

STRINGdb Package Vignette

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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_d
```

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"                    "get_aliases"
[13] "get_annotations"         "get_bioc_graph"
[15] "get_clusters"            "get_enrichment"
[17] "get_enrichment_figure"   "get_graph"
[19] "get_homologs"            "get_homologs_besthits"
[21] "get_homology_graph"      "get_interaction_partners"
[23] "get_interactions"        "get_link"
[25] "get_neighbors"           "get_paralogs"
[27] "get_pathways_benchmarking_blackList" "get_png"
[29] "get_ppi_enrichment"      "get_ppi_enrichment_full"
[31] "get_proteins"            "get_pubmed"
[33] "get_pubmed_interaction"  "get_subnetwork"
[35] "get_summary"             "get_term_proteins"
[37] "getClass"                "getRefClass"
[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
```

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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 Revestarol has been performed and compared to a control composed by A549 lung cancer cells threatened 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 %).

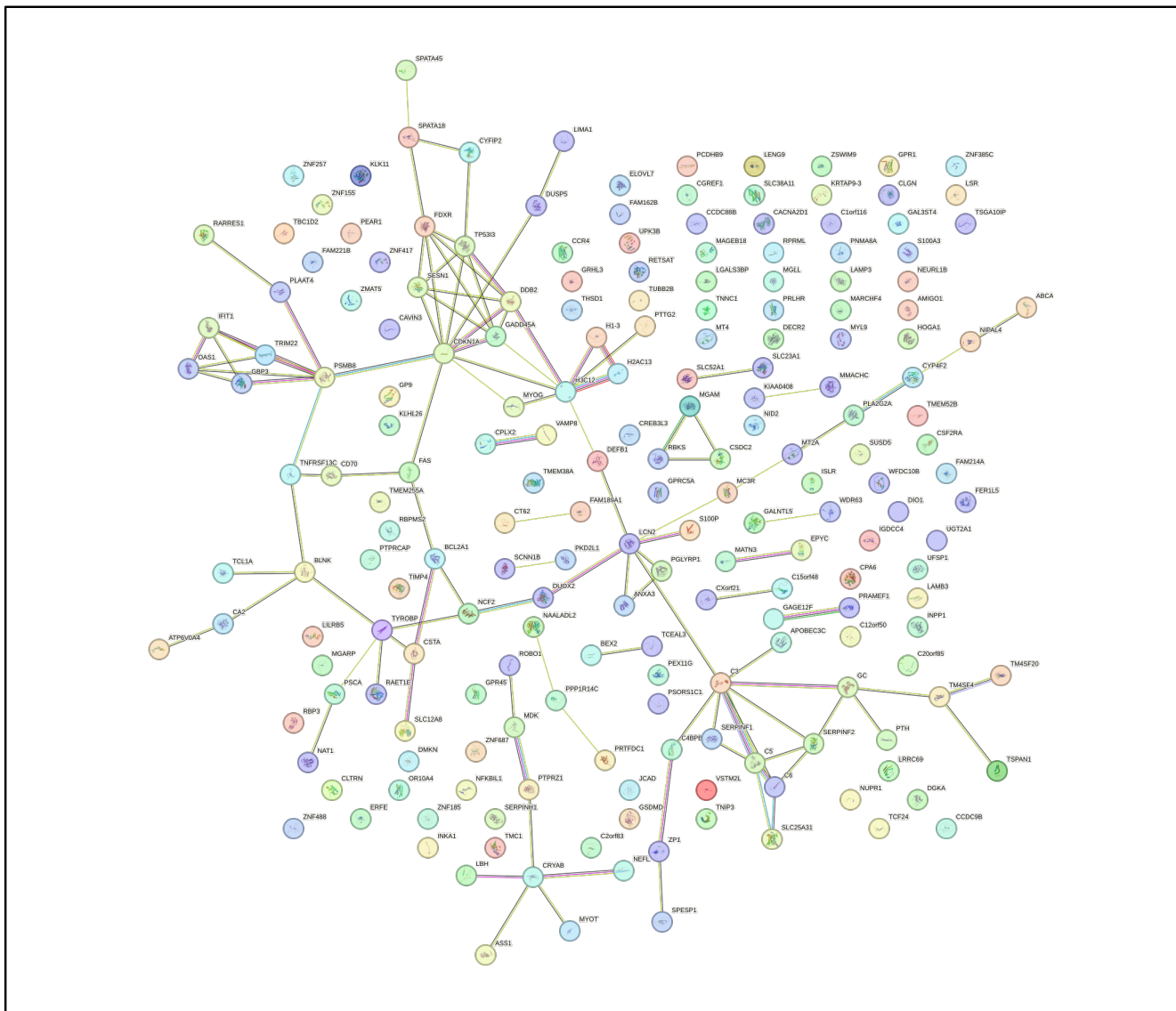
If you set to FALSE the "removeUnmappedRows" parameter, than the rows which corresponds to unmapped genes are left and you can manually inspect them.

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 )
```


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	BT0:0000392	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. ENSP00000008938, 9606. ENSP00000014914, 9606. ENSP00000187762, 9606. ENSP00000216286, 9606. ENSP00000  
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
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12
13

```

```

p_value    fdr
1 1.28e-05 0.0294
2 3.51e-05 0.0403
3 7.80e-07 0.0122
4 4.15e-05 0.0182
5 1.55e-05 0.0182
6 8.88e-06 0.0182
7 1.30e-04 0.0441
8 1.53e-05 0.0371
9 4.71e-05 0.0317
10 8.55e-05 0.0317
11 1.30e-04 0.0452
12 2.69e-09 0.0138
13 5.58e-05 0.0436

```

```

1
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10
11
12 (2024) Identification of BBC3 as a novel indicator for predicting prostate cancer development and
13 p53 transcri

```

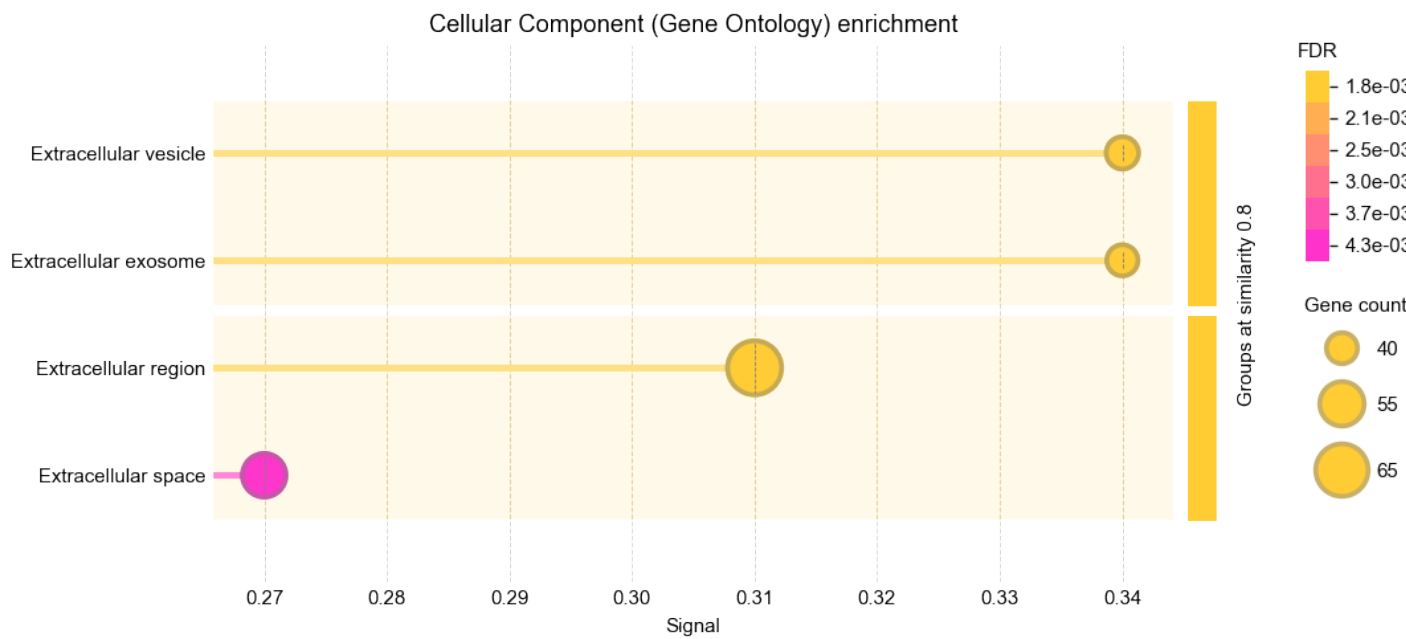
You can also retrieve an enrichment figure directly from STRING for a selected category. The image can be returned as a PNG array or as SVG markup, and you can customize the category, similarity-based grouping, color palette, the number of terms shown, and the variable displayed on the X-axis.

```

> 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 5fe05e6 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 5fe05e6 (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.ENSP00000000000			
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

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- 10
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- 15
- 16
- 17
- 18
- 19
- 20

9606. ENSP00000008938, 9606. ENSP00000216286, 9606. ENSP00000223642, 9606. ENSP00000243611, 9606. ENSP00000

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```

                                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", "springlass", "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 Peptidyl-prolyl cis-trans isomerase FKBP4, N-terminally processed; Immunophilin protein with PPIase
4 Cytochrome P450 26B1; Involved in the metabolism of retinoic acid (RA), rendering this classical mo
5
6
```

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	cooccurrence	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.ENSPO0000269305	9606.ENSPO0000212015	999	887
195401	9606.ENSPO0000269305	9606.ENSPO0000254719	999	982
219212	9606.ENSPO0000269305	9606.ENSPO0000258149	999	999
270101	9606.ENSPO0000269305	9606.ENSPO0000262367	999	998
286703	9606.ENSPO0000269305	9606.ENSPO0000263253	999	999
121197	9606.ENSPO0000278616	9606.ENSPO0000233146	999	324
126836	9606.ENSPO0000278616	9606.ENSPO0000234420	999	324
336588	9606.ENSPO0000278616	9606.ENSPO0000265433	999	990
363176	9606.ENSPO0000278616	9606.ENSPO0000269305	999	929
401207	9606.ENSPO0000278616	9606.ENSPO0000325863	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.ENSPO0000269305      9606 9606.ENSPO0000269305
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.ENSPO0000269305      9597 9597.ENSPPAP00000011040
2          9606 9606.ENSPO0000269305      9598 9598.ENSPTRP00000014836
3          9606 9606.ENSPO0000269305      9606      9606.ENSPO0000269305
4          9606 9606.ENSPO0000269305      9601 9601.ENSPPYP00000008923
5          9606 9606.ENSPO0000269305      61621 61621.ENS RBIP00000028632
6          9606 9606.ENSPO0000269305      61622 61622.ENSRR0P00000026843
7          9606 9606.ENSPO0000269305      591936 591936.ENSPT0P00000010553
8          9606 9606.ENSPO0000269305      60711 60711.ENS SCAP00000007551
9          9606 9606.ENSPO0000269305      9541 9541.ENS MFAP00000038526
10         9606 9606.ENSPO0000269305      9544 9544.ENS MMUP00000011334
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.