove_homologous_interactions"
[51] "set_background"          "show"
[53] "show#envRefClass"        "trace"
[55] "untrace"                 "usingMethods"

> STRINGdb$help("get_graph")   # To visualize their documentation.

Call:
$get_graph()
```

Description:

Return an igraph object with the entire STRING network.

We invite the user to use the functions of the iGraph package to conveniently

search/analyze the network.

References:

Csardi G, Nepusz T: The igraph software package for complex network research, InterJournal, Complex Systems 1695. 2006.
<http://igraph.sf.net>

See Also:

In order to simplify the most common tasks, we do also provide convenient functions that wrap some iGraph functions.

```
get_interactions(string_ids) # returns the interactions in between the input proteins
get_neighbors(string_ids)    # Get the neighborhoods of a protein (or of a vector of proteins).
get_subnetwork(string_ids)   # returns a subgraph from the given input proteins
```

Author(s):

Andrea Franceschini

For all the methods that we are going to explain below, you can always use the help function in order to get additional information/parameters with respect to those explained in this guide.

As an example, we use the analyzed data of a microarray study taken from GEO (Gene Expression Omnibus, GSE9008). This study investigates the activity of Resveratrol, a natural phytoestrogen found in red wine and a variety of plants, in A549 lung cancer cells. Microarray gene expression profiling after 48 hours exposure to Resveratrol has been performed and compared to a control composed by A549 lung cancer cells treated only with ethanol. This data is already analyzed for differential expression using the limma package: the genes are sorted by *fdr* corrected *p*values and the log fold change of the differential expression is also reported in the table.

```
> data(diff_exp_example1)
> head(diff_exp_example1)
```

	pvalue	logFC	gene
1	0.0001018	3.333461	VSTM2L
2	0.0001392	3.822383	TBC1D2
3	0.0001720	3.306056	LENG9
4	0.0001739	3.024605	TMEM27
5	0.0001990	3.854414	LOC100506014
6	0.0002393	3.082052	TSPAN1

As a first step, we map the gene names to the STRING database identifiers using the "map" method. In this particular example, we map from gene HUGO names, but our mapping function supports several other common identifiers (e.g. Entrez GeneID, ENSEMBL proteins, RefSeq transcripts ... etc.).

The map function adds an additional column with STRING identifiers to the dataframe that is passed as first parameter.

```
> example1_mapped <- string_db$map( diff_exp_example1, "gene", removeUnmappedRows = TRUE )
```

Warning: we couldn't map to STRING 15% of your identifiers

As you may have noticed, the previous command prints a warning showing the number of genes that we failed to map. In this particular example, we cannot map all the probes of the microarray that refer to position of the chromosome that are not assigned to a real gene (i.e. all the LOC genes). If we remove all these LOC genes before the mapping we obtain a much lower percentage of unmapped genes (i.e. < 6 %).

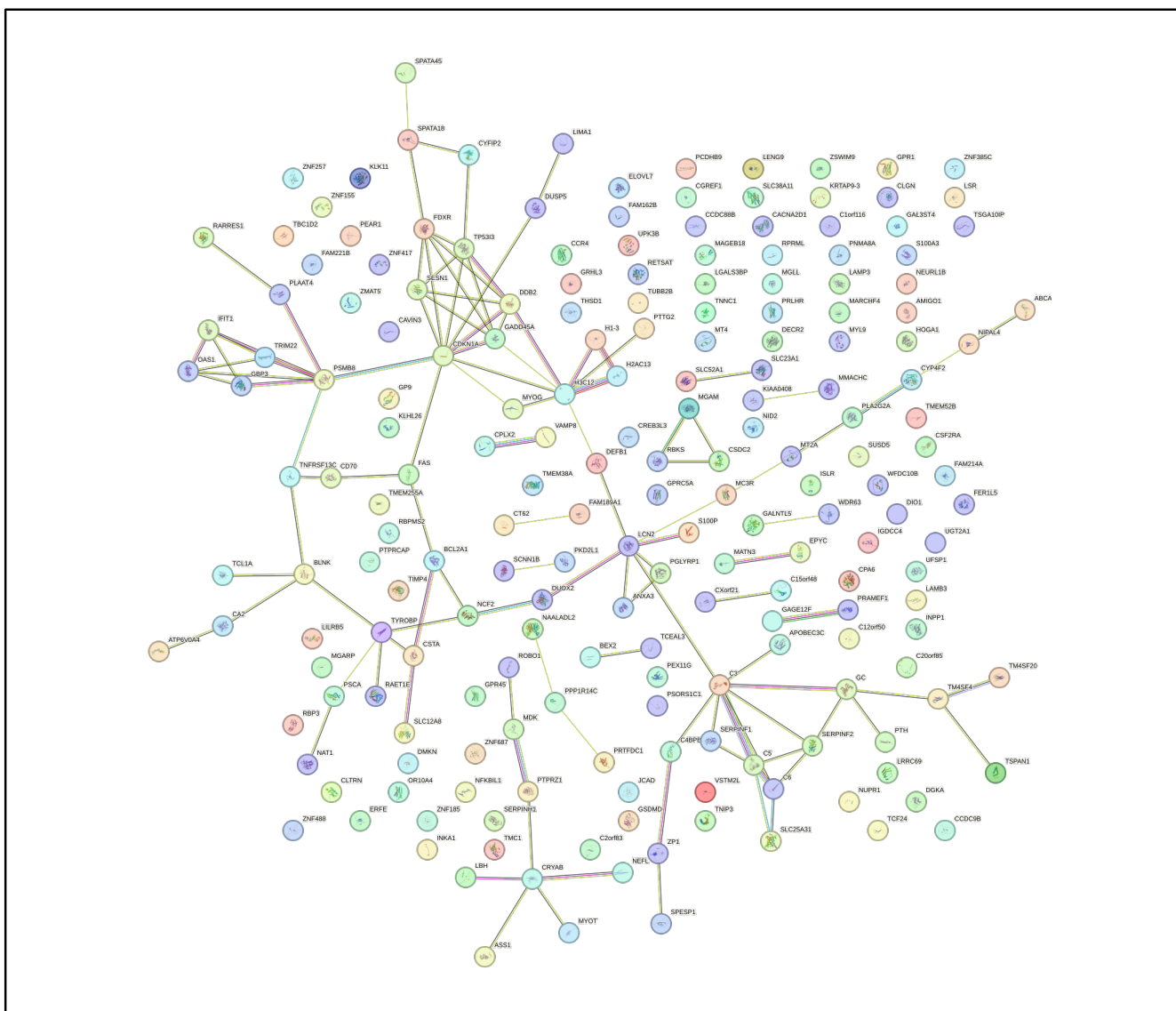
If you set to FALSE the "removeUnmappedRows" parameter, than the rows which corresponds to unmapped genes are left and you can manually inspect them.

Finally, we extract the genes with p-value < 0.05 and, for the examples below, we focus on the top 200 genes sorted by p-value. The image shows clearly the genes and how they are possibly functionally related. On the top of the plot, we insert a pvalue that represents the probability that you can expect such an equal or greater number of interactions by chance.

```
> example1_mapped_pval05 <- subset(example1_mapped, pvalue < 0.05)
> example1_mapped_pval05 <- example1_mapped_pval05[order(example1_mapped_pval05$pvalue), ]
> hits <- example1_mapped_pval05$STRING_id[1:200]

> string_db$plot_network( hits )
```

proteins: 200
interactions: 117
expected interactions: 62 (p-value: 4.2e-10)



If you want more control over the appearance of the network image, the `get_png` and `get_link` methods expose additional styling options. In particular, you can switch between **evidence** and **confidence** edge styles, hide node labels, hide disconnected proteins, disable the structure pictures inside bubbles, use the flat node design, center node labels, and change the label font size.

2 PAYLOAD MECHANISM

This R library provides the ability to interact with the STRING payload mechanism. The payload appears as an additional colored "halo" around the bubbles.

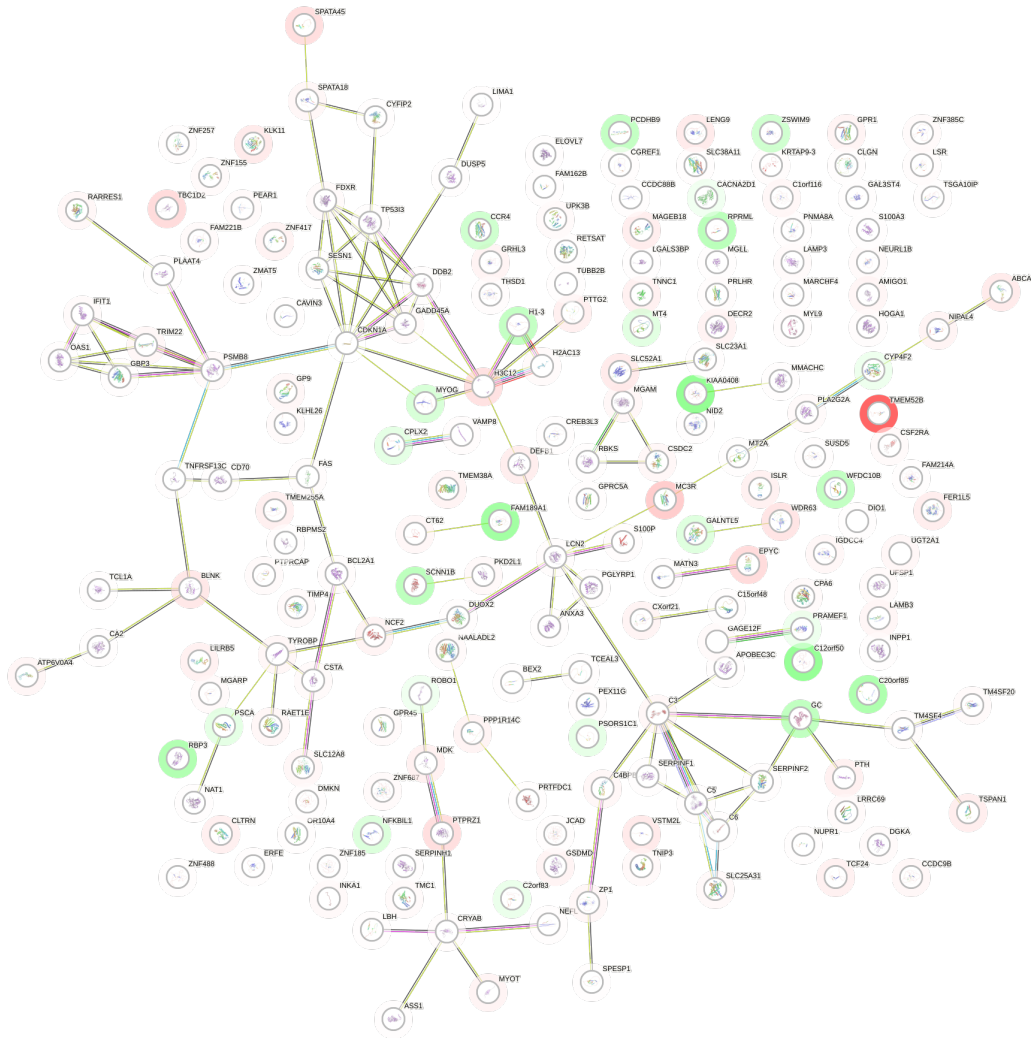
For example, this allows to color in green the genes that are down-regulated and in red the genes that are up-regulated. For this mechanism to work, we provide a function that posts the information on our web server.

```
> # filter by p-value and add a color column
> # (i.e. green down-regulated genes and red for up-regulated genes)
> example1_mapped_pval05 <- string_db$add_diff_exp_color( subset(example1_mapped, pvalue<0.05),
+                                                         logFcColStr="logFC" )

> # post payload information to the STRING server
> payload_id <- string_db$post_payload( example1_mapped_pval05$STRING_id,
+                                     colors=example1_mapped_pval05$color )

> # display a STRING network png with the "halo"
> string_db$plot_network( hits, payload_id=payload_id )
```

proteins: 200
interactions: 117
expected interactions: 62 (p-value: 4.2e-10)



3 ENRICHMENT

We provide a method to compute the enrichment in Gene Ontology (Process, Function and Component), KEGG and Reactome pathways, PubMed publications, UniProt Keywords, and PFAM/INTERPRO/SMART domains for your set of proteins all in one simple call. The enrichment itself is computed using an hypergeometric test and the FDR is calculated using Benjamini-Hochberg procedure.

```
> enrichment <- string_db$get_enrichment( hits )
> head(enrichment, n=20)
```

	category	term	number_of_genes	number_of_genes_in_background
1	COMPARTMENTS	GOCC:0005576	42	2079
2	COMPARTMENTS	GOCC:0043230	17	524
3	Process	GO:0006952	35	1394
4	Component	GO:0005576	67	4175
5	Component	GO:0070062	42	2096
6	Component	GO:1903561	43	2120
7	Component	GO:0005615	54	3247
8	TISSUES	BTO:0000392	10	171
9	Keyword	KW-0391	17	537
10	Keyword	KW-0732	55	3277
11	KEGG	hsa04115	6	72
12	PMID	PMID:39331229	6	8
13	WikiPathways	WP4963	7	90

ncbiTaxonId

1	9606
2	9606
3	9606
4	9606
5	9606
6	9606
7	9606
8	9606
9	9606
10	9606
11	9606
12	9606
13	9606

1	
2	
3	
4	9606.ENSPP00000008938,9606.ENSPP00000014914,9606.ENSPP00000187762,9606.ENSPP00000216286,9606.ENSPP00000
5	
6	
7	
8	
9	
10	
11	
12	
13	


```

1
2
3
4 PGLYRP1,GPRC5A,TMEM38A,NID2,C5,RARRES1,C4BPB,C3,ISLR,SERPINF1,THSD1,TUBB2B,EPYC,LGALS3BP,C6,VAMP8,
5
6
7 PGLYRP1,GPRC5A,TMEM38
8
9
10 PGLYRP1,NID2,C5,C4BPB,
11
12
13
14 p_value fdr
15 1 1.28e-05 0.0294
16 2 3.51e-05 0.0403
17 3 7.80e-07 0.0122
18 4 4.15e-05 0.0182
19 5 1.55e-05 0.0182
20 6 8.88e-06 0.0182
21 7 1.30e-04 0.0441
22 8 1.53e-05 0.0371
23 9 4.71e-05 0.0317
24 10 8.55e-05 0.0317
25 11 1.30e-04 0.0452
26 12 2.69e-09 0.0138
27 13 5.58e-05 0.0436
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

```

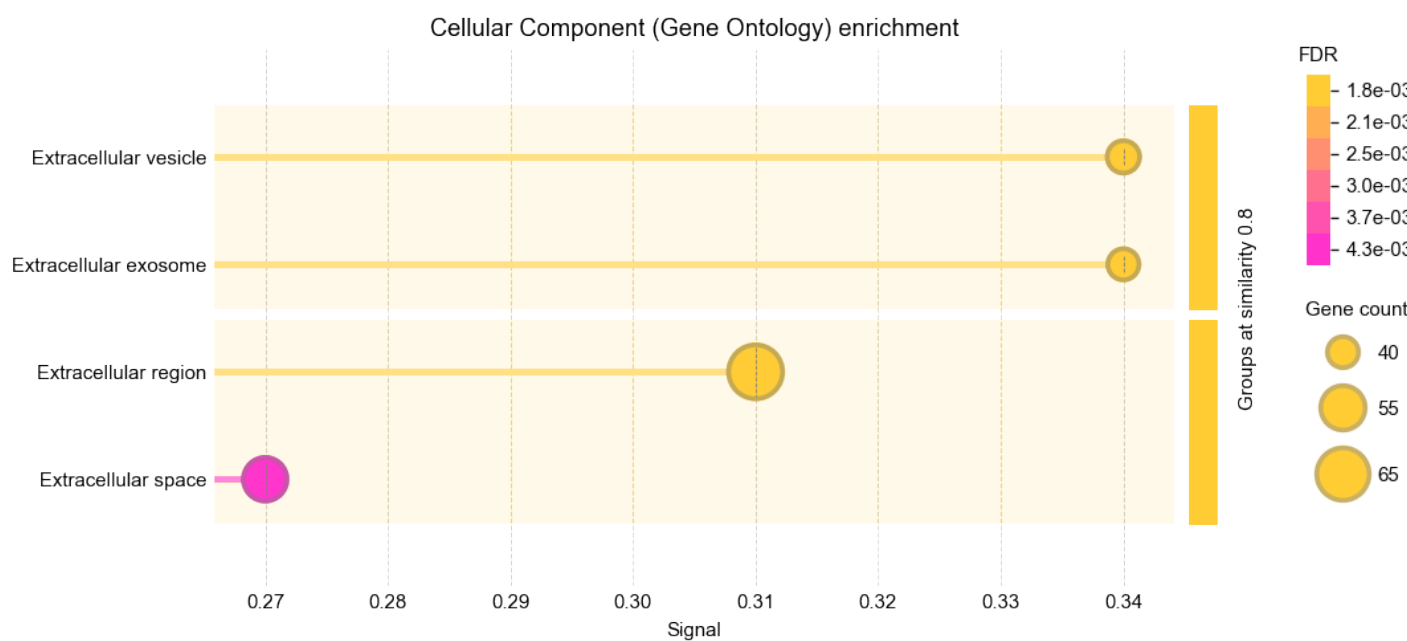
You can also retrieve an enrichment figure directly from STRING for a selected category. The image can be returned as a PNG array or as SVG markup, and you can customize the category, similarity-based grouping, color palette, the number of terms shown, and the variable displayed on the X-axis.

```

> enrichment_img <- string_db$get_enrichment_figure(
+ hits,

```

```
+   category = "Component",
+   group_by_similarity = 0.8,
+   color_palette = "yellow_pink",
+   x_axis = "signal"
+ )
> grid::grid.newpage()
> grid::grid.raster(enrichment_img, interpolate = FALSE)
```



If you have performed your experiment on a predefined set of proteins, it is important to run the enrichment statistics using that set as a background (otherwise you would get a wrong p-value !). Hence, before to launch the method above, you may want to set the background:

```

> backgroundV <- example1_mapped$STRING_id
> string_db$set_background(backgroundV)

IGRAPH 293e91b UN-- 17434 1702440 --
+ attr: name (v/c), neighborhood (e/n), fusion (e/n), cooccurrence
| (e/n), coexpression (e/n), experimental (e/n), database (e/n),
| textmining (e/n), combined_score (e/n)
+ edges from 293e91b (vertex names):
[1] 9606.ENSP00000000233--9606.ENSP00000493357
[2] 9606.ENSP00000000233--9606.ENSP00000371175
[3] 9606.ENSP00000000233--9606.ENSP00000354878
[4] 9606.ENSP00000000233--9606.ENSP00000310226
[5] 9606.ENSP00000000233--9606.ENSP00000258098
[6] 9606.ENSP00000000233--9606.ENSP00000363232
+ ... omitted several edges

```

If you already have a `STRINGdb` object, calling `set_background` is sufficient and you do not need to instantiate a new object again. Passing `backgroundV` to the constructor is simply an alternative when you already know the background at initialization time:

```

> string_db <- STRINGdb$new( score_threshold=400, backgroundV = backgroundV )

```

Once the background has been set, the enrichment results can change substantially because the statistical test is now performed against the selected background rather than the whole proteome. In many cases the enrichment signals become smaller, which is expected: the test is now calibrated against the proteins that were actually measurable or considered in the experiment, rather than against all proteins in the organism.

```

> enrichment_background_corrected <- string_db$get_enrichment( hits )
> head(enrichment_background_corrected, n=20)

```

	category	term	number_of_genes	number_of_genes_in_background
1	Process	GO:0006952	35	1298
2	PMID	PMID:39331229	6	8
	ncbiTaxonId			
1		9606		
2		9606		
1	9606.ENSP00000008938,9606.ENSP00000223642,9606.ENSP00000224337,9606.ENSP00000243611,9606.ENSP000002			
2				
1	PGLYRP1,C5,BLNK,C4BPB,C3,TYROBP,LGALS3BP,C6,VAMP8,ANXA3,MGLL,DEFB1,SERPINF2,PTPRCAP,CCR4,WFDC10B,SC			
2				
	p_value	fdr		
1	2.38e-06	0.0306		
2	5.45e-09	0.0197		
1				
2	(2024) Identification of BBC3 as a novel indicator for predicting prostate cancer development and c			

If you just want to know which terms are assigned to your set of proteins, and not necessarily which ones are enriched, you can use "get_ annotations" method. This method outputs the terms from most categories (the exceptions are KEGG terms due to licensing issues and PubMed due to the size of the output) that are associated with your set of proteins.

```
> annotations <- string_db$get_ annotations( hits )
> head( annotations, n=20)
```

	category	term_id	number_of_genes	ratio_in_set	species
1	COMPARTMENTS	GOCC:0000109	1	0.005	9606
2	COMPARTMENTS	GOCC:0000139	1	0.005	9606
3	COMPARTMENTS	GOCC:0000151	2	0.010	9606
4	COMPARTMENTS	GOCC:0000152	1	0.005	9606
5	COMPARTMENTS	GOCC:0000228	1	0.005	9606
6	COMPARTMENTS	GOCC:0000307	1	0.005	9606
7	COMPARTMENTS	GOCC:0000323	6	0.030	9606
8	COMPARTMENTS	GOCC:0000502	1	0.005	9606
9	COMPARTMENTS	GOCC:0000785	2	0.010	9606
10	COMPARTMENTS	GOCC:0000786	1	0.005	9606
11	COMPARTMENTS	GOCC:0000791	1	0.005	9606
12	COMPARTMENTS	GOCC:0001533	1	0.005	9606
13	COMPARTMENTS	GOCC:0001650	1	0.005	9606
14	COMPARTMENTS	GOCC:0001669	1	0.005	9606
15	COMPARTMENTS	GOCC:0001725	2	0.010	9606
16	COMPARTMENTS	GOCC:0001726	2	0.010	9606
17	COMPARTMENTS	GOCC:0002133	1	0.005	9606
18	COMPARTMENTS	GOCC:0005576	42	0.210	9606
19	COMPARTMENTS	GOCC:0005577	1	0.005	9606
20	COMPARTMENTS	GOCC:0005579	3	0.015	9606

```
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18 9606. ENSP00000008938, 9606. ENSP00000216286, 9606. ENSP00000223642, 9606. ENSP00000243611, 9606. ENSP00000
19
20
```

```

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18 PGLYRP1,NID2,C5,C4BPB,C3,SERPINF1,THSD1,TUBB2B,LGALS3BP,C6,CSTA,ANXA3,ZP1,CA2,TIMP4,DEFB1,PSCA,SER
19
20

```

```

description
1      Nucleotide-excision repair complex
2      Golgi membrane
3      Ubiquitin ligase complex
4      Nuclear ubiquitin ligase complex
5      Nuclear chromosome
6 Cyclin-dependent protein kinase holoenzyme complex
7      Lytic vacuole
8      Proteasome complex
9      Chromatin
10     Nucleosome
11     Euchromatin
12     Cornified envelope
13     Fibrillar center
14     Acrosomal vesicle
15     Stress fiber
16     Ruffle
17     Polycystin complex
18     Extracellular region
19     Fibrinogen complex
20     Membrane attack complex

```

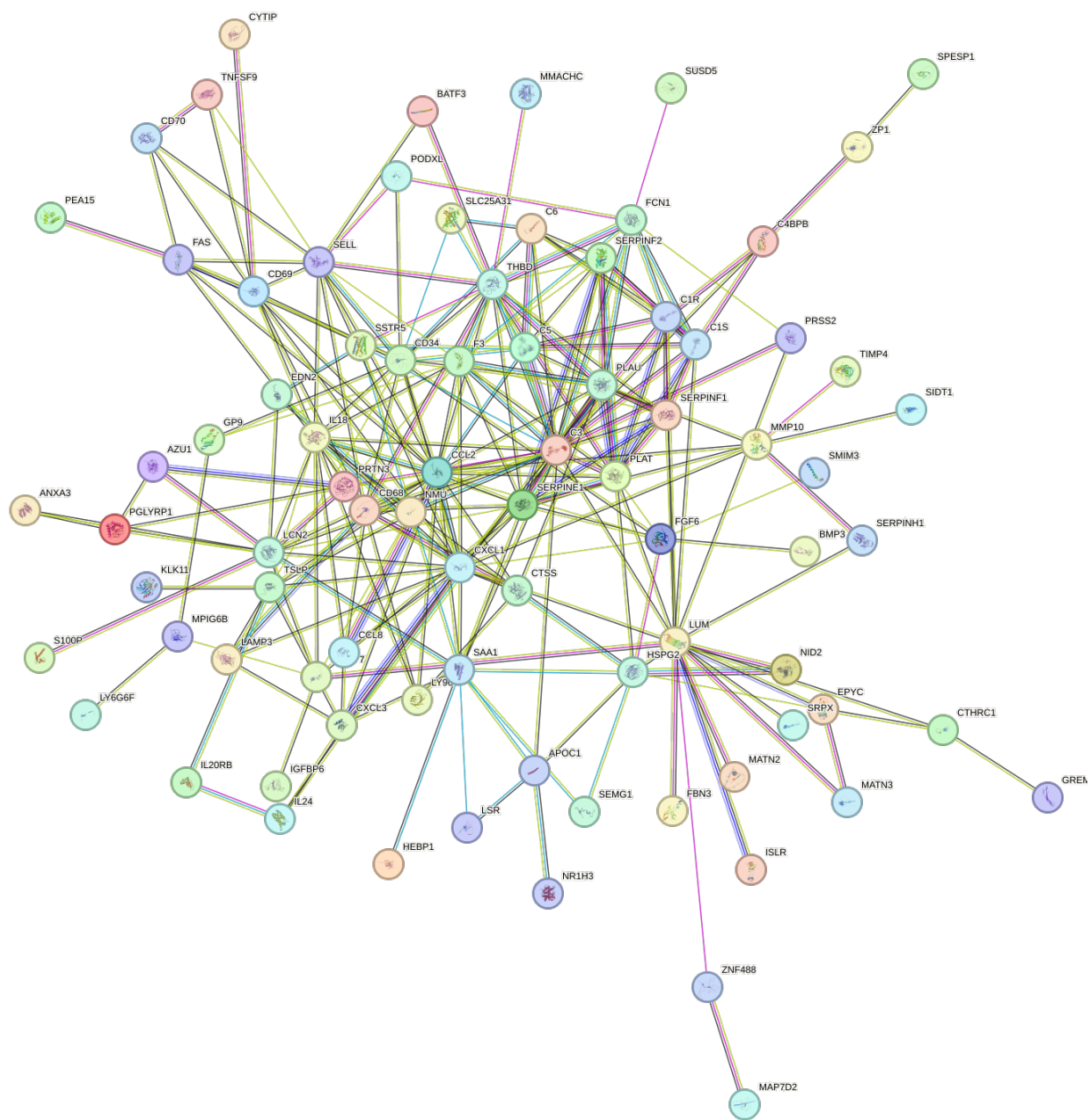
4 CLUSTERING

The iGraph package provides several clustering/community algorithms: "fastgreedy", "walktrap", "spinglass", "edge.betweenness". We encapsulate this in an easy-to-use function that returns the clusters in a list.

```
> # get clusters
> clustersList <- string_db$get_clusters(example1_mapped_pval05$STRING_id[1:600])
```

Now we visualize the first four clusters one by one.

```
> par(mar = c(0, 0, 0.5, 0))
> string_db$plot_network(clustersList[[1]], add_summary = FALSE)
> par(mar = c(0, 0, 0.5, 0))
> string_db$plot_network(clustersList[[2]], add_summary = FALSE)
> par(mar = c(0, 0, 0.5, 0))
> string_db$plot_network(clustersList[[3]], add_summary = FALSE)
> par(mar = c(0, 0, 0.5, 0))
> string_db$plot_network(clustersList[[4]], add_summary = FALSE)
```



5 ADDITIONAL PROTEIN INFORMATION

You can get a table that contains all the proteins that are present in our database of the species of interest. The protein table also includes the preferred name, the size and a short description of each protein.

```
> string_proteins <- string_db$get_proteins()
> head(string_proteins)
```

	protein_external_id	preferred_name	protein_size
1	9606.ENSP00000000233	ARF5	180
2	9606.ENSP00000000412	M6PR	277
3	9606.ENSP00000001008	FKBP4	459
4	9606.ENSP00000001146	CYP26B1	512
5	9606.ENSP00000002125	NDUFAF7	441
6	9606.ENSP00000002165	FUCA2	467

```
1
2
3
4
5
6
```

Peptidyl-prolyl cis-trans isomerase FKBP4, N-terminally processed; Immunophilin protein with PPIase
Cytochrome P450 26B1; Involved in the metabolism of retinoic acid (RA), rendering this classical mo

In the following section we will show how to query STRING with R on some specific proteins. In the examples, we will use the famous tumor proteins TP53 and ATM .

First we need to get the STRING identifier of those proteins, using our mp method:

```
> tp53 = string_db$mp( "tp53" )
> atm = string_db$mp( "atm" )
```

The mp method (i.e. map proteins) is an alternative to our map method, to be used when you need to map only one or few proteins.

It takes in input a vector of protein aliases and returns a vector with the STRING identifiers of those proteins.

You can retrieve the interactions that connect certain input proteins between each other.

The "get_interactions" method returns a data frame describing the interactions among the queried proteins. The table contains the STRING identifiers in the **from** and **to** columns, the corresponding preferred names in **from_name** and **to_name**, the **combined_score**, and any additional evidence scores available for the current **link_data** setting. This makes it easy to inspect both the interacting proteins and the supporting scores for each interaction.

```
> string_db$get_interactions( c(tp53, atm) )
```

	from	to	combined_score	from_name	to_name
1	9606.ENSP00000269305	9606.ENSP00000278616	999	TP53	ATM

	neighborhood	fusion	cooccurence	coexpression	experimental	database	textmining
1	0	0	0	103	929	900	975

If you want to retrieve the first-shell interaction partners of one or more proteins from the locally loaded graph, you can use the "get_interaction_partners" method.
The output keeps the same interaction-table structure as "get_interactions".

```
> string_db$get_interaction_partners( c(tp53, atm), limit=5 )[ , c("from", "to", "combined_score", "experimental") ]
```

	from	to	combined_score	experimental
30659	9606.ENSP00000269305	9606.ENSP00000212015	999	887
195401	9606.ENSP00000269305	9606.ENSP00000254719	999	982
219212	9606.ENSP00000269305	9606.ENSP00000258149	999	999
270101	9606.ENSP00000269305	9606.ENSP00000262367	999	998
286703	9606.ENSP00000269305	9606.ENSP00000263253	999	999
121197	9606.ENSP00000278616	9606.ENSP00000233146	999	324
126836	9606.ENSP00000278616	9606.ENSP00000234420	999	324
336588	9606.ENSP00000278616	9606.ENSP00000265433	999	990
363176	9606.ENSP00000278616	9606.ENSP00000269305	999	929
401207	9606.ENSP00000278616	9606.ENSP00000325863	999	907

	from_name	to_name
30659	TP53	SIRT1
195401	TP53	RPA1
219212	TP53	MDM2
270101	TP53	CREBBP
286703	TP53	EP300
121197	ATM	MSH2
126836	ATM	MSH6
336588	ATM	NBN
363176	ATM	TP53
401207	ATM	MRE11

You can also output only interactions supported by a particular type of evidence. Here we retrieve only experimentally supported interactions, keeping only the protein names together with the experimental score:

```
> interaction_partners_exp <- string_db$get_interaction_partners( c(tp53, atm), limit=5 )
> interaction_partners_exp <- subset(interaction_partners, experimental > 0,
+                                   select = c("from_name", "to_name", "experimental"))
> interaction_partners_exp
```

	from_name	to_name	experimental
30659	TP53	SIRT1	887
195401	TP53	RPA1	982
219212	TP53	MDM2	999
270101	TP53	CREBBP	998
286703	TP53	EP300	999
121197	ATM	MSH2	324
126836	ATM	MSH6	324

336588	ATM	NBN	990
363176	ATM	TP53	929
401207	ATM	MRE11	907

STRING provides a way to get homologous proteins: in our database we store ALL-AGAINST-ALL alignments within species. You can retrieve all paralogs of the protein using "get_paralogs" method.

```
> # Get all homologs of TP53 in human.
> string_db$get_paralogs(tp53)
```

	ncbiTaxonId_A	stringId_A	ncbiTaxonId_B	stringId_B
1	9606	9606.ENSPPAP000000269305	9606	9606.ENSPPAP000000269305
	bitscore			
1	815.8			

STRING also stores best hits (as measured by bitscore) between proteins from different species. "get_homologs_bests" lets you retrieve these homologs.

```
> # get the best hits of TP53 in all STRING species
> tp53_bests <- string_db$get_homologs_bests(tp53)
> tp53_bests_100 <- subset(tp53_bests, bitscore > 100)
> nrow(tp53_bests_100)
```

```
[1] 318
```

```
> head(tp53_bests_100, n=10)
```

	ncbiTaxonId_A	stringId_A	ncbiTaxonId_B	stringId_B
1	9606	9606.ENSPPAP000000269305	9597	9597.ENSPPAP00000011040
2	9606	9606.ENSPPAP000000269305	9598	9598.ENSPPAP00000014836
3	9606	9606.ENSPPAP000000269305	9606	9606.ENSPPAP000000269305
4	9606	9606.ENSPPAP000000269305	9601	9601.ENSPPAP00000008923
5	9606	9606.ENSPPAP000000269305	61621	61621.ENSPPAP00000028632
6	9606	9606.ENSPPAP000000269305	61622	61622.ENSPPAP00000026843
7	9606	9606.ENSPPAP000000269305	591936	591936.ENSPPAP00000010553
8	9606	9606.ENSPPAP000000269305	60711	60711.ENSPPAP00000007551
9	9606	9606.ENSPPAP000000269305	9541	9541.ENSPPAP00000038526
10	9606	9606.ENSPPAP000000269305	9544	9544.ENSPPAP00000011334
	bitscore			
1	815.8			
2	815.8			
3	815.8			
4	799.3			
5	786.6			
6	786.6			
7	785.8			

```

8      785.0
9      783.9
10     783.9

```

... or you can specify the species of interest:

```

> # get the homologs of the following two proteins in the mouse (i.e. species_id=10090)
> string_db$get_homologs_besthits(c(tp53, atm), target_species_id=10090)

```

	ncbiTaxonId_A	stringId_A	ncbiTaxonId_B	stringId_B
1	9606	9606.ENSP00000278616	10090	10090.ENSMUSP00000156344
2	9606	9606.ENSP00000269305	10090	10090.ENSMUSP00000104298

	bitscore
1	5328.8
2	598.2

6 CITATION

Please cite:

Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, Gable AL, Fang T, Doncheva NT, Pyysalo S, Bork P, Jensen LJ, von Mering C. The STRING database in 2023: protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Res.* 2023 Jan 6;51(D1):D638-D646. doi: 10.1093/nar/gkac1000.