

Package ‘HarmonizR’

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Title Handles missing values and makes more data available

Version 1.9.0

Description An implementation, which takes input data and makes it available for proper batch effect removal by ComBat or Limma. The implementation appropriately handles missing values by dissecting the input matrix into smaller matrices with sufficient data to feed the ComBat or limma algorithm. The adjusted data is returned to the user as a rebuild matrix. The implementation is meant to make as much data available as possible with minimal data loss.

Depends R (>= 4.2.0)

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binary_matrix_reduction	
<i>Creating a binary existence matrix</i>	

Description

This function reduces its input matrix to a binary existence matrix based on the given description file (and information on how many values a batch needs) for proper adjustment.

Usage

```
binary_matrix_reduction(binary_data, batch_list, needed_values)
```

Arguments

- binary_data The input data.frame that should become binary.
- batch_list Information about the sample’s batch affiliations.
- needed_values Information, how many values are needed to render a a batch ‘valid’.

Value

A binary existence matrix returned as a data.frame

blocking	<i>Blocking</i>
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Description

This function performs blocking on the given description and therefore influences how the dataset will be split later down the pipeline.

Usage

```
blocking(batch_list, block)
```

Arguments

batch_list	The list with information about batch-affiliations for every sample.
block	The blocking parameter (how many batches should always get blocked together).

Value

Returns an updated 'batch_list' with blocking included

build_key_list	<i>Creation of keys</i>
----------------	-------------------------

Description

Calculates a list of usable keys based on the passed batch listings

Usage

```
build_key_list(batch_list)
```

Arguments

batch_list	The list with information about batch-affiliations for every sample.
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Value

A list element with usable keys

fetch_batch_overview	<i>Fetching batch list</i>
----------------------	----------------------------

Description

The fetch_batch_overview function extracts the overview over the batch distribution in list format.

Usage

```
fetch_batch_overview(batch_data)
```

Arguments

batch_data	This is a data.frame and simultaneously the result from read_description()
------------	--

Value

Batch distribution as list

find_na	<i>Finding NAs for the sorting process</i>
---------	--

Description

Creates an overview of NAs based on both the passed input data.frame and the batch list

Usage

```
find_na(df, batch_list)
```

Arguments

df	The data.frame passed initially by the user.
batch_list	The list with information about batch-affiliations for every sample.

Value

An overview of the NA-distribution

format_from_S4	<i>Format data taken from S4</i>
----------------	----------------------------------

Description

This function converts passed S4 summarized experiment data to HarmonizR input

Usage

```
format_from_S4(data)
```

Arguments

data	Data (S4 format) passed by the user. No description file is needed when using S4 data
------	---

Value

Data and description as data.frames

format_to_s4	<i>Format data taken from HarmonizR back to S4</i>
--------------	--

Description

This function converts passed HarmonizR output to a S4 summarized experiment data structure

Usage

```
format_to_s4(cured_data, s4_saved)
```

Arguments

cured_data	The HarmonizR output
s4_saved	The original S4 input

Value

The HarmonizR output formatted as S4 data

harmonizR

Main function

Description

This function executes the entire HarmonizR program and executes all other functions found in this package. Therefore, this is the only function in need of calling.

Usage

```
harmonizR(
  data_as_input = NULL,
  description_as_input = NULL,
  ...,
  algorithm = "ComBat",
  ComBat_mode = 1,
  plot = FALSE,
  sort = FALSE,
  block = NULL,
  output_file = "cured_data",
  verbosity = 1,
  cores = FALSE,
  ur = TRUE
)
```

Arguments

data_as_input	Path to input data. Additionally, the input can be a data.frame with proper row- and column names.
description_as_input	Path to input description. Additionally, the input can be a data.frame with three columns total.
...	Unsettable parameter. Used to make all parameters below optional. Documented to adhere with Bioconductor guidelines.
algorithm	Optional. Pass either "ComBat" or "limma" to select the preferred adjustment method. Defaults to ComBat.
ComBat_mode	Optional. Pass a number between 1 and 4 to select the desired ComBat parameters. Can only be set when ComBat is used. For information on the meaning of the numbers, please view the SOP. Defaults to 1.
plot	Optional. Takes either "samplemeans" for sample specific means, "feature-means" for feature specific means or "CV" for the coefficient of variation as input and creates before/after plots for the given data. When set, additionally writes out a .pdf file. Defaults to FALSE -> Turned off.
sort	Optional. Method to sort by. Either FALSE or "sparsity_sort", "seriation_sort" or "jaccard_sort".

block	Optional. How many batches should be treated as one during blocking. Greatly affects the number of sub-dataframes produced and reduces runtime. Turned off by default.
output_file	Optional. Takes a string as input for the .tsv file name. This can also be a path. Defaults to "cured_data", hence yielding a "cured_data.tsv" file in the work directory from which it was called. Can be turned off by passing FALSE.
verbosity	Optional. Toggles the amount of information printed out by the HarmonizR algorithm during execution. Takes a number from 0 (also "mute") to any positive number. The higher, the more information will be printed. For the standard user, anything above 2 is rarely needed. Defaults to 1.
cores	Optional. Manually sets the number of cores the user wants to be used during HarmonizR's execution. Takes a positive integer. Defaults to the amount of available cores.
ur	Optional. Toggles the functionality of the removal of unique combinations for increased data rescue. Defaults to TRUE. Not recommended to set to FALSE, as it exists for testing and reproducibility purposes.

Value

The batch effect adjusted data.frame. Additionally, a .tsv file by default called "cured_data.tsv" will be written out as a result

Examples

```
# create a dataframe with 3 rows and 6 columns filled with random numbers
df <- data.frame(matrix(rnorm(n = 3*6), ncol = 6))
# set the column names
colnames(df) <- c("A", "B", "C", "D", "E", "F")
# create a vector of row names
row_names <- c("F1", "F2", "F3")
# set the row names
rownames(df) <- row_names

# create a vector of batch numbers
batch <- rep(1:3, each = 2)
# create a dataframe with 6 rows and 3 columns
des <- data.frame(ID = colnames(df), sample = 1:6, batch = batch)

# use the harmonizR() function; turning off creation of an output .tsv file
harmonizR(df, des, output_file = FALSE, cores = 1)
```

jaccard

Jaccard-based sorting

Description

Calculates a order to sort by based on the Jaccard similarity of all given batches

Usage

```
jaccard(binary_df)
```

Arguments

binary_df	The input matrix passed by the user reduced to presence and absence of features in batches (binary)
-----------	---

Value

A template for batch-sorting based on Jaccard similarity

```
jaccard_index_absence
```

Jaccard index on zeroes (absence)

Description

Calculates the Jaccard index for two given lists a and b based on common zeroes

Usage

```
jaccard_index_absence(a, b)
```

Arguments

a	First list with either 0 or 1 entries to be compared against the second list.
b	Second list with either 0 or 1 entries to be compared against the first list.

Value

The Jaccard similarity based on absent values

```
jaccard_index_existence
```

Jaccard index on ones (existence)

Description

Calculates the Jaccard index for two given lists a and b based on common ones

Usage

```
jaccard_index_existence(a, b)
```

Arguments

- a First list with either 0 or 1 entries to be compared against the second list.
- b Second list with either 0 or 1 entries to be compared against the first list.

Value

The Jaccard similarity based on existing values

read_description	<i>Reading description</i>
------------------	----------------------------

Description

The read_description function reads in a file via its file path and converts it to a for the rest of the workflow readable format.

Usage

```
read_description(description_source)
```

Arguments

- description_source
 - Usually the path to the description file. It can also be a correctly formatted data.frame.

Value

Description as data.frame

read_main_data	<i>Reading main data</i>
----------------	--------------------------

Description

The read_main_data function reads in a file via its file path and converts it to a for the rest of the workflow readable format.

Usage

```
read_main_data(data_source)
```

Arguments

- data_source
 - Usually the path to the input data. It can also be passed directly as a correctly formatted data.frame.

Value

To-be-adjusted data as data.frame

rebuild

Rebuilding

Description

The rebuild function rebuilds the sub-dataframes to one big output data.frame.

Usage

```
rebuild(cured_subdfs)
```

Arguments

cured_subdfs a list of data.frames, which are the result from splitting().

Value

The rebuild() function returns the adjusted data.frame and writes out cured_data.tsv

sorting

Sorting the input data.frame

Description

Creates an overview of NAs based on both the passed input data.frame and the batch list

Usage

```
sorting(df, batch_list, batch_data, order_to_go_by, verbosity)
```

Arguments

df	The data.frame passed initially by the user.
batch_list	The list with information about batch-affiliations for every sample.
batch_data	The full data.frame passed as description by the user.
order_to_go_by	The template to sort by.
verbosity	Toggles the amount of information printed out by the HarmonizR algorithm during execution. Passed on from the main function.

Value

Correctly sorted data and description as two elements of a list

*splitting**Splitting*

Description

This function splits the data.frame. The data is very sensitive to its specific input. Only to be called via `harmonizR()`

Usage

```
splitting(  
  affiliation_list,  
  main_data,  
  batch_data,  
  block_list,  
  algorithm,  
  ComBat_mode,  
  block,  
  verbosity,  
  cores  
)
```

Arguments

<code>affiliation_list</code>	An overview of which protein has which missing value distribution.
<code>main_data</code>	This is the input data.frame read in by the <code>HarmonizR</code> .
<code>batch_data</code>	This is the description data.frame read in by the <code>HarmonizR</code> .
<code>block_list</code>	An overview of the batch groupings in list form. If the <code>block</code> parameter was used, the groupings are changed accordingly.
<code>algorithm</code>	Either "ComBat" or "limma". Based on the selected algorithm for the <code>harmonizR()</code> function.
<code>ComBat_mode</code>	The chosen ComBat mode influences the parameters the ComBat algorithm is using. Based on the <code>ComBat_mode</code> parameter given to the <code>harmonizR()</code> function. Not active during limma execution.
<code>block</code>	The <code>block</code> parameter is here used to determine whether there are single-batch dataframes at all present.
<code>verbosity</code>	Toggles the amount of stuff printed out by the <code>HarmonizR</code> algorithm during execution.
<code>cores</code>	Manually sets the number of cores the user wants to be used during <code>HarmonizR</code> 's execution. A positive integer.

Value

Returns a list of 'chopped up' data.frames

spotting_missing_values

Spotting

Description

This function spots missing values within the given data.frame.

Usage

```
spotting_missing_values(
  main_data,
  batch_list,
  block_list,
  needed_values,
  verbosity
)
```

Arguments

main_data	This is the input data.frame read in by the HarmonizR.
batch_list	An overview of the batch groupings in list form (comes from the user).
block_list	An overview of the batch groupings in list form (comes from the blocking function). If blocking is FALSE, this list will be the same as 'batch_list'.
needed_values	The number of values needed to be present in a batch in order to be valid.
verbosity	Toggles the amount of stuff printed out by the HarmonizR algorithm during execution.

Value

A list of vectors to pass to the upcoming splitting() function.

unique_removal

Remove unique combinations

Description

The unique_removal function changes the gathered information of the features in a way that guarantees no single-line sub-dataframes to appear, causing less data loss

Usage

```
unique_removal(affiliation_list)
```

Arguments

affiliation_list
An overview of which protein has which missing value distribution.

Value

Updated version of the passed affiliation_list

visual	<i>Visualize feature means</i>
--------	--------------------------------

Description

The visual functions turn their input dataframes into easily plottable results.

Usage

visual(input_dataframe, batch_list)

Arguments

input_dataframe
A data.frame object as input.
batch_list
A list object giving information about which column corresponds to which batch.

Value

A data.frame object, which is ready to be plotted

visual2	<i>Visualize sample means</i>
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Description

The visual functions turn their input dataframes into easily plottable results.

Usage

visual2(input_dataframe, batch_list)

Arguments

input_dataframe
A data.frame object as input.
batch_list
A list object giving information about which column corresponds to which batch.

Value

A data.frame object, which is ready to be plotted

visual3	<i>Visualize CV</i>
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Description

The visual functions turn their input dataframes into easily plottable results.

Usage

```
visual3(input_dataframe, batch_list)
```

Arguments

- input_dataframe A data.frame object as input.
- batch_list A list object giving information about which column corresponds to which batch.

Value

A data.frame object, which is ready to be plotted

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