

# Package ‘HarmonizR’

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**Title** Handles missing values and makes more data available

**Version** 1.8.0

**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)

**License** GPL-3

**Encoding** UTF-8

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**biocViews** BatchEffect

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binary\_matrix\_reduction

*Creating a binary existence matrix*

---

## 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> |
|----------|-----------------|

---

**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. |
|------------|----------------------------------------------------------------------|

**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> |
|---------|-------------------------------|

---

**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`*Visualize CV*

---

**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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