OmicInt Package: exploring omics data and regulatory networks using integrative analyses and machine learning

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```
library(OmicInt)
```

1. Package Overview

OmicInt is an R package developed for an in-depth exploration of significantly changed genes, gene expression patterns, and associated epigenetic features as well as the related miRNA environment. The package helps to assess gene clusters based on their known interactors (proteome level) using several different resources, e.g., UniProt [1] and STRING DB [2]. Moreover, *OmicInt* provides an easy Gaussian mixture modelling [3,4] pipeline for an integrative analysis that can be used by a non-expert to explore gene expression data. Specifically, the package builds on a previously developed method to explore gene networks using significantly changed genes, their log-fold-change values (LFC), and the predicted interactome complexity [5]. This approach can aid in studying specific gene networks, understanding cellular perturbation events, and exploring interactions that might not be easily detectable otherwise [5]. To this end, the package offers many different utilities to help researchers quickly explore their data in a user-friendly way where machine learning is made easily accessible to non-experts (Fig.1&2).

Before starting the analysis the user must ensure that the supplied data is in the right format. There are several different options to prepare a data frame (CSV format) that contains all the relevant experimental information (Fig.1; Eq.1-4). Depending on the selection, the downstream analyses will provide interactive graphs and maps (Fig.2).

The key analytical parameter in the machine learning pipeline and exploratory analyses is a specific score, namely LFC_{score}, which can have a different derivation depending on the selected parameters (Eq.1-3). The user has several options to select from since the equations were expanded with additional data based on the earlier derivation of the multi-*omics* equation [5]. The score α values are downloaded automatically from curated database images which were generated via text mining to retrieve, update, and integrate data in an easier-to-use format (i.e., database image) for the analyses. Databases used include Disgenet [6], Uniprot [1], and STRING DB [2]. For example, α_{asoc} score allows to infer how strongly a gene is linked to a disease or pathological phenotype ranging from 0 (no link) to 1 (the strongest association) (Eq.1) [6]. Similarly, α_{spec} captures how specific a gene is when describing the pathology (Eq.2). Association scores are based on different curated resources as described earlier [6]. The user can choose from different types of scores ("association_score", "specificity_score", or the geometric mean of both) when selecting the type of the equation for LFC_{score}. Scores β_{cell} and γ_{prot} are scaled values for single cell and proteome data, respectively. That is, β_{cell} has to be provided by the user if they have such experimental information integrated where a gene value from a single cell data cluster is extracted using a pseudo-bulk differential gene expression approach. The LFC scores from pseudo-bulk data need to be scaled according to the equation 4. The same approach should be applied when calculating γ_{prot} for protein (corresponding gene) values.

$$LFC_{score} = LFC(1 + \alpha_{asoc} + \beta_{cell} + \gamma_{prot})$$

Equation 1. LFC_{score} equation where LFC - Log Fold Change, base 2; α_{asoc} - a disease association score; β_{cell} - scaled single cell LFC; γ_{prot} - scaled proteome LFC.

$$LFC_{score} = LFC(1 + \alpha_{spec} + \beta_{cell} + \gamma_{prot})$$

Equation 2. LFC_{score} equation where LFC - Log Fold Change, base 2; α_{spec} - a disease specificity score; β_{cell} - scaled single cell LFC; γ_{prot} - scaled proteome LFC.

$$LFC_{score} = LFC(1 + \sqrt{\alpha_{asoc} \cdot \alpha_{spec}} + \beta_{cell} + \gamma_{prot})$$

Equation 3. LFC_{score} equation where LFC - Log Fold Change, base 2; α_{asoc} and α_{spec} are integrated using a geometric average score; β_{cell} - scaled single cell LFC; γ_{prot} - scaled proteome LFC.

$$LFC_{scaled} = \frac{LFC_{gene}}{LFC_{median}}$$

Equation 4. β_{cell} or γ_{prot} scaling example where LFC_{gene} - a gene specific value and LFC_{median} - a median value for all available LFC values per specific condition and gene set.

OmicInt provides many other valuable tools to map the interactome using information on the target cellular location or protein class/function type. In addition, density functions allow for an in-depth assessment of gene distributions which may hint at potential functions or dominating processes within a specific condition. Epigenetic feature (CpG islands, GC%) and miRNA exploration tools also provide additional information on the epigenome and non-coding regulome which might be relevant for some genes and conditions, especially if a higher enrichment of these patterns can be found.
Currently, the analyses are only available for Human data sets.

2. Package functions and tutorial

2.1. Preprocessing

Data pre-processing relies on the *score_genes* function that collects data from STRINGDB [2] and disease association databases to scale and prepare additional score integration. Several key parameters should be provided; *data* parameter requires a data frame containing gene names as row names and a column with LFC values. The example is provided in Figure 1; parameter *alpha* has a default value set as “association” which gives a score from 0 to 1 based on how strongly a gene is associated with a pathological phenotype; other options are “specificity” - to give values based on how specific a gene is when describing a disease and “geometric” - to give a geometric mean score of both association and specificity. In addition, it is possible to add weighted single cell and proteomics data by selecting additional parameters. Parameter *beta* is set to have a default value as FALSE; if TRUE, please supply data with a column *beta* that contains information on gene associations from single cell studies. Similarly, parameter *gamma* has a default value FALSE; if TRUE, the user needs to supply data with a column *gamma* that contains information on gene associations from proteome studies.

The function returns a data frame for the downstream analyses.

Example table with only LFC values

	A	B	C
1	Symbol	log2FoldChange	pvalue
2	SAR1A	-2.18777269502012	2.65652091646361E-05
3	C6orf62	-2.6742131704395	1.691567369484E-07
4	AXL	-2.78650785919511	0.000173959539412
5	BICC1	-3.59855326113771	0.00027388866015
6	CAPZA1	-1.73278403064529	0.000232183462116
7	TXNIP	1.46062912017625	7.347204828615 1E-05
8	HNRNPH1	-1.81995372081358	0.000592319156385
9	RAB31	-1.79837938364367	0.00041973140141
10	UBE2B	-2.06138280667398	0.000125275768063
11	PAFAH1B2	-1.56007182816026	0.001391919840109
12	EIF2S3	-1.74298250448705	0.001063319998638
13	YWHAG	-1.55076880524874	0.000815638927099
14	ENAH	-1.69808760167615	0.000269611887499
15	PPP3CA	-2.67216823748962	3.98459567587323E-06

Example table with LFC, beta, and gamma values

	A	B	C	D	E
1	Symbol	log2FoldChange	pvalue	beta	gamma
2	SAR1A	-2.18777269502012	2.656520916463 61E-05	0.25	0
3	C6orf62	-2.6742131704395	1.6915673694844E-07	0	0.3
4	AXL	-2.78650785919511	0.000173959539412	0	0.56
5	BICC1	-3.59855326113771	0.00027388866015	0	0
6	CAPZA1	-1.73278403064529	0.000232183462116	0.4	0
7	TXNIP	1.46062912017625	7.347204828615 1E-05	0	0.75
8	HNRNPH1	-1.81995372081358	0.000592319156385	0	0
9	RAB31	-1.79837938364367	0.00041973140141	0	0.02
10	UBE2B	-2.06138280667398	0.000125275768063	0.41	0
11	PAFAH1B2	-1.56007182816026	0.001391919840109	0	0
12	EIF2S3	-1.74298250448705	0.001063319998638	0.7	0
13	YWHAG	-1.55076880524874	0.000815638927099	0.8	0
14	ENAH	-1.69808760167615	0.000269611887499	0	0.015
15	PPP3CA	-2.67216823748962	3.98459567587323E-06	0	0

Metadata file example

	A	B
1	Sample_ID	Condition
2	CAD1	hypertension
3	CAD2	hypertension
4	CAD3	hypertension
5	CAD4	hypertension
6	CAD5	hypertension
7	CAD6	hypertension
8	CAD10	hypertension
9	CAD11	hypertension
10	N10	healthy
11	N12	healthy
12	N13	healthy
13	N14	healthy
14	N15	healthy
15	RF2	CKD

Normalised count table example

	A	B	C	D	E	F
1	Symbol	CAD1	CAD2	CAD3	CAD4	CAD5
2	MT-CYB	9384.55930132127	11923.5039503911	34985.4747081763	4216.00298751307	12402.4413183367
3	MT-ND4	10934.2964538035	12360.328040959	24509.2381415289	5360.27179089838	12871.5303032926
4	MT-CO1	9722.28571644071	11516.7510834493	12963.1580920346	5587.18655703799	11594.0474618033
5	MT-CO3	8205.9264136993	10957.0042717434	17443.7581673424	5740.20990972336	13001.3144166671
6	FN1	192.371263022342	249.538399563515	211.313998100786	748.609107229636	466.544198419069
7	COL1A2	138.536021504896	178.317080449193	135.124152051885	504.138579737424	331.670511967011
8	ACTB	777.02198590181	690.05544741877	1249.03562947764	1889.20954257112	2393.7958689793
9	MT-ATP6	6347.89277812717	7713.00507741775	11965.5224075336	3373.85049516584	7503.72723493652
10	MT-CO2	5702.58768313804	4504.35275998582	8569.36665664999	1882.92091163884	5782.60327385963
11	MT-ND1	6299.08215915135	9499.34127387032	10046.9718242743	4573.4068454974	11624.5849002453
12	MT-ND5	3404.89957517343	3910.3142020397	5409.21359962516	2197.61448454146	2744.12814888307
13	MALAT1	6320.61625575833	6583.48771279727	2876.10032088432	2196.56637938608	3348.09082029103
14	SAR1A	3043.84455539642	4617.25173991519	9943.43858399882	3869.86625994907	4469.49342085468
15	MT-ND4L	2144.79602205507	3601.68848587763	3118.47429106776	1752.16979350528	3407.46917281709

Figure 1. Required data format expamples for the normalised gene expression values, LFC values, and the meta data file.

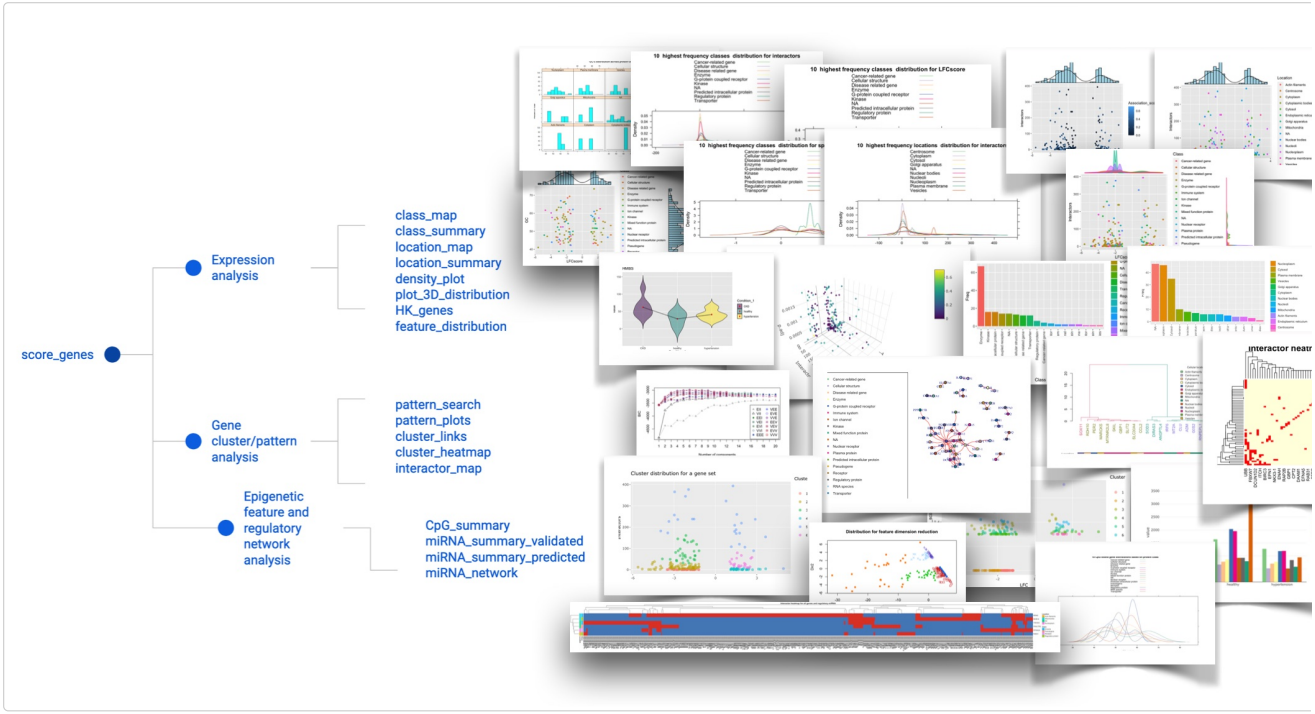


Figure 2. Schematic representation of package functions and specific analyses.

```
#data<-score_genes("data.csv")
#head(data)

#   Symbol log2FoldChange       pvalue Interactors Association_score
#1   SAR1A      -2.187773 2.656521e-05          24         0.0000000
#2 C6orf62      -2.674213 1.691567e-07           0         0.0000000
#3     AXL      -2.786508 1.739595e-04           2         0.3230769
#4   BICC1      -3.598553 2.738887e-04           3         0.3000000
#5  CAPZA1      -1.732784 2.321835e-04          66         0.3789474
#6   TXNIP       1.460629 7.347205e-05          30         0.3000000
#  Specificity_score  LFCscore
```

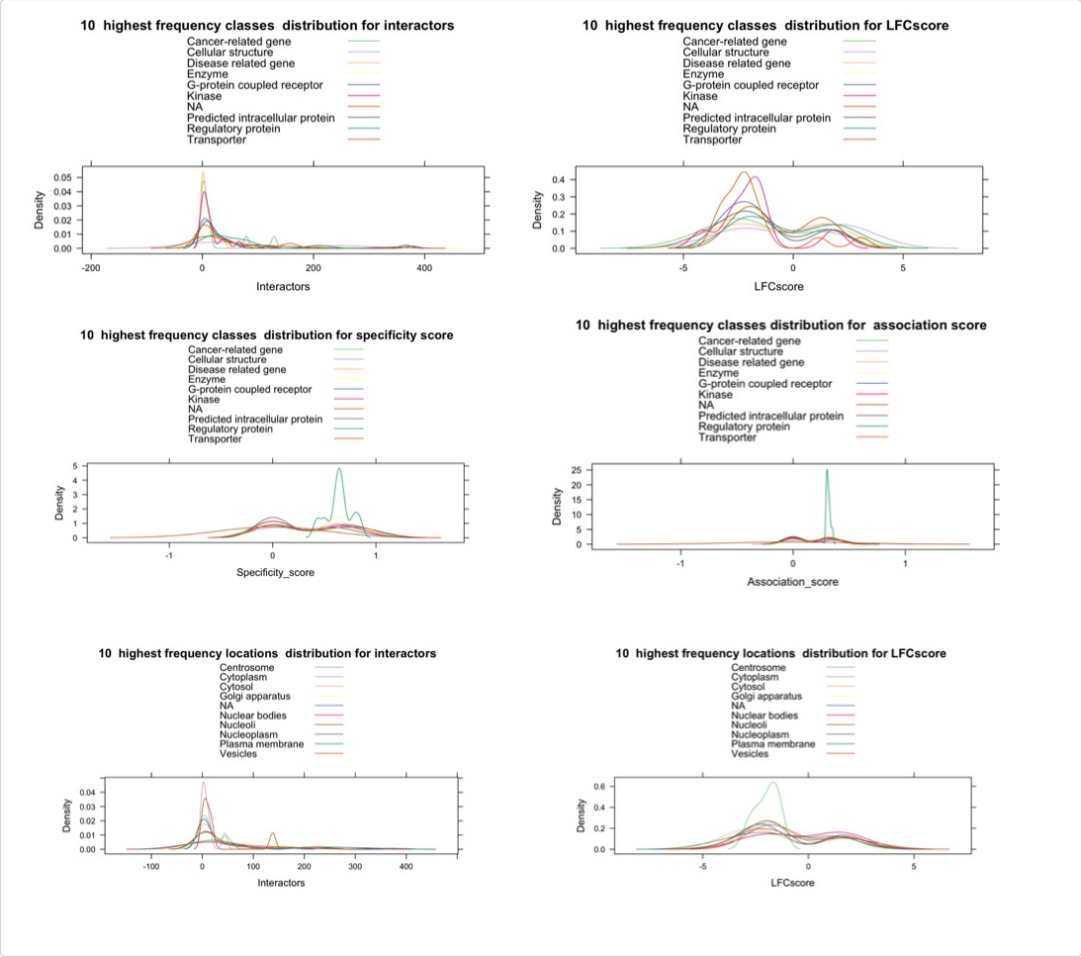
```
#1            0.000 -2.187773
#2            0.000 -2.674213
#3            0.590 -3.686764
#4            0.751 -4.678119
#5            0.601 -2.389418
#6            0.631  1.898818
```

2.2. Expression overview and exploratory analyses

Function *density_plot* plots a density plot for gene expression data prepared by the *score_genes* function. The plots can be used for a quick assessment of the overall parameters.

The plots allow the evaluation of how hey parameters, such as LFC, LFC_{score}, and disease association or specificity scores, associate with the highest frequency protein classes and cellular locations. For example, the most frequent protein classes may have specific distribution patterns hinting at cellular processes. Similarly, examining distributions for cellular locations might highlight the most involved and/or affected cellular strictures.

```
#density_plot(data)
```

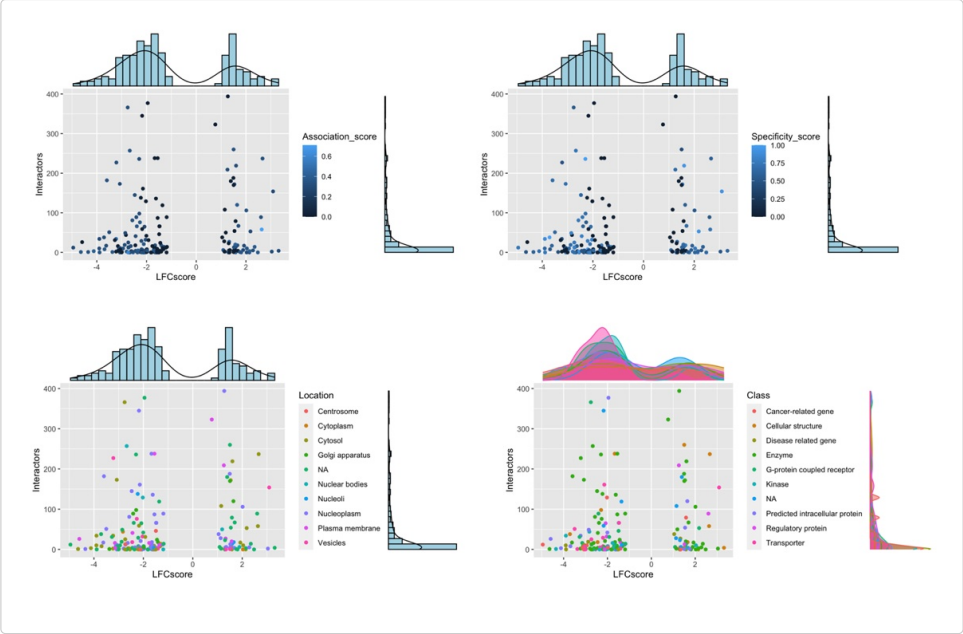


Density plot examples.

Function *feature_distribution* also provides a way to visualise main feature distributions through density plots combined with LFC_{score} and interactor number scatter plots. These plots allow to quickly assess if there are any dependencies between LFC_{score} and the interactor numbers. These plots also help to see if any obvious gene clusters emerge.

The function might issue a warning if the data points were missing or too few for density plotting; however, it does not affect the overall visualisation.

```
#feature_distribution(data)
```

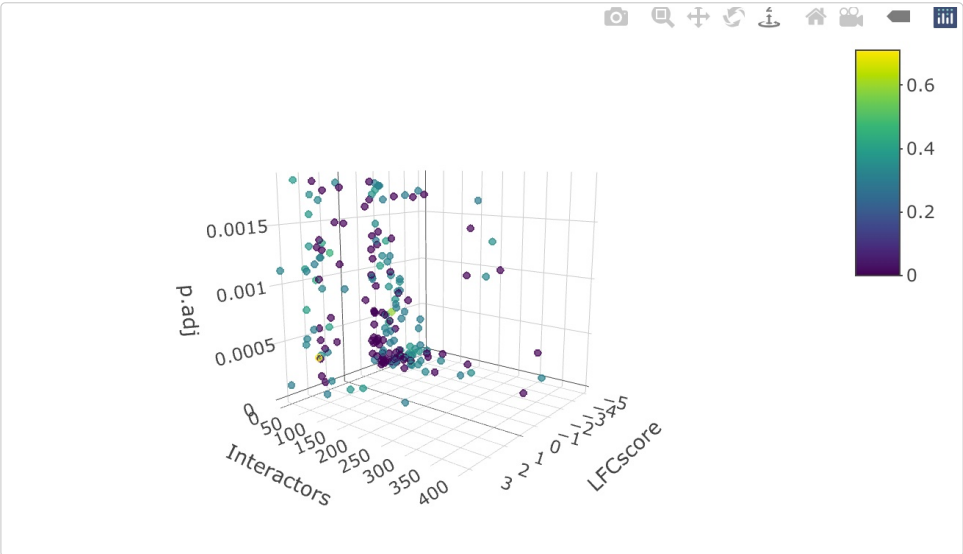


Feature distribution plot examples.

Function *plot_3D_distribution* allows to explore 3D distribution between the number of interactors, LFC_{score} and p.adj values. In addition to providing a data parameter, the user can select how to color data points depending on association or specificity score (e.g., selecting “specificity”)

This analysis can help identify specific clusters for the expression patterns and interactors based on the significance of how the gene expression changed in a given condition. In addition, coloring based on gene association or specificity in the context of diseases can help capture additional patterns in the data.

```
#plot_3D_distribution(data)
```

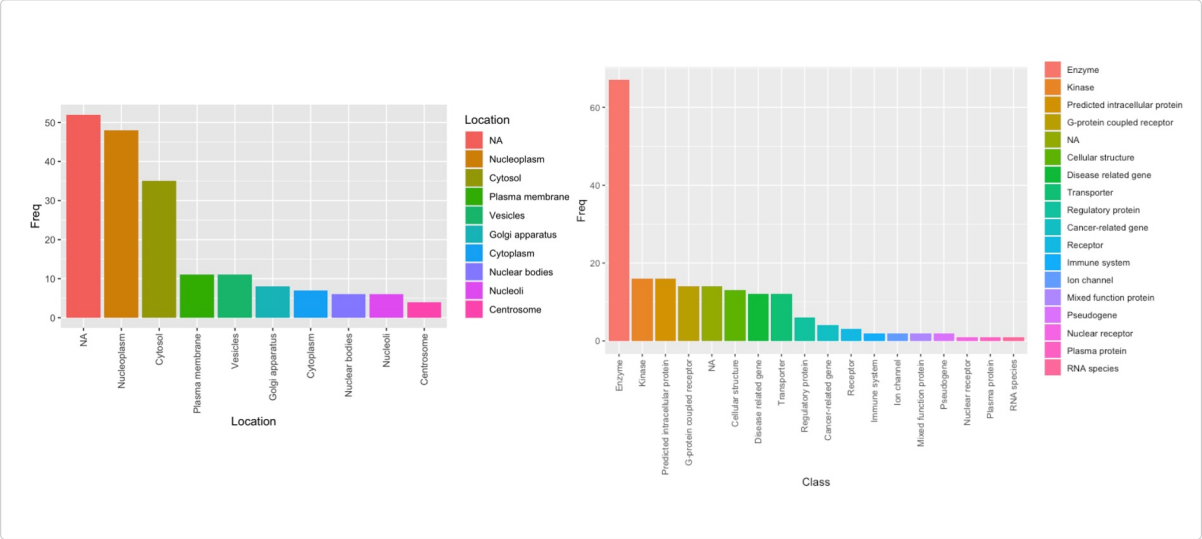


Interactive 3D feature distribution.

Function *class_summary* provides analysis on main protein classes where a barplot helps to visualise the class distribution. Similarly, the function *location_summary* summarises the location distribution data.

```
#class_summary(data)
```

```
#location_summary(data)
```



Location and class summary plots.

Function *location_map* allows the visualisation of how the highest and lowest LFC_{score} genes cluster based on the protein cellular location data. The user can specify the number of the top and lowest genes to consider. The function returns a dendogram generated based on LFC_{score}. The “euclidean” method is used for distance calculation and the “Ward.D2” method - for hclust generation.

Gene labels are colored to indicate major clusters where the hclust generated cluster number is doubled. In addition, to achieve a finer separation of lower dendogram branches the following equation is used to set the height for the color differentiation of different branches (Eq.5). This equation takes the mean value for hclust function height calculation and multiplies by the dendrogram cluster number scaled twice.

The plot also provides cellular location visualisation for each gene (Fig.3).

$$H_{dendogram} = \frac{hclust_{height}}{hclust_{n}} \cdot dendogram_{cluster\_number} \cdot 2$$

Equation 5.The height calculation for the color differentiation of different dendogram branches.

```
#location_map(data)
```

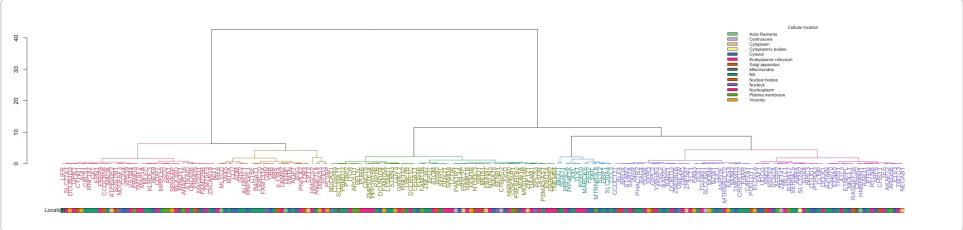


Figure 3. Dendogram with mapped cellular locations where coloured gene symbols represent the identified clusters and coloured branches show smaller subclusters.

Similarly, the function *class_map* provides a visualisation of how the highest and lowest LFC_{score} genes cluster based on protein class. In addition to a data frame generated by *score_genes*, the function also requires a *num* parameter to specify the number of genes to consider from the top upregulated and downregulated genes, if this option is not selected all genes will be used (Fig.4).

```
#class_map(data)
```

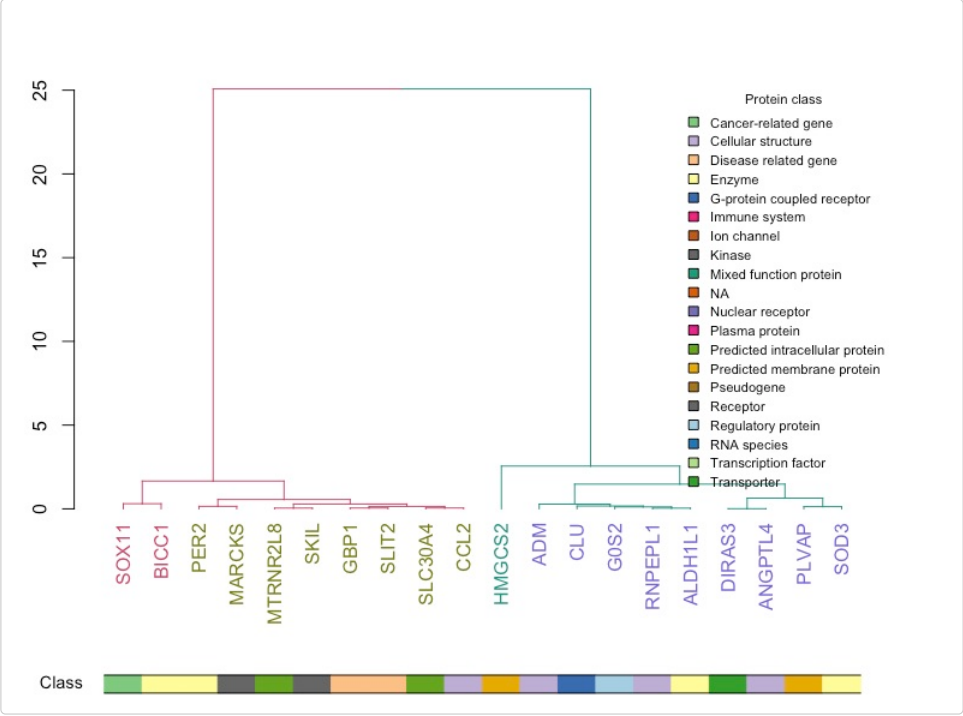


Figure 4.Dendogram with mapped protein functions where coloured gene symbols represent the identified clusters and coloured branches show smaller subclusters.

HK_genes function provides a convenient overview of the house keeping genes and allows to check if these genes varied throughout conditions. Depending on the number of conditions separate plots will be generated (Fig.5). Inspecting housekeeping genes can help understand if there was any significant variation between samples groups which might have arisen from biological or technical variation.

```
#HK_genes(data)
```

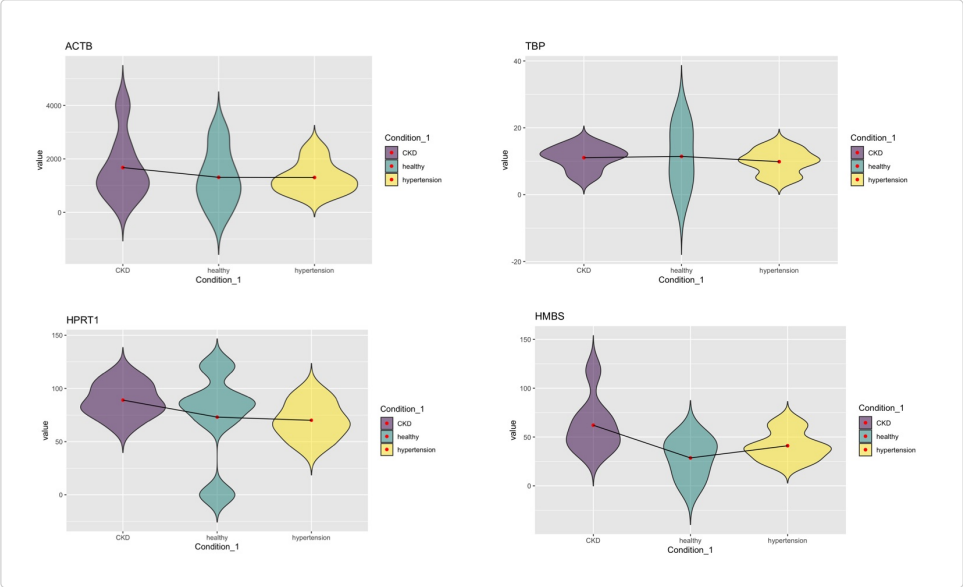


Figure 5. House keeping gene distribution example. The red marker indicates the mean for the group and violin plots allow to assess global distribution patterns.

2.3. Cluster analyses

Function *cluster_genes* helps to select an optimal number of clusters and a model to be fitted during the EM phase of clustering for Gaussian mixture models (GMM). The function provides summaries and helps to visualise gene clusters based on generated data using *score_genes* function. Weighted gene expression is clustered based on the interactome complexity, i.e., the number of known interactors according to STRING DB [2], with a cutoff of 700 for the score threshold. The function also provides scatter and dimension reduction plots to analyse the clusters and features in your data.

Required parameters include a data data frame containing a processed expression file from *score_genes* with LFC_{score} and a *max_range* number for cluster exploration during model selection (the default value is 20 clusters). The *clusters* parameter can be provided for the number of clusters to test when the cluster number estimation is not based on the best BIC output (user then also needs to supply *modelNames*). The *modelNames* parameter can only be supplied when the *clusters* value is also specified. This option will model based on the user parameters.

The function not only provides a summarised modelling output and plots but also returns a data frame with assigned clusters which can be used by more advanced users in other machine learning pipelines or data comparison studies.

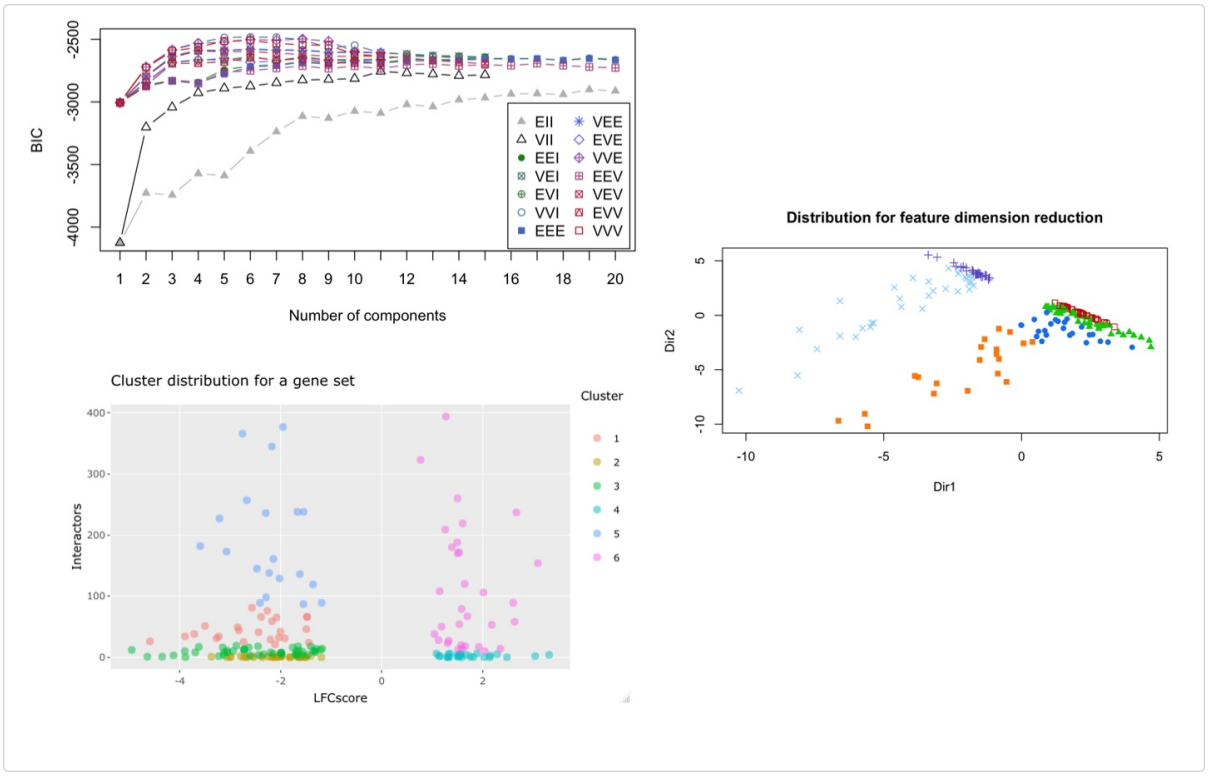
The user is advised to set seed before using the function to get reproducible results.

```
#model_report<-cluster_genes(data)

#head(model_report)
```

```
#Best BIC values:
#             VVI,6        VVI,7        VVI,5
#BIC      -2481.986 -2483.544400 -2485.429861
#BIC diff     0.000    -1.558131    -3.443592
```

```
#       Interactors  LFCscore Cluster Symbol
#CAPZA1          66 -2.389418       1 CAPZA1
#RAB31            0 -2.542398       2  RAB31
#UBE2B            2 -2.061383       2  UBE2B
#YWHAG           21 -2.111448       1  YWHAG
#ENAH            29 -2.207514       1   ENAH
#PPP3CA          51 -3.500322       1 PPP3CA
```



GMM analysis examples.

Function *cluster_links* provides the same Gaussian mixture modeling pipeline as *cluster_genes*; however, instead of the interactor number clustering, the user can select a specific disease score *type* (default “association”). This parameter can define either the association or specificity for a disease, i.e., if the gene has known links to disease phenotypes and how specific it is when describing a pathology.

The functions also provide scatter and dimension reduction plots to analyse the clusters and features in the data.

An additional output is a model report summarising the cluster assignments which can be used in other modelling analyses.

Function *pattern_search* explores the occurrences of specific patterns in gene sets, specifically it searches each condition under investigation for emerging patterns (e.g., if multiple conditions are provided) to group genes that changed in a similar manner.

The search algorithm works by first generating potential patterns to search depending on the number of subclasses. For example, if a condition has several subclasses as in the case example, where Condition 1 has a healthy group, hypertensive, and CKD patients. Then potential pattern scenarios are generated: “up-up-up” or “down-up-down”. Following this the overall expression for each gene is calculated using geometric mean across all conditions, this gives a basal line against which an individual gene expression value is weighed to deduce if it is in a ‘up’ or ‘down’ state.

Comparing against a baseline is a more universal approach rather than performing a pair wise comparisons which may not be effective for multiple subclasses or complex interactions. Averaging expression using a geometric mean method provides a baseline for comparisons taking into account all the extreme values which might result either from biological or technical effects. It is important to note that taking a geometric mean might not be optimal in all cases, but in a balanced experiment it should provide additional information for the downstream analyses.

The function returns a summary of how many genes are identified for each pattern type across conditions.

```
# "Condition subclasses"
#
#[1] "CKD"          "healthy"      "hypertension"
#
#pattern_search(data, meta)
#
#
#               Gene count
#down_down_down          0
#down_down_up         2679
#down_up_down          670
#down_up_up           1076
#up_down_down         5503
#up_down_up           2550
#up_up_down           2856
#up_up_up              361
```

The returned gene list contains groups of genes for the different types of patterns.

```
#$up_up_down
```

```
#   [1] "A4GALT"        "AASDHPPT"      "AATF"
#   [4] "ABCC11"        "ABCC9"         "ABCG2"
#   [7] "ABHD13"        "ABHD2"         "ABI3"
#  [10] "ABI3BP"        "ABITRAM"       "ABO"
```

This analysis can be followed by *pattern_plots* which allows to explore distributions for a selected pattern group. The user must provide a subsetted data frame and low/high parameters to select a specific range. The selection is needed because in some instances the expression values might differ significantly and visualising all data points will prevent exploring any meaningful subsets.

The outputs allow to evaluate how genes distribute in a subset for different conditions (Fig.6) and how individual gene values vary in a selected subgroup (Fig.7).

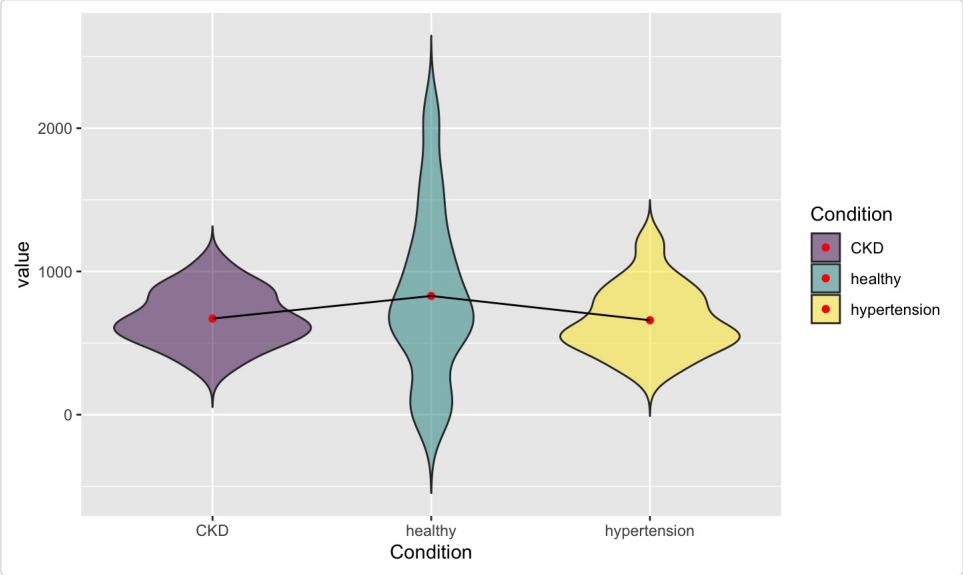


Figure 6. Gene distribution patterns for a specific expression pattern subset where mean values (signified with a red point) are connected to highlight the pattern features with respect to the mean value (the example is from a “down-up-down” pattern group).

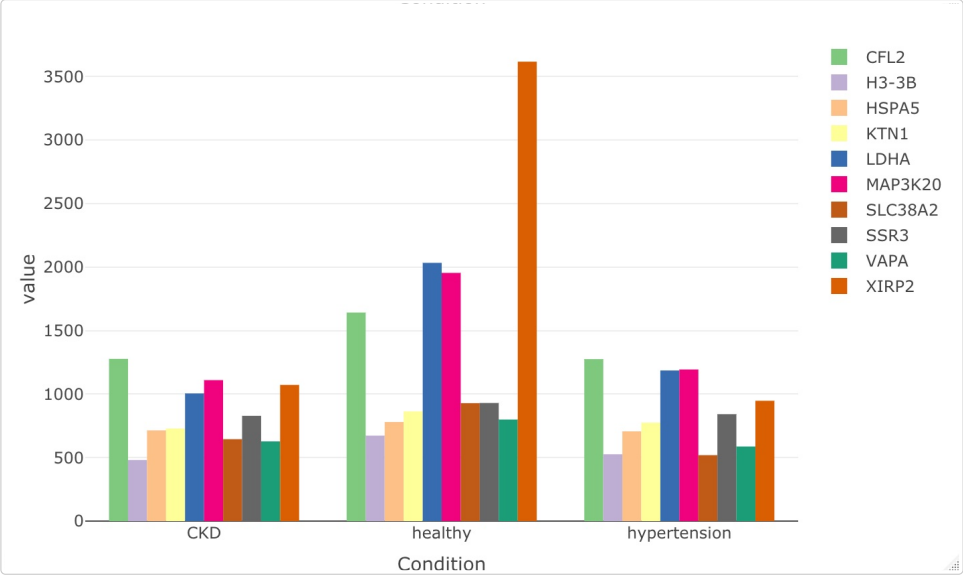


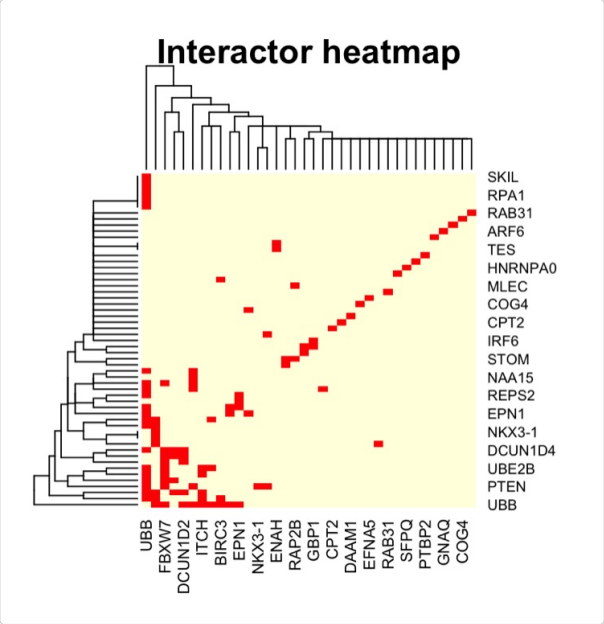
Figure 7. Individual gene distributions when selecting a specific expression pattern and range (the example is

from a “down-up-down” pattern group).

Function *cluster_heatmap* uses the information mined from the STRING database [2] to map experimental, referenced, and inferred interactions to see if there are any interactors in the set of significantly changed genes. This heatmap function provides a clustered visualisation of all the genes that have shared interactions.

This information allows to quickly assess how many genes in a condition that changed significantly might be part of the same regulatory cluster.

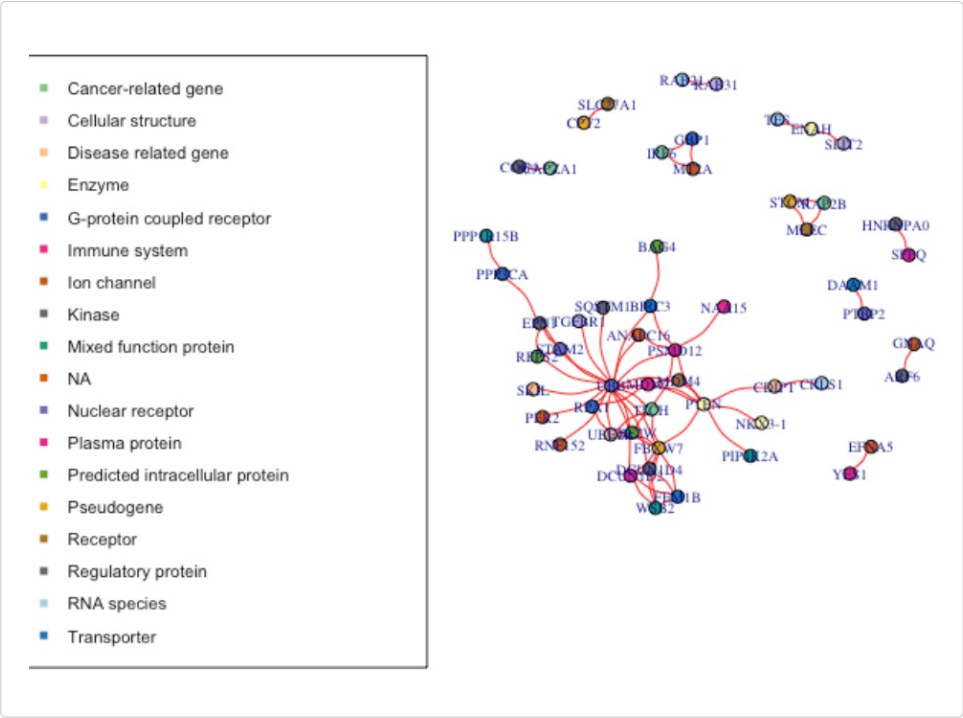
```
#cluster_heatmap(data)
```



Cluster heatmap examples.

Function *interactor_map* helps to visualise information mined from the STRING database [2] and map direct and referenced interactions to see if there are any interactors in the set of significantly changed genes and how they are linked.

```
#interactor_map(data)
```

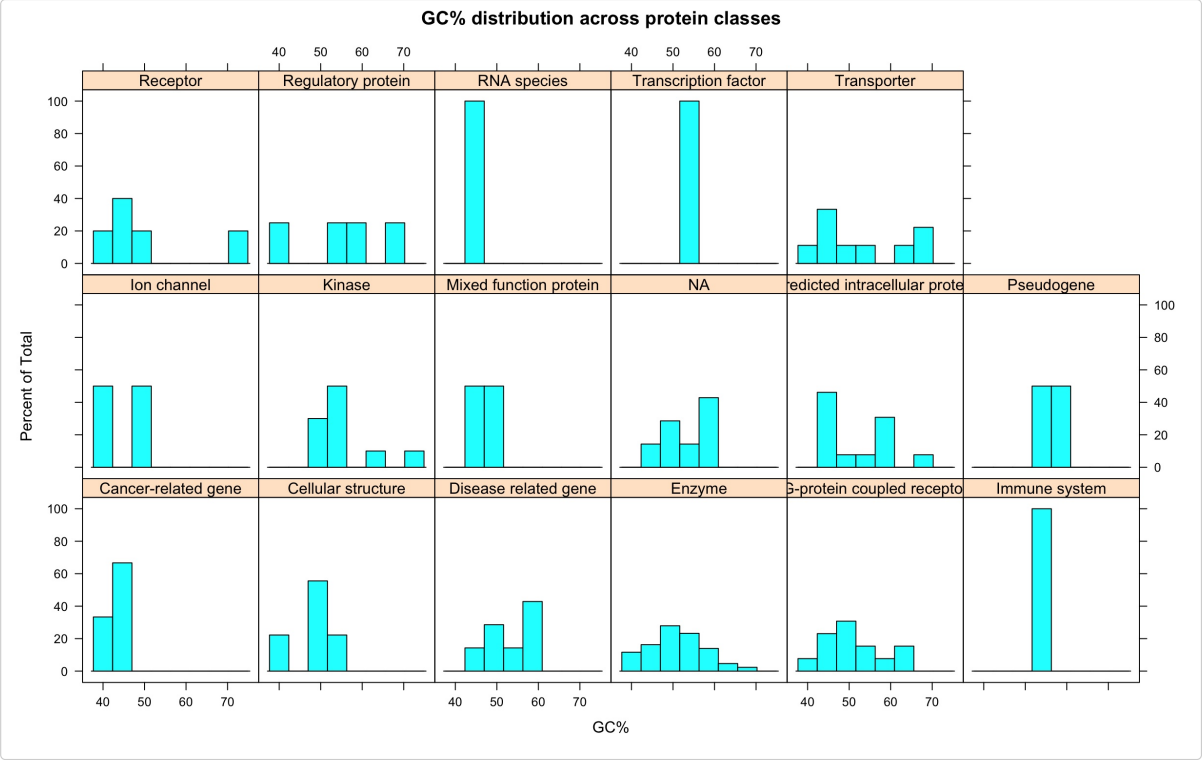


Interactor map examples.

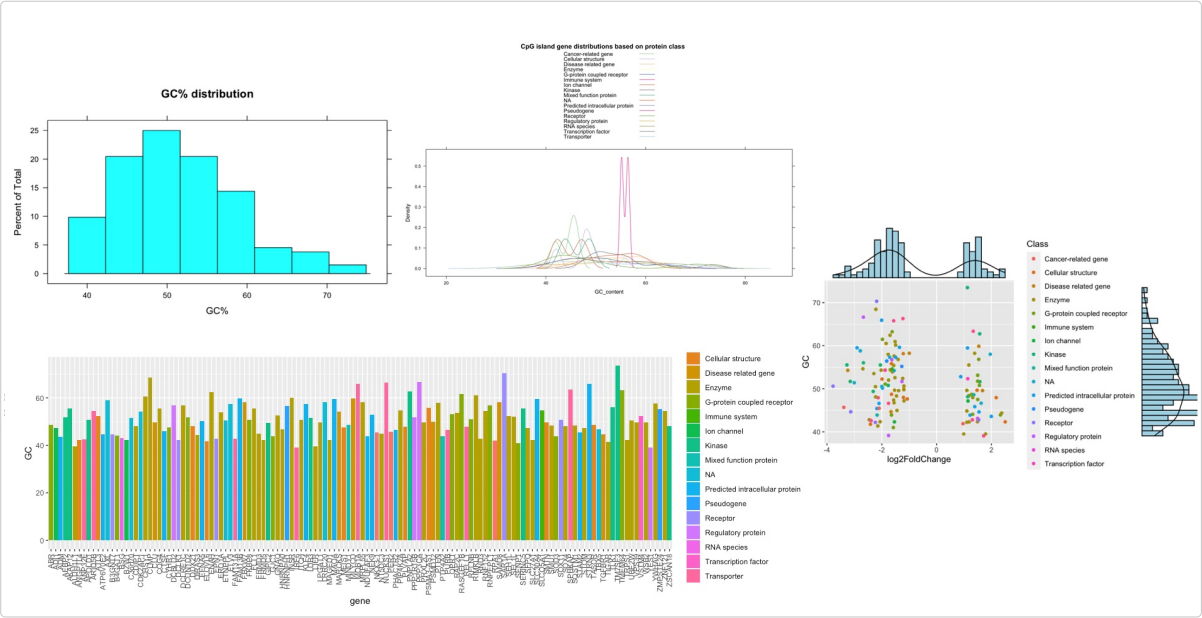
2.4. Epigenomics integration

Function *CpG_summary* provides information on the gene CpG island and GC content. The function checks genes against known CpG islands and provides various plots to assess emerging data features. CpG islands were retrieved from the data available with the Genome Reference Consortium (Human Build 38) [6], this information was cross-referenced with the Ensembl database [7] to retrieve overlaps between CpG islands and genes. The function provides a number of analytical plots to assess whether the CpG profile (via GC %) has any influence on the gene expression, interactor number, disease specificity, and disease associations. All this information is provided in the context of the assigned protein classes/functional groups. This analysis provides additional insights into the complex interplay between the genome, transcriptome, and epigenome. In addition, the function outputs a data table that contains genomic locations and gene information based on the Ensembl database so that the user can perform additional analyses.

```
#cpg_genes<-CpG_summary(data)
#head(cpg_genes)
```



CpG summary examples.



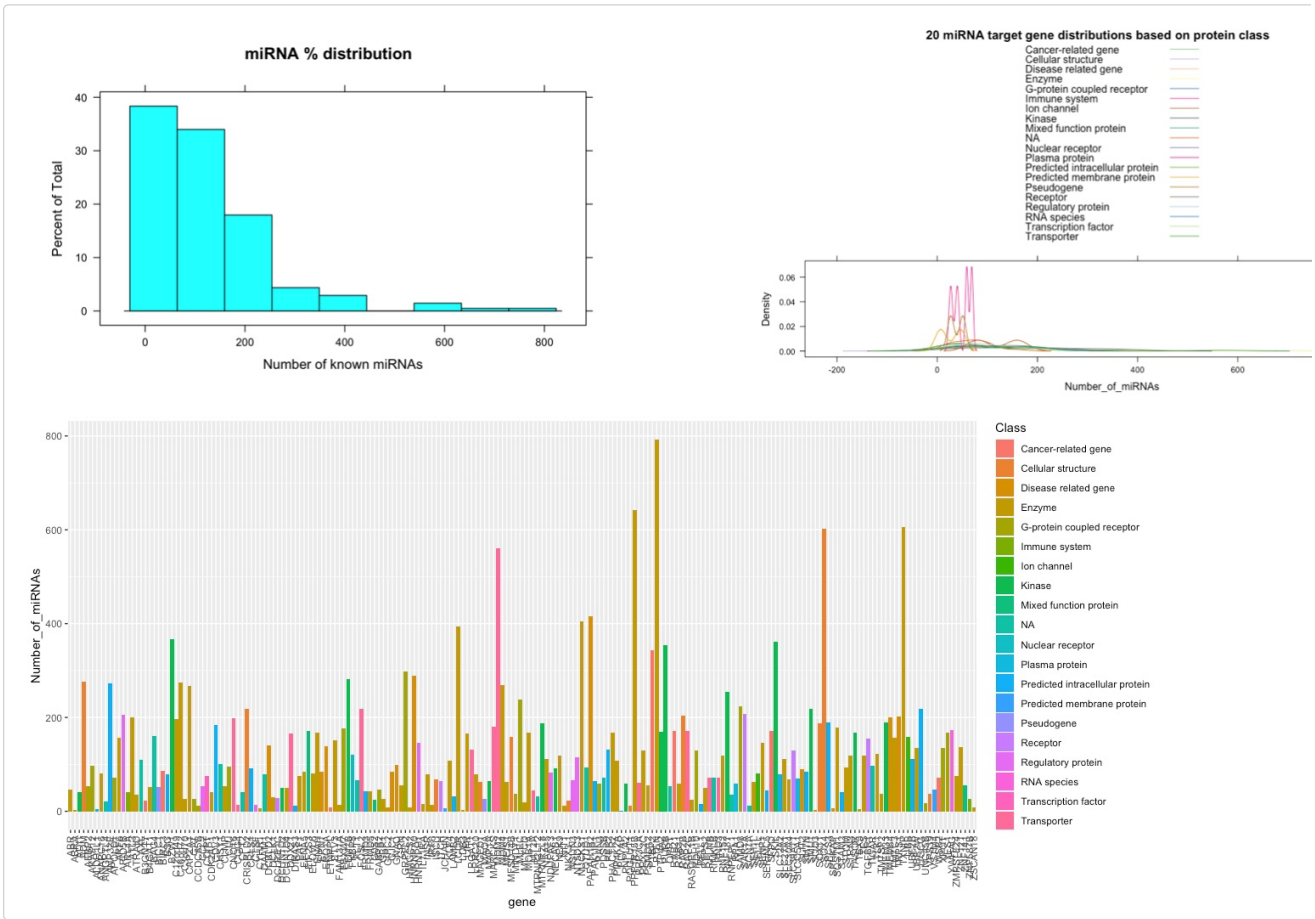
CpG symmary examples.

```
#   Symbol log2FoldChange       pvalue Association_score
#1   SAR1A      -2.187773 2.656521e-05         0.0000000
#2 C6orf62      -2.674213 1.691567e-07         0.0000000
#3     AXL      -2.786508 1.739595e-04         0.3230769
#4   BICC1      -3.598553 2.738887e-04         0.3000000
#5  CAPZA1      -1.732784 2.321835e-04         0.3789474
#6   TXNIP       1.460629 7.347205e-05         0.3000000
#  Specificity_score  LFCscore                  CpG GC_content
#1             0.000 -2.187773 chr1:1211340:1214153      70.33
```

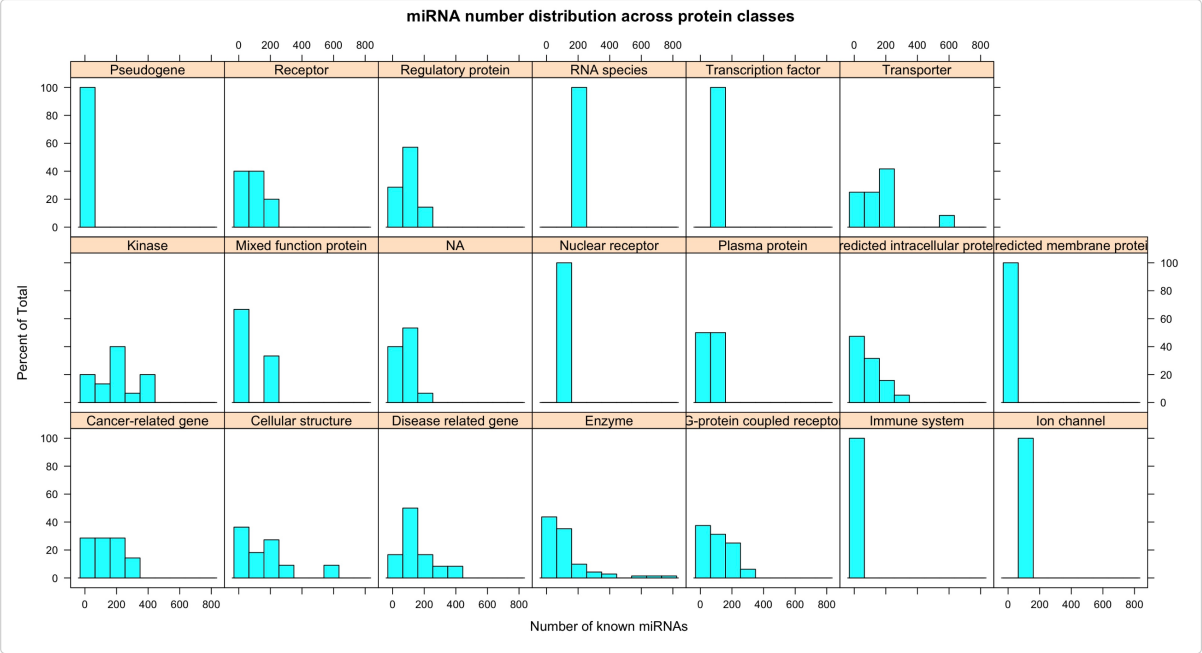
```
#2            0.000 -2.674213                    NA         NA
#3            0.590 -3.686764 chr1:1471765:1497848      58.83
#4            0.751 -4.678119                    NA         NA
#5            0.601 -2.389418                    NA         NA
#6            0.631  1.898818                    NA         NA
#                Class
#1           Receptor
#2                 NA
#3         Pseudogene
#4             Enzyme
#5             Enzyme
#6 Regulatory protein
```

Function *miRNA_summary_validated* allows to check how many of the differentially expressed genes have known miRNAs. The information on validated/known miRNAs is collected from mining multiple databases, namely miRecords, TarBase, miRTarBase,PhenomiR, miR2Disease, Pharmaco-miR. The function also returns a data table with miRNA information that can be used in designing RNA interference experiments.

```
#df<-miRNA_summary_validated(data)
#head(df)
```



Validated miRNA summary examples.



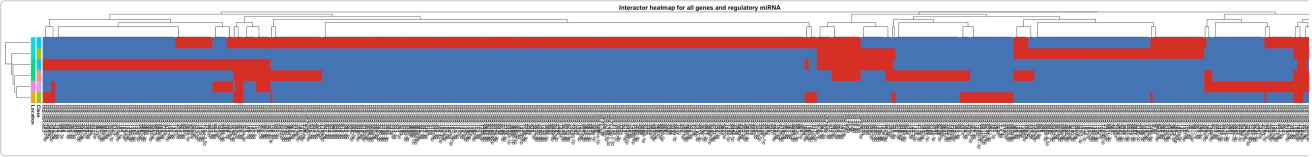
Validated miRNA summary examples.

Function *miRNA_summary_predicted* is similar to the earlier function; however, it allows to check how many of the differentially expressed genes have predicted miRNAs. The information is collected from mining multiple databases that use algorithms to infer likely miRNAs. The databases include miRTarBase, PITA, PicTar, miRecords, miRanda, DIANA-microT, miRDB, TarBase, TargetScan, MicroCosm, and EIMMo.The function also returns a data table with miRNA information that can be used in designing RNA interference experiments.

```
#df<-miRNA_summary_predicted(data)
```

Function *miRNA_network* allows to examine if a gene set has shared regulatory miRNAs. This could help explore the regulatory network and how some genes are controlled by several miRNAs.

```
#df<-miRNA_network(c("PIP4K2A","MOB1A","PHACTR2","MDM2","YWHAG" ,"RAB31"  ))
#head(df)
```



miRNA network plot example.

3. Discussion

OmicInt package provides a unique combination of functions and tools for researchers to explore gene expression data sets. A special focus of the package is also making machine learning, specifically Gaussian mixture models [3,4], more accessible to the researchers that do not have a background in the ML/AI field.

In addition, advanced functions for epigenomics analysis permit the exploration of the epigenetic regulatory layer. This might be helpful when identifying genes that may depend on epigentic regulation. Specifically, if a CpG island containing gene changed expression during treatment or disease progression, it might suggest that there is an epigenetic component controlling the expression levels. Similarly, exploring a gene's miRNA network could hint at other interacting genes which might not have been picked up by the differential expression analysis or help prepare for RNA interference studies. Moreover, miRNA interactome analysis provides the first in-depth look into what genes are controlled by the same set of miRNAs.

OmicInt offers a comprehensive, evolving, and adaptable platform for gene expression analysis in the context of the transcriptome, proteome, and epigenome.

4. Package comments

The package has the following dependencies: ggplot2,mclust,gtools,tidyr,pheatmap, viridis, dplyr,stringr,reshape2,plotly, methods,lattice, stats, knitr, rmarkdown, RColorBrewer, igraph, ggExtra, dendextend,STRINGdb, utils, graphics, RCurl, tidyselect.

Please note that plotly is used to build interactive plots which will appear on the Viewer tab in RStudio.

Version: v1.1.ų

Github pages: https://github.com/AusteKan/OmicInt

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5.References

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