# Package 'cellmarkeraccordion'

May 12, 2025

Title Single-cell and spatial omics annotation in health and disease

Version 1.0.0

**Description** cellmarkeraccordion is an R package designed to obtain a robust identification of healthy and disease critical populations in single-cell and spatial omics datasets in multiple tissues.

Additionally, the cellmarkeraccordion allows an easy interpretation of the results. The cellmarkeraccordion package allows to automatically annotate normal and disease critical cell populations based on the built-in Accordion gene marker database. It requires in input only the counts matrix (raw or normalized) or a Seurat object. In addition, by exploiting the built-in cell cycle labeling you can easily assign the cell cycle phase to each cell. The users can also customize the annotation by simply providing their own genes list as input, which can be associated with cell types or even to specific pathways or signatures of interest. Importantly, the Accordion implements novel options to explore annotation results by inspecting for each group of cells the top marker genes which mostly impacted the annotation, together with the top cell types and their relationship based on the cell ontology tree.

```
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      ggraph (>= 2.1.0),
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      knitr (>= 1.45),
      methods (>= 4.2.3),
      stats (>= 4.2.3)
```

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**Suggests** testthat (>= 3.0.0)

Config/testthat/edition 3

# **R** topics documented:

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# Description

This function performs cell types annotation exploiting the built-in Accordion gene marker database. It takes in input either a Seurat object or a raw or normalized count matrix and return in output the cell types assignment and the detailed information of the annotation results (added to the Seurat object or as a list).

# Usage

```
accordion(
  data,
  cluster_info = "seurat_clusters",
  assay = "RNA",
  database = NULL,
  CL_celltypes = NULL,
  species = "Human",
  tissue = NULL,
  root_cell_types = NULL,
  include_descendants = FALSE,
  ECs_threshold = NULL,
  SPs_threshold = NULL,
```

```
log2FC_threshold = NULL,
min_n_marker = 5,
max_n_marker = 30,
combined_score_quantile_threshold = NULL,
annotation_resolution = "cluster",
cluster_score_quantile_threshold = 0.75,
allow_unknown = TRUE,
annotation_name = "accordion",
include_detailed_annotation_info = TRUE,
condition_group_info = NULL,
celltype_group_info = NULL,
group_markers_by = "celltype_cluster",
top_cell_score_quantile_threshold = 0.9,
n_{top_celltypes} = 5,
n_{top_markers} = 5,
top_marker_score_quantile_threshold = 0.75,
plot = TRUE,
color_by = "cell_type"
```

#### **Arguments**

data

Either a Seurat object (version 4 or 5) or a raw or normalized count matrix with genes on rows and cells on columns. If raw counts are provided, data are lognormalized exploiting the NormalizeData() function from the Seurat package.

cluster\_info

in case data is a Seurat object, cluster\_info should be need to be a character string specifying the name of the column in the metadata that contains cluster ids; if data is a count matrix, cluster\_info should be need to be a data frame or data table containing cluster identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "cluster", which specifies the clustering id's for each cell. This parameter is necessary only when the input is a count matrix and only if the annotation\_resolution parameter is set to "cluster". Default is "seurat\_clusters".

assay

Character string specifying the Assay of the Seurat object. This parameter is necessary only in case data is a Seurat object. Default is "RNA".

database

Data table returns from the "marker\_database\_integration()" function. By default is set to NULL and the Accordion database is used for the annotation.

CL\_celltypes

Character string or character string vector specifying the cell types to annotate. Run the function "list\_celltypes()" to obtain the available cell types. If this parameter is not specified, all cell types present in the Accordion database are used for the annotation. Default is NULL.

species

Character string or character string vector specifying the species. Currently, either "Human" and/or "Mouse" are supported. If multiple species are selected, marker genes are merged together. Default is "Human".

tissue

Character string or character string vector specifying the tissue. Run the function "list\_tissues()" to obtain the available tissues. If multiple tissues are selected cell types and markers from the selected tissues are aggregated. If NULL, all tissues are considered. Default is NULL.

root\_cell\_types

Character string or vector specifying one or more cell types to be used as root

terms. Only the descendant cell types of the specified roots will be use for the annotation, excluding the root terms themselves. Default is NULL.

#### include\_descendants

Logical value indicating whether include all the tissues that are descendants of the selected tissue(s) according to the uberon ontology. If TRUE,cell types and markers from the selected tissues and their descendants are aggregated. Default is FALSE.

ECs\_threshold

Integer value (currently in (1,17)) specifying the minimum evidence consistency score (ECs) for each marker. Only markers >= this threshold are kept. If NULL, no filter is applied. Default is NULL.

SPs\_threshold

numeric value in (0,1) specifying the minimum specificity score (SPs) for each marker. Only markers <= this threshold are kept. If NULL, no filter is applied. Default is NULL.

log2FC\_threshold

numeric value specifying the minimum log2FC threshold for each marker reporting this information. Only markers <= this threshold or without any log2FC are kept. If NULL, no filter is applied. Default is NULL.

min\_n\_marker

Integer value specifying the minimum number of markers to keep for each cell type. Only cell types with a number of markers >= this threshold are kept. Default is 5.

max\_n\_marker

Integer value specifying the maximum number of markers to keep for each cell type. For the selection, markers are ranked according to their combined score, obtained by multiplying evidence consistency score and specificity score. If NULL, no filter is applied. Default is 30.

## combined\_score\_quantile\_threshold

numeric value in (0,1) specifying the combined score quantile threshold. For the selection, markers are ranked according to their combined score, obtained by multiplying evidence consistency score and specificity score. Only markers > the quantile\_threshold are kept. If NULL, no filter is applied. Default is NULL.

#### annotation\_resolution

Character string or character string vector specifying the resolution of the annotation. Either "cluster" and/or "cell" are supported. Default is "cluster".

# ${\tt cluster\_score\_quantile\_threshold}$

numeric value in (0,1) specifying the cluster score quantile threshold. For each cell a score specific for each cell type is computed. To annotate a cluster cl, for each cell type the cluster\_score\_quantile\_threshold is computed across cells belonging to that cluster and the cell type with the maximum score is then assigned to the cluster cl. Default is 0.75.

allow\_unknown

Logical value indicating whether to allow cells or clusters to be labeled as "unknown". If it is set to TRUE, cells or clusters with negative scores are assigned to the "unknown" category. Default is TRUE.

#### annotation\_name

Character string specifying the name of the column in either the metadata of the input Seurat object or in the input cluster\_info where the annotation will be stored. Per cluster and per cell annotation results will be stored in the annotation\_name\_per\_cluster and annotation\_name\_per\_cell columns respectively. If include\_detailed\_annotation\_info parameter is set to TRUE, the detailed information the stored in a list named annotation\_name. Default is "accordion".

#### include\_detailed\_annotation\_info

Logical value indicating whether to store information on the top cell types and markers in the output. If TRUE, a nested list named annotation\_name is created. If resolution\_annotation is set to "cluster" and/or "cell, sublists named "cluster\_resolution" and/or "cell\_resolution" are then added. Inside the sublist "detailed\_annotation\_info" the n\_top\_markers markers, group by group\_markers\_by and the n\_top\_celltypes cell types are then included. If a Seurat object is provided as input the list is stored in the misc slot of the object (object@misc@annotation\_name). If the input is a count matrix, the list is returned in the final output. Default is TRUE.

## condition\_group\_info

in case data is a Seurat object, condition\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains condition ids for each cell; if data is a count matrix, condition\_group\_info should be need to be a data frame or data table containing condition identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "condition", which specifies the condition id's for each cell. Default is NULL.

# celltype\_group\_info

in case data is a Seurat object, celltype\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains cell types ids for each cell; if data is a count matrix, celltype\_group\_info should be need to be a data frame or data table containing cell types identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "CL\_celltype", which specifies the cell types for each cell. Default is NULL.

## group\_markers\_by

Character string or character string vector specifying the classification of marker genes. It possible to retrieve n\_top\_markers marker genes for each cell type identified with cluster ("celltype\_cluster") or cell ("celltype\_cell") resolution; n\_top\_markers marker genes per cluster ("cluster") or per cell ("cell") can be also obtained. Additionally, by setting group\_markers\_by to "score\_cell", the n\_top\_markers marker genes only for cells with a score greater than top\_cell\_score\_quantile\_there retrieved. Either "celltype\_cluster", "celltype\_cell", "cluster", "cell" or "score\_cell". Default is "celltype\_cluster".

## top\_cell\_score\_quantile\_threshold

numeric value in (0,1) specifying the cell score quantile threshold. For each cell type a score specific for each cell is computed. The top\_cell\_score\_quantile\_threshold is computed across cells belonging to the same cell type, and only cells with a score greater than the top\_cell\_score\_quantile\_threshold are kept. This parameter is necessary only when group\_markers\_by is set to "score\_cell". Default is 0.90.

#### n\_top\_celltypes

Integer value specifying the number of the top cell types to be included in the output for each cluster and cell depending on the selected annotation\_resolution parameter Default is 5.

n\_top\_markers

Integer value specifying the number of the top markers to be included in the output for each cell type, cluster or cell depending on the selected annotation\_resolution and group\_markers\_by parameters. Default is 5.

#### top\_marker\_score\_quantile\_threshold

numeric value in (0,1) specifying the marker score quantile threshold. For each marker a score specific for each cell is computed. To identify the n\_top\_markers

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for a cluster cl or a cell type ct, the top\_marker\_score\_quantile\_threshold is computed across cells belonging to that cluster or labeled as ct, and the n\_top\_markers with the maximum score are reported. Default is 0.75.

plot Logical value indicating whether to store plots displaying detailed annotation in-

formation. This parameter can be set to TRUE only when include\_detailed\_annotation\_info

is set to TRUE. If TRUE, lollipop plots displaying the top <code>n\_top\_markers</code> group by <code>group\_markers\_by</code> and top <code>n\_top\_celltypes</code> for each annotation\_resolution together with the cell types hierarchies based on the cell ontology structure are

stored in the annotation\_name list. Default is TRUE.

color\_by Character string specifying if the plot reporting the top cell types for each clus-

ter/cell is colored based on the assigned cell type ("CL\_celltype") or on cluster

id ("cluster"). Default is "CL\_celltype.

#### **Details**

If a Seurat object was provided in input, the function returns the Seurat object with markers-based scaled data in the scale.data slot and cell types annotation results in the metadata. If include\_detailed\_annotation\_in and plot were set to TRUE, a list containing cell types and markers information, together with ggplot objects, is stored in the "misc@annotation\_name" slot. If a count matrix was provided in input, the function returns a list containing the following elements:

"scaled\_matrix": normalized and scaled expression matrix;

If annotation\_resolution is set to "cell":

"cell\_annotation": data table containing cell types annotation results for each cell;

If annotation\_resolution is set to "cluster":

"cluster\_annotation": data table containing cell types annotation results for each cell;

If include\_detailed\_annotation\_info is set to TRUE:

"annotation\_name": list containing detailed information of cell types annotation.

## Value

A Seurat object or a list

accordion\_cellcycle Automatically identify and interpreting cell cycle state of single-cell populations

#### **Description**

This function identifies cell cycle states exploiting the collection of marker genes associated to each phase, including G0. It takes in input either a Seurat object or a raw or normalized count matrix and return in output the cell cycle assignment and the detailed informations of the annotation results (added to the Seurat object or as a list).

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#### Usage

```
accordion_cellcycle(
  data.
  cluster_info = "seurat_clusters",
  assay = "RNA"
  species = "Human",
  annotation_resolution = "cell",
  annotation_name = "accordion_cell_cycle",
  cluster_score_quantile_threshold = 0.75,
  allow_unknown = FALSE,
  include_detailed_annotation_info = FALSE,
  condition_group_info = NULL,
  celltype_group_info = NULL,
  group_markers_by = "celltype_cell",
  n_top_celltypes = 5,
  n_{top_markers} = 5,
  top_marker_score_quantile_threshold = 0.75,
  plot = FALSE
)
```

## **Arguments**

data

Either a Seurat object (version 4 or 5) or a raw or normalized count matrix with genes on rows and cells on columns. If raw counts are provided, data are lognormalized exploiting the NormalizeData() function from the Seurat package.

cluster\_info

in case data is a Seurat object, cluster\_info should be need to be a character string specifying the name of the column in the metadata that contains cluster ids; if data is a count matrix, cluster\_info should be need to be a data frame or data table containing cluster identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "cluster", which specifies the clustering id's for each cell. This parameter is necessary only when the input is a count matrix and only if the annotation\_resolution parameter is set to "cluster". Default is "seurat\_clusters".

assay

Character string specifying the Assay of the Seurat object. This parameter is necessary only in case data is a Seurat object. Default is "RNA".

species

Character string or character string vector specifying the species. Currently, either "Human" and/or "Mouse" are supported. If multiple species are selected, marker genes are merged together. Default is "Human".

annotation\_resolution

Character string or character string vector specifying the resolution of the annotation. Either "cluster" and/or "cell" are supported. Default is "cell".

annotation\_name

Character string specifying the name of the column in either the metadata of the input Seurat object or in the input cluster\_info where the annotation will be stored. Per cluster and per cell annotation results will be stored in the annotation\_name\_per\_cluster and annotation\_name\_per\_cell columns respectively. If include\_detailed\_annotation\_info parameter is set to TRUE, the detailed information the stored in a list named annotation\_name. Default is "accordion\_cell\_cycle".

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#### cluster\_score\_quantile\_threshold

numeric value in (0,1) specifying the cluster score quantile threshold. For each cell a score specific for each cell type is computed. To annotate a cluster cl, for each cell type the cluster\_score\_quantile\_threshold is computed across cells belonging to that cluster and the cell type with the maximum score is then assigned to the cluster cl. Default is 0.75.

allow\_unknown

Logical value indicating whether to allow cells or clusters to be labeled as "unknown". If it is set to TRUE, cells or clusters with negative scores are assigned to the "unknown" category. Default is TRUE.

## include\_detailed\_annotation\_info

Logical value indicating whether to store information on the top cell types and markers in the output. If TRUE, a nested list named annotation\_name is created. If resolution\_annotation is set to "cluster" and/or "cell, sublists named "cluster\_resolution" and/or "cell\_resolution" are then added. Inside the sublist "detailed\_annotation\_info" the n\_top\_markers markers, group by group\_markers\_by and the n\_top\_celltypes cell types are then included. If a Seurat object is provided as input the list is stored in the misc slot of the object (object@misc@annotation\_name). If the input is a count matrix, the list is returned in the final output. Default is FALSE.

## condition\_group\_info

in case data is a Seurat object, condition\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains condition ids for each cell; if data is a count matrix, condition\_group\_info should be need to be a data frame or data table containing condition identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "condition", which specifies the condition id's for each cell. Default is NULL.

# celltype\_group\_info

in case data is a Seurat object, celltype\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains cell types ids for each cell; if data is a count matrix, celltype\_group\_info should be need to be a data frame or data table containing cell types identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "cell\_type", which specifies the cell types for each cell. Default is NULL.

#### group\_markers\_by

Character string or character string vector specifying the classification of marker genes. It possible to retrieve n\_top\_markers marker genes for each cell type identified with cluster ("celltype\_cluster") or cell ("celltype\_cell") resolution; n\_top\_markers marker genes per cluster ("cluster") or per cell ("cell") can be also obtained. Either "celltype\_cluster", "celltype\_cell", "cluster" and/or "cell". Default is "celltype\_cell".

#### n\_top\_celltypes

Integer value specifying the number of the top cell types to be included in the output for each cluster and cell depending on the selected annotation\_resolution parameter Default is 5.

n\_top\_markers

Integer value specifying the number of the top markers to be included in the output for each cell type, cluster or cell depending on the selected annotation\_resolution and group\_markers\_by parameters. Default is 5.

#### top\_marker\_score\_quantile\_threshold

numeric value in (0,1] specifying the marker score quantile threshold. For each marker a score specific for each cell is computed. To identify the n\_top\_markers

for a cluster cl or a cell type ct, the top\_marker\_score\_quantile\_threshold is computed across cells belonging to that cluster or labeled as ct, and the n\_top\_markers with the maximum score are reported. Default is 0.75.

plot

Logical value indicating whether to store plots displaying detailed annotation information. This parameter can be set to TRUE only when include\_detailed\_annotation\_info is set to TRUE. If TRUE, lollipop plots displaying the top n\_top\_markers group by group\_markers\_by and n\_top\_celltypes for each annotation\_resolution together with the cell types hierarchies based on the cell ontology structure are stored in the annotation\_name list. Default is FALSE.

#### Details

If a Seurat object was provided in input, the function returns the Seurat object with markers-based scaled data in the scale.data slot and cell types annotation results in the metadata. If include\_detailed\_annotation\_in and plot were set to TRUE, a list named annotation\_name containing cell types and markers information, together with ggplot objects, is stored in the "misc" slot. If a count matrix was provided in input, the function returns a list containing the following elements:

"scaled\_matrix": normalized and scaled expression matrix;

If annotation\_resolution is set to "cell":

"cell\_annotation": data table containing cell types annotation results for each cell;

If annotation\_resolution is set to "cluster":

"cluster\_annotation": data table containing cell types annotation results for each cell;

If include\_detailed\_annotation\_info is set to TRUE:

"annotation\_name": list containing detailed information of cell types annotation.

#### Value

A Seurat object or a list

accordion\_custom

Automatically annotating and interpreting single-cell populations with custom marker genes sets

#### **Description**

This function performs cell types or signatures/pathways annotation based on custom marker genes set. It takes in input either a Seurat object or a raw or normalized count matrix and a table of marker genes associated to cell types or even to pathways and return in output the cell types/pathways assignment and the detailed information of the annotation results (added to the Seurat object or as a list).

#### Usage

```
accordion_custom(
  data,
 marker_table,
 category_column = "cell_type",
 marker_column = "marker",
 marker_type_column = "marker_type",
 weight_column = "weight",
  cluster_info = "seurat_clusters",
  assay = "RNA",
 min_n_marker = 5,
 max_n_marker = 30,
 combined_score_quantile_threshold = NULL,
  annotation_resolution = "cluster",
  cluster_score_quantile_threshold = 0.75,
  allow_unknown = TRUE,
  annotation_name = "accordion_custom",
  include_detailed_annotation_info = TRUE,
  condition_group_info = NULL,
  celltype_group_info = NULL,
  group_markers_by = "celltype_cluster",
  top_cell_score_quantile_threshold = 0.9,
  n_{top_celltypes} = 5,
 n_{top_markers} = 5,
  top_marker_score_quantile_threshold = 0.75,
  plot = TRUE
)
```

## **Arguments**

data

Either a Seurat object (version 4 or 5) or a raw or normalized count matrix with genes on rows and cells on columns. If raw counts are provided, data are lognormalized exploiting the NormalizeData() function from the Seurat package.

marker\_table

Data table or data frame containing cell type markers. The table needs to have at least two columns, the category\_column, which specifies cell types or categories, and the marker\_column, which specifies the corresponding markers on each row. Columns indicating the marker type (either positive or negative), and the marker weight can be optionally included.

category\_column

String characters specifying the name of the marker\_table column containing cell types or categories. Default is "cell\_type".

marker\_column

String characters specifying the name of the marker\_table column containing markers. Default is "marker".

marker\_type\_column

Optional string characters specifying the name of the marker\_table column containing string characters indicating the type of markers, either "positive" or "negative". If no marker\_type\_column is found in the marker\_table all markers are considered "positive". Default is "marker\_type".

weight\_column

Optional string characters specifying the name of the marker\_table column containing numeric value indicating the weight for each marker. If no weight\_column is found in the marker\_table all markers are equally weighted as 1. Default is "weight".

cluster\_info

in case data is a Seurat object, cluster\_info should be need to be a character string specifying the name of the column in the metadata that contains cluster ids; if data is a count matrix, cluster\_info should be need to be a data frame or data table containing cluster identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "cluster", which specifies the clustering id's for each cell. This parameter is necessary only when the input is a count matrix and only if the annotation\_resolution parameter is set to "cluster". Default is "seurat\_clusters".

assay

Character string specifying the Assay of the Seurat object. This parameter is necessary only in case data is a Seurat object. Default is "RNA".

min\_n\_marker

Integer value specifying the minimum number of markers to keep for each cell type. Only cell types with a number of markers >= this threshold are kept. Default is 5.

max\_n\_marker

Integer value specifying the maximum number of markers to keep for each cell type. For the selection, markers are ranked according to their combined score, obtained by multiplying evidence consistency score and SPs score. If NULL, no filter is applied. Default is 30.

#### combined\_score\_quantile\_threshold

numeric value in (0,1] specifying the combined score quantile threshold. For the selection, markers are ranked according to their combined score, obtained by multiplying weight and SPs score. Only markers > the quantile\_threshold are kept. If NULL, no filter is applied. Default is NULL.

#### annotation\_resolution

Character string or character string vector specifying the resolution of the annotation. Either "cluster" and/or "cell" are supported. Default is "cluster".

#### cluster\_score\_quantile\_threshold

numeric value in (0,1) specifying the cluster score quantile threshold. For each cell a score specific for each cell type is computed. To annotate a cluster cl, for each cell type the cluster\_score\_quantile\_threshold is computed across cells belonging to that cluster and the cell type with the maximum score is then assigned to the cluster cl. Default is 0.75.

allow\_unknown

Logical value indicating whether to allow cells or clusters to be labeled as "unknown". If it is set to TRUE, cells or clusters with negative scores are assigned to the "unknown" category. Default is TRUE.

## annotation\_name

Character string specifying the name of the column in either the metadata of the input Seurat object or in the input cluster\_info where the annotation will be stored. Per cluster and per cell annotation results will be stored in the annotation\_name\_per\_cluster and annotation\_name\_per\_cell columns respectively. If include\_detailed\_annotation\_info parameter is set to TRUE, the detailed information the stored in a list named annotation\_name. Default is "accordion\_custom".

## include\_detailed\_annotation\_info

Logical value indicating whether to store information on the top cell types and markers in the output. If TRUE, a list named annotation\_name is created. If resolution\_annotation is set to "cluster" and/or "cell, sublists named "cluster\_resolution" and/or "cell\_resolution" are then added. Inside the sublist "detailed\_annotation\_info" the n\_top\_markers markers, group by group\_markers\_by and the n\_top\_celltypes cell types are then included. If a Seurat object is provided as input the list is stored in the misc slot of the object (object@misc@annotation\_name).

If the input is a count matrix, the list is returned in the final output. Default is TRUE.

#### condition\_group\_info

in case data is a Seurat object, condition\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains condition ids for each cell; if data is a count matrix, condition\_group\_info should be need to be a data frame or data table containing condition identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "condition", which specifies the condition id's for each cell. Default is NULL.

## celltype\_group\_info

in case data is a Seurat object, celltype\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains cell types ids for each cell; if data is a count matrix, celltype\_group\_info should be need to be a data frame or data table containing cell types identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "cell\_type", which specifies the cell types for each cell. Default is NULL.

#### group\_markers\_by

Character string or character string vector specifying the classification of marker genes. It possible to retrieve n\_top\_markers marker genes for each cell type identified with cluster ("celltype\_cluster") or cell ("celltype\_cell") resolution; n\_top\_markers marker genes per cluster ("cluster") or per cell ("cell") can be also obtained. Additionally, by setting group\_markers\_by to "score\_cell", the n\_top\_markers marker genes only for cells with a score greater than top\_cell\_score\_quantile\_there retrieved. Either "celltype\_cluster", "celltype\_cell", "cluster", "cell" or "score\_cell". Default is "celltype\_cluster".

#### top\_cell\_score\_quantile\_threshold

numeric value in (0,1] specifying the cell score quantile threshold. For each cell type/signature a score specific for each cell is computed. The top\_cell\_score\_quantile\_threshol is computed across cells belonging to the same cell type/signature, and only cells with a score greater than the top\_cell\_score\_quantile\_threshold are kept. This parameter is necessary only when group\_markers\_by is set to "score\_cell". Default is 0.90.

### n\_top\_celltypes

Integer value specifying the number of the top cell types to be included in the output for each cluster and cell depending on the selected annotation\_resolution parameter Default is 5.

# n\_top\_markers

Integer value specifying the number of the top markers to be included in the output for each cell type, cluster or cell depending on the selected annotation\_resolution and group\_markers\_by parameters. Default is 5.

## top\_marker\_score\_quantile\_threshold

numeric value in (0,1] specifying the marker score quantile threshold. For each marker a score specific for each cell is computed. To identify the n\_top\_markers for a cluster cl or a cell type ct, the top\_marker\_score\_quantile\_threshold is computed across cells belonging to that cluster or labeled as ct, and the n\_top\_markers with the maximum score are reported. Default is 0.75.

plot

Logical value indicating whether to store plots displaying detailed annotation information. This parameter can be set to TRUE only when include\_detailed\_annotation\_info is set to TRUE. If TRUE, lollipop plots displaying the top n\_top\_markers group by group\_markers\_by and op n\_top\_celltypes for each annotation\_resolution

together with the cell types hierarchies based on the cell ontology structure are stored in the annotation\_name list. Default is TRUE.

#### **Details**

If a Seurat object was provided in input, the function returns the Seurat object with markers-based scaled data in the scale.data slot and cell types annotation results in the metadata. If include\_detailed\_annotation\_in and plot were set to TRUE, a list containing cell types and markers information, together with ggplot objects, is stored in the "misc@annotation\_name" slot. If a count matrix was provided in input, the function returns a list containing the following elements:

"scaled\_matrix": normalized and scaled expression matrix;

If annotation\_resolution is set to "cell":

"cell\_annotation": data table containing cell types annotation results for each cell;

If annotation\_resolution is set to "cluster":

"cluster\_annotation": data table containing cell types annotation results for each cell;

If include\_detailed\_annotation\_info is set to TRUE:

"annotation\_name": list containing detailed information of cell types annotation.

#### Value

A Seurat object or a list

accordion\_disease

Automatically annotating and interpreting aberrant single-cell populations with the built-in Cell Marker Accordion disease database

# Description

This function identified aberrant populations exploiting the built-in Accordion gene marker disease database. It takes in input either a Seurat object or a raw or normalized count matrix and return in output the cell types assignment and the detailed information of the annotation results (added to the Seurat object or as a list).

#### Usage

```
accordion_disease(
  data,
  disease = NULL,
  tissue = NULL,
  cluster_info = "seurat_clusters",
  assay = "RNA",
  database = NULL,
  NCIT_celltypes = NULL,
  species = "Human",
  include_descendants = FALSE,
  ECs_threshold = NULL,
  SPs_threshold = NULL,
```

```
log2FC_threshold = NULL,
malignant_quantile_threshold = 0.95,
min_n_marker = 5,
max_n_marker = 30,
combined_score_quantile_threshold = NULL,
annotation_resolution = "cluster",
cluster_score_quantile_threshold = 0.75,
allow_unknown = TRUE,
annotation_name = "accordion_disease",
include_detailed_annotation_info = TRUE,
condition_group_info = NULL,
celltype_group_info = NULL,
group_markers_by = "celltype_cluster",
top_cell_score_quantile_threshold = 0.9,
n_{top_celltypes} = 5,
n_{top_markers} = 5,
top_marker_score_quantile_threshold = 0.75,
plot = TRUE,
color_by = "cell_type"
```

#### **Arguments**

data Either a Seurat object (version 4 or 5) or a raw or normalized count matrix with

genes on rows and cells on columns. If raw counts are provided, data are log-normalized exploiting the NormalizeData() function from the Seurat package.

disease Character string or character string vector specifying diseases to consider. Run

the function "list\_diseases()" to obtain the available diseases. If NULL, all dis-

eases are considered. Default is NULL.

tissue Character string or character string vector specifying the tissue. Run the function

"list\_tissues()" to obtain the available tissues. If multiple tissues are selected cell types and markers from the selected tissues are aggregated. If NULL, all tissues

are considered. Default is NULL.

cluster\_info in case data is a Seurat object, cluster\_info should be need to be a character

string specifying the name of the column in the metadata that contains cluster ids; if data is a count matrix, cluster\_info should be need to be a data frame or data table containing cluster identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "cluster", which specifies the clustering id's for each cell. This parameter is necessary only when the input is a count matrix and only if the annotation\_resolution parameter is set to "cluster". Default is

"seurat\_clusters".

assay Character string specifying the Assay of the Seurat object. This parameter is

necessary only in case data is a Seurat object. Default is "RNA".

database Data table returns from the "marker\_database\_integration()" function. By de-

fault is set to NULL and the Accordion database is used for the annotation.

NCIT\_celltypes Character string or character string vector specifying the cell types to annotate. Run the function "list\_aberrant\_celltypes()" to obtain the available aberrant cell

types. If this parameter is not specified, all aberrant cell types are used for the

annotation. Default is NULL.

species

Character string or character string vector specifying the species. Currently, either "Human" and/or "Mouse" are supported. If multiple species are selected, marker genes are merged together. Default is "Human".

#### include\_descendants

Logical value indicating whether include all the tissues that are descendants of the selected tissue(s) according to the uberon ontology. If TRUE,cell types and markers from the selected tissues and their descendants are aggregated. Default is FALSE

ECs\_threshold

Integer value specifying the minimum evidence consistency score (ECs) for each marker. Only markers >= this threshold are kept. If NULL, no filter is applied. Default is NULL.

SPs\_threshold

numeric value in (0,1) specifying the minimum specificity score (SPs) for each marker. Only markers <= this threshold are kept. If NULL, no filter is applied. Default is NULL.

log2FC\_threshold

numeric value specifying the minimum log2FC threshold for each marker reporting this information. Only markers <= this threshold or without any log2FC are kept. If NULL, no filter is applied. Default is NULL.

malignant\_quantile\_threshold

numeric value in (0,1) specifying the malignant quantile threshold. If an aberant cell type is provide in input, a malignant score specific for each cell is computed. The malignant\_quantile\_threshold is computed across cells, and only cells with a score greater than the top\_cell\_score\_quantile\_threshold are labeled as malignant. If annotation\_resolution is set to "cell", a cell

min\_n\_marker

Integer value specifying the minimum number of markers to keep for each cell type. Only cell types with a number of markers >= this threshold are kept. Default is 5.

max\_n\_marker

Integer value specifying the maximum number of markers to keep for each cell type. For the selection, markers are ranked according to their combined score, obtained by multiplying evidence consistency score and SPs score. If NULL, no filter is applied. Default is 30.

combined\_score\_quantile\_threshold

numeric value in (0,1) specifying the combined score quantile threshold. For the selection, marers are ranked according to their combined score, obtained by multiplying evidence consistency score and SPs score. Only markers > the quantile\_threshold are kept. If NULL, no filter is applied. Default is NULL.

annotation\_resolution

Character string or character string vector specifying the resolution of the annotation. Either "cluster" and/or "cell" are supported. Default is "cluster".

cluster\_score\_quantile\_threshold

numeric value in (0,1) specifying the cluster score quantile threshold. For each cell a score specific for each cell type is computed. To annotate a cluster cl, for each cell type the cluster\_score\_quantile\_threshold is computed across cells belonging to that cluster and the cell type with the maximum score is then assigned to the cluster cl. Default is 0.75.

allow\_unknown

Logical value indicating whether to allow cells or clusters to be labeled as "unknown". If it is set to TRUE, cells or clusters with negative scores are assigned to the "unknown" category. Default is TRUE.

annotation\_name

Character string specifying the name of the column in either the metadata of the input Seurat object or in the input cluster\_info where the annotation

will be stored. Per cluster and per cell annotation results will be stored in the annotation\_name\_per\_cluster and annotation\_name\_per\_cell columns respectively. If include\_detailed\_annotation\_info parameter is set to TRUE, the detailed information the stored in a list named annotation\_name. Default is "accordion disease".

## include\_detailed\_annotation\_info

Logical value indicating whether to store information on the top cell types and markers in the output. If TRUE, a nested list named annotation\_name is created. If resolution\_annotation is set to "cluster" and/or "cell, sublists named "cluster\_resolution" and/or "cell\_resolution" are then added. Inside the sublist "detailed\_annotation\_info" the n\_top\_markers markers, group by group\_markers\_by and the n\_top\_celltypes cell types are then included. If a Seurat object is provided as input the list is stored in the misc slot of the object (object@misc@annotation\_name). If the input is a count matrix, the list is returned in the final output. Default is TRUE.

#### condition\_group\_info

in case data is a Seurat object, condition\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains condition ids for each cell; if data is a count matrix, condition\_group\_info should be need to be a data frame or data table containing condition identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "condition", which specifies the condition id's for each cell. Default is NULL.

# celltype\_group\_info

in case data is a Seurat object, celltype\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains cell types ids for each cell; if data is a count matrix, celltype\_group\_info should be need to be a data frame or data table containing cell types identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "NCIT\_celltype", which specifies the cell types for each cell. Default is NULL.

#### group\_markers\_by

Character string or character string vector specifying the classification of marker genes. It possible to retrieve n\_top\_markers marker genes for each cell type identified with cluster ("celltype\_cluster") or cell ("celltype\_cell") resolution; n\_top\_markers marker genes per cluster ("cluster") or per cell ("cell") can be also obtained. Additionally, by setting group\_markers\_by to "score\_cell", the n\_top\_markers marker genes only for cells with a score greater than top\_cell\_score\_quantile\_there retrieved. Either "celltype\_cluster", "celltype\_cell", "cluster", "cell" or "score\_cell". Default is "celltype\_cluster".

#### top\_cell\_score\_quantile\_threshold

numeric value in (0,1) specifying the cell score quantile threshold. For each cell type a score specific for each cell is computed. The top\_cell\_score\_quantile\_threshold is computed across cells belonging to the same cell type, and only cells with a score greater than the top\_cell\_score\_quantile\_threshold are kept. This parameter is necessary only when group\_markers\_by is set to "score\_cell". Default is 0.90.

#### n\_top\_celltypes

Integer value specifying the number of the top cell types to be included in the output for each cluster and cell depending on the selected annotation\_resolution parameter Default is 5.

n\_top\_markers

Integer value specifying the number of the top markers to be included in the output for each cell type, cluster or cell depending on the selected annotation\_resolution and group\_markers\_by parameters. Default is 5.

top\_marker\_score\_quantile\_threshold

numeric value in (0,1) specifying the marker score quantile threshold. For each marker a score specific for each cell is computed. To identify the n\_top\_markers for a cluster cl or a cell type ct, the top\_marker\_score\_quantile\_threshold is computed across cells belonging to that cluster or labeled as ct, and the n\_top\_markers with the maximum score are reported. Default is 0.75.

plot

Logical value indicating whether to store plots displaying detailed annotation information. This parameter can be set to TRUE only when include\_detailed\_annotation\_info is set to TRUE. If TRUE, lollipop plots displaying the top n\_top\_markers group by group\_markers\_by and op n\_top\_celltypes for each annotation\_resolution together with the cell types hierarchies based on the cell ontology structure are stored in the "accordion" list. Default is TRUE.

color\_by

Character string specifying if the plot reporting the top cell types for each cluster/cell is colored based on the assigned cell type ("CL\_celltype") or on cluster id ("cluster"). Default is "CL\_celltype.

#### **Details**

If a Seurat object was provided in input, the function returns the Seurat object with markers-based scaled data in the scale.data slot and cell types annotation results in the metadata. If include\_detailed\_annotation\_in and plot were set to TRUE, a list containing cell types and markers information, together with ggplot objects, is stored in the "misc@annotation\_name" slot. If a count matrix was provided in input, the function returns a list containing the following elements:

"scaled\_matrix": normalized and scaled expression matrix;

If annotation\_resolution is set to "cell":

"cell\_annotation": data table containing cell types annotation results for each cell;

If annotation\_resolution is set to "cluster":

"cluster\_annotation": data table containing cell types annotation results for each cell;

If include\_detailed\_annotation\_info is set to TRUE:

"annotation\_name": list containing detailed information of cell types annotation.

#### Value

A Seurat object or a list

18 accordion\_plot

accordion\_marker

accordion marker: Cell Marker Accordion database

## **Description**

```
accordion marker: Cell Marker Accordion database
```

#### Usage

```
data(accordion_marker)
```

#### **Format**

A data table

accordion\_plot

Interpreting annotation results

#### **Description**

This function generates lollipop plots displaying the detailed annotation results obtained with the  $accordion\_annotation, accordion\_disease\_annotation \ and \ accordion\_custom\_annotation$ functions.

## Usage

```
accordion_plot(
 data,
  info_to_plot = "accordion",
 resolution = "cluster",
  group_markers_by = "celltype_cluster",
  color_by = "cell_type",
 condition_group_info = NULL,
  celltype_group_info = NULL
)
```

# **Arguments**

data

A Seurat object or a list containing "detailed\_annotation\_info", from either accordion(), accordion\_disease() or accordion\_custom() functions, run with in-

clude\_detailed\_annotation\_info parameter set to TRUE.

Character string or character string vector specifying the list from which extract info\_to\_plot

the detailed annotation information, either "accordion", "accordion\_disease" or "accordion\_custom", for which returns the plot, either "accordion", "accor-

dion\_disease" or "accordion\_custom".

resolution Character string or character string vector specifying the annotation resolution

for which provided the plots. Either "cluster" and/or "cell" are supported. De-

fault is "cluster".

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group\_markers\_by

Character string or character string vector specifying the classification of marker genes. It is possible to retrieve top marker genes for each cell type identified with cluster ("celltype\_cluster") or cell ("celltype\_cell") resolution; top marker genes per cluster ("cluster") or per cell ("cell") can be also obtained. Additionally, by setting group\_markers\_by to "score\_cell", the n\_top\_markers marker genes only for cells with a score greater than top\_cell\_score\_quantile\_threshold are retrieved. Either "celltype\_cluster", "celltype\_cell", "cluster", "cell" or "score\_cell". Default is "celltype cluster".

color\_by

Character string specifying if the plot reporting the top cell types for each cluster/cell is colored based on the assigned cell type ("cell\_type") or on cluster id ("cluster"). Default is "cell\_type.

condition\_group\_info

in case data is a Seurat object, condition\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains condition ids for each cell; if data is a count matrix, condition\_group\_info should be need to be a data frame or data table containing condition identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "condition", which specifies the condition id's for each cell. Default is NULL.

celltype\_group\_info

in case data is a Seurat object, celltype\_group\_info should be need to be a character string specifying the name of the column in the metadata that contains cell types ids for each cell; if data is a count matrix, celltype\_group\_info should be need to be a data frame or data table containing cell types identity for each cell. The data frame or data table should contain at least two columns, one named "cell", which specifies cell id's, and one named "CL\_celltype" or "NCIT\_celltype", which specifies the cell types for each cell. Default is NULL.

# **Details**

Display the top cell types (or pathways) and top markers. It takes in input either a Seurat object or a raw or normalized count matrix and a table of marker genes associated to cell types or even to pathways and return in output the cell types/pathways assignment and the detailed information of the annotation results (added to the Seurat object or as a list).

If a Seurat object was provided in input, the function returns the Seurat object with a list of ggplot objects added to the "misc" slot in the info\_to\_plot list. If a list was provided in input, the function returns the same list with the addition of the ggplot objects.

#### Value

A Seurat object or a list.

cell\_cycle\_markers

cell cycle markers: Collection of markers assiciated to cell cycle

## **Description**

cell\_cycle\_markers: Collection of markers assiciated to cell cycle

# Usage

```
data(cell_cycle_markers)
```

## **Format**

A data table

cell\_onto

cell\_onto: Cell ontology

# Description

```
cell_onto: Cell ontology
```

# Usage

```
data(cell_onto)
```

# **Format**

Cell ontology

disease\_accordion\_marker

disease\_accordion\_marker: Cell Marker Accordion disease database

# Description

```
disease_accordion_marker: Cell Marker Accordion disease database
```

# Usage

```
data(disease_accordion_marker)
```

# **Format**

A data table

gene\_description 21

| gene_description | gene_description: table containing gene description for human and |
|------------------|---|
|                  | mouse genes (human112_GRCh38.p14 and mouse112_GRCm39)             |

# Description

gene\_description: table containing gene description for human and mouse genes (human112\_GRCh38.p14 and mouse112\_GRCm39)

## Usage

```
data(gene_description)
```

#### **Format**

data table

```
list_aberrant_celltypes
```

List aberrant cell types available in the Cell Marker Accordion disease database

# Description

List aberrant cell types available in the Cell Marker Accordion disease database

# Usage

```
list_aberrant_celltypes(
  species = c("Human", "Mouse"),
  disease = NULL,
  tissue = NULL
)
```

# Arguments

| species | Character string or character string vector specifying the species for which to extract the associate list of available cell types. Currently, either "Human" and/or "Mouse" are supported. Default is c("Mouse", "Human"). |
|---------|---|
| disease | Character string or character string vector specifying diseases to consider. If NULL, information from all diseases are considered. Default is NULL.  |
| tissue  | Character string or character string vector specifying the tissue for which to extract the associate list of available cell types. If NULL, information from all tissues are retrieved.                                     |

#### Value

List of aberrant cell types available in the Cell Marker Accordion disease database

22 list\_diseases

list\_celltypes

List cell types available in the Cell Marker Accordion database

#### **Description**

List cell types available in the Cell Marker Accordion database

#### Usage

```
list_celltypes(species = c("Human", "Mouse"), tissue = NULL)
```

## **Arguments**

species Character string or character string vector specifying the species for which to ex-

tract the associate list of available cell types. Currently, either "Human" and/or

"Mouse" are supported. Default is c("Mouse", "Human").

tissue Character string or character string vector specifying the tissue for which to

extract the associate list of available cell types. If NULL, information from all

tissues are retrieved.

#### Value

List of cell types available in the Cell Marker Accordion database

list\_diseases

List diseases available in the Cell Marker Accordion disease database

# **Description**

List diseases available in the Cell Marker Accordion disease database

#### Usage

```
list_diseases(
  species = c("Human", "Mouse"),
  tissue = NULL,
  aberrant_celltype = NULL
)
```

#### **Arguments**

species Character string or character string vector specifying the species for which to

extract the associate list of available diseases Currently, either "Human" and/or

"Mouse" are supported. Default is c("Mouse", "Human").

tissue Character string or character string vector specifying the tissue for which to

extract the associate list of available diseases. If NULL, information from all

tissues are retrieved.

list\_disease\_tissues 23

```
aberrant_celltype
```

Character string or character string vector specifying the aberrant celltype for which to extract the associate list of available tissues. If NULL, information from all aberrant cell types are retrieved. @return List of diseases available in the Cell Marker Accordion disease database

#### **Description**

List tissues available in the Cell Marker Accordion disease database

## Usage

```
list_disease_tissues(
  species = c("Human", "Mouse"),
  disease = NULL,
  aberrant_celltype = NULL
)
```

## **Arguments**

species

Character string or character string vector specifying the species for which to extract the associate list of available tissues. Currently, either "Human" and/or "Mouse" are supported. Default is c("Mouse", "Human").

disease

Character string or character string vector specifying diseases to consider. If NULL, information from all diseases are considered. Default is NULL.

aberrant\_celltype

Character string or character string vector specifying the aberrant celltype for which to extract the associate list of available tissues. f NULL, information from all cell types are retrieved.

# Value

List of tissues available in the Cell Marker Accordion disease database

list\_tissues

List tissues available in the Cell Marker Accordion database

## **Description**

List tissues available in the Cell Marker Accordion database

#### Usage

```
list_tissues(species = c("Human", "Mouse"), celltype = NULL)
```

## **Arguments**

species Character string or character string vector specifying the species for which to

extract the associate list of available tissues. Currently, either "Human" and/or

"Mouse" are supported. Default is c("Mouse", "Human").

celltype Character string or character string vector specifying the celltype for which to

extract the associate list of available tissues. If NULL, information from all cell

types are retrieved.

#### Value

List of tissues available in the Cell Marker Accordion database

marker\_database\_integration

Create an augmented database by integrated custom set of markers genes with the Accordion database

## **Description**

This function performs markers integration provided by the users and the accordion database, either physiological ("healthy") or disease ("disease). It takes in input a table of marker genes associated to cell types and return the integrated database of custom and accordion markers. This new integrated database can be used as input for the "accordion" or "disease\_accordion" function to provide the annotation.

# Usage

```
marker_database_integration(
  marker_table,
  database = "healthy",
  species_column = "species",
  disease_column = "disease",
  tissue_column = "tissue",
  celltype_column = "cell_type",
  marker_column = "marker",
  marker_type_column = "marker_type",
  resource_column = "resource")
```

# Arguments

marker\_table Data table or data frame containing cell type markers. The table needs to have

at least two columns, the celltype\_column, which specifies cell types, and the marker\_column, which specifies the corresponding markers on each row. Columns indicating the marker type (either positive or negative), species, con-

dition, tissue and resource can be optionally included.

database String characters specifying the accordion database to use for integration. Either "healthy" or "diseases" are supported, where "healthy" refers to the physiological

"healthy" or "disease" are supported, where "healthy" refers to the physiological accordion database, while "disease" refers to the disease accordion database.

Default is "healthy"

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species\_column String characters specifying the name of the marker\_table column containing species. Default is "species".

disease\_column String characters specifying the name of the marker\_table column containing

diseases. Default is "disease".

 ${\tt tissue\_column} \quad String \ characters \ specifying \ the \ name \ of \ the \ {\tt marker\_table} \ column \ containing$ 

tissues. Default is "tissue".

celltype\_column

String characters specifying the name of the marker\_table column containing

cell types. Default is "cell\_type".

marker\_column String characters specifying the name of the marker\_table column containing

markers. Default is "marker".

marker\_type\_column

String characters specifying the name of the marker\_table column containing marker types. Default is "marker\_type".

resource\_column

String characters specifying the name of the marker\_table column containing resources. Default is "resource".

#### Value

A data table

uberon\_onto

uberon\_onto: Uberon anatomy ontology

## **Description**

uberon\_onto: Uberon anatomy ontology

## Usage

data(uberon\_onto)

## **Format**

Uberon ontology

# **Index**

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