

Package ‘batchtma’

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Title Batch Effect Adjustments

Version 0.2.0

Description Different adjustment methods for batch effects in biomarker data, such as from tissue microarrays. Some methods attempt to retain differences between batches that may be due to between-batch differences in “biological” factors that influence biomarker values.

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Depends R (>= 4.1.0)

Imports broom (>= 0.7.0), dplyr (>= 1.0.4), geepack, ggplot2, limma, nnet, purrr (>= 0.3.0), quantreg, rlang (>= 0.4.0), stringr, tibble, tidyr (>= 1.1.0)

Suggests knitr, rmarkdown, testthat (>= 3.0.0)

VignetteBuilder knitr

URL <https://stopsack.github.io/batchtma/>,
<https://github.com/stopsack/batchtma/>

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adjust_batch	<i>Adjust for batch effects</i>
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Description

adjust_batch generates biomarker levels for the variable(s) markers in the dataset data that are corrected (adjusted) for batch effects, i.e. differential measurement error between levels of batch.

Usage

```
adjust_batch(
  data,
  markers,
  batch,
  method = c("simple", "standardize", "ipw", "quantreg", "quantnorm"),
  confounders = NULL,
  suffix = "_adjX",
  ipw_truncate = c(0.025, 0.975),
  quantreg_tau = c(0.25, 0.75),
  quantreg_method = "fn"
)
```

Arguments

data	Data set
markers	Variable name(s) to batch-adjust. Select multiple variables with tidy evaluation, e.g., markers = starts_with("biomarker").
batch	Categorical variable indicating batch.
method	Method for batch effect correction: <ul style="list-style-type: none"> • simple Simple means per batch will be subtracted. No adjustment for confounders. • standardize Means per batch after standardization for confounders in linear models will be subtracted. If no confounders are supplied, method = simple is equivalent and will be used. • ipw Means per batch after inverse-probability weighting for assignment to a specific batch in multinomial models, conditional on confounders, will be subtracted. Stabilized weights are used, truncated at quantiles defined by the ipw_truncate parameters. If no confounders are supplied, method = simple is equivalent and will be used. • quantreg Lower quantiles (default: 25th percentile) and ranges between a lower and an upper quantile (default: 75th percentile) will be unified between batches, allowing for differences in both parameters due to confounders. Set the two quantiles using the quantreg_tau parameters.

	<ul style="list-style-type: none"> • <code>quantnorm</code> Quantile normalization between batches. No adjustment for confounders.
<code>confounders</code>	Optional: Confounders, i.e. determinants of biomarker levels that differ between batches. Only used if <code>method = standardize</code> , <code>method = ipw</code> , or <code>method = quantreg</code> , i.e. methods that attempt to retain some of these "true" between-batch differences. Select multiple confounders with tidy evaluation, e.g., <code>confounders = c(age, age_squared, sex)</code> .
<code>suffix</code>	Optional: What string to append to variable names after batch adjustment. Defaults to <code>"_adjX"</code> , with X depending on method: <ul style="list-style-type: none"> • <code>_adj2</code> from <code>method = simple</code> • <code>_adj3</code> from <code>method = standardize</code> • <code>_adj4</code> from <code>method = ipw</code> • <code>_adj5</code> from <code>method = quantreg</code> • <code>_adj6</code> from <code>method = quantnorm</code>
<code>ipw_truncate</code>	Optional and used for <code>method = ipw</code> only: Lower and upper quantiles for truncation of stabilized weights. Defaults to <code>c(0.025, 0.975)</code> .
<code>quantreg_tau</code>	Optional and used for <code>method = quantreg</code> only: Quantiles to scale. Defaults to <code>c(0.25, 0.75)</code> .
<code>quantreg_method</code>	Optional and used for <code>method = quantreg</code> only: Algorithmic method to fit quantile regression. Defaults to <code>"fn"</code> . See parameter <code>method</code> of <code>rq</code> .

Details

If no true differences between batches are expected, because samples have been randomized to batches, then a method that returns adjusted values with equal means (`method = simple`) or with equal rank values (`method = quantnorm`) for all batches is appropriate.

If the distribution of determinants of biomarker values (`confounders`) differs between batches, then a method that retains these "true" differences between batches while adjusting for batch effects may be appropriate: `method = standardize` and `method = ipw` address means; `method = quantreg` addresses lower values and dynamic range separately.

Which method to choose depends on the properties of batch effects (affecting means or also variance?) and the presence and strength of confounding. For the two mean-only confounder-adjusted methods, the choice may depend on whether the confounder–batch association (`method = ipw`) or the confounder–biomarker association (`method = standardize`) can be modeled better. Generally, if batch effects are present, any adjustment method tends to perform better than no adjustment in reducing bias and increasing between-study reproducibility. See references.

All adjustment approaches except `method = quantnorm` are based on linear models. It is recommended that variables for markers and confounders first be transformed as necessary (e.g., [log](#) transformations or [splines](#)). Scaling or mean centering are not necessary, and adjusted values are returned on the original scale. Parameters `markers`, `batch`, and `confounders` support tidy evaluation.

Observations with missing values for the markers and confounders will be ignored in the estimation of adjustment parameters, as are empty batches. Batch effect-adjusted values for observations with existing marker values but missing confounders are based on adjustment parameters derived from the other observations in a batch with non-missing confounders.

Value

The data dataset with batch effect-adjusted variable(s) added at the end. Model diagnostics, using the attribute `.batchtma` of this dataset, are available via the `diagnose_models` function.

Author(s)

Konrad H. Stopsack

References

Stopsack KH, Tyekucheva S, Wang M, Gerke TA, Vaselkiv JB, Penney KL, Kantoff PW, Finn SP, Fiorentino M, Loda M, Lotan TL, Parmigiani G+, Mucci LA+ (+ equal contribution). Extent, impact, and mitigation of batch effects in tumor biomarker studies using tissue microarrays. *eLife* 2021;10:e71265. doi: <https://doi.org/10.7554/elife.71265> (This R package, all methods descriptions, and further recommendations.)

Rosner B, Cook N, Portman R, Daniels S, Falkner B. Determination of blood pressure percentiles in normal-weight children: some methodological issues. *Am J Epidemiol* 2008;167(6):653-66. (Basis for `method = standardize`)

Bolstad BM, Irizarry RA, Åstrand M, Speed TP. A comparison of normalization methods for high density oligonucleotide array data based on variance and bias. *Bioinformatics* 2003;19:185–193. (`method = quantnorm`)

See Also

<https://stopsack.github.io/batchtma/>

Examples

```
# Data frame with two batches
# Batch 2 has higher values of biomarker and confounder
df <- data.frame(
  tma = rep(1:2, times = 10),
  biomarker = rep(1:2, times = 10) +
    runif(max = 5, n = 20),
  confounder = rep(0:1, times = 10) +
    runif(max = 10, n = 20)
)

# Adjust for batch effects
# Using simple means, ignoring the confounder:
adjust_batch(
  data = df,
  markers = biomarker,
  batch = tma,
  method = simple
)
# Returns data set with new variable "biomarker_adj2"

# Use quantile regression, include the confounder,
# change suffix of returned variable:
```

```
adjust_batch(  
  data = df,  
  markers = biomarker,  
  batch = tma,  
  method = quantreg,  
  confounders = confounder,  
  suffix = "_batchadjusted"  
)  
# Returns data set with new variable "biomarker_batchadjusted"
```

batchtma

batchtma: Methods to address batch effects

Description

The goal of the batchtma is to provide functions for batch effect-adjusting biomarker data. It implements different methods that address batch effects while retaining differences between batches that may be due to “true” underlying differences in factors that drive biomarker values (confounders).

Functions

[adjust_batch](#): Adjust for batch effects

[diagnose_models](#): Model diagnostics after batch adjustment

[plot_batch](#): Plot biomarkers by batch

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References

Stopsack KH, Tyekucheva S, Wang M, Gerke TA, Vasselkiv JB, Penney KL, Kantoff PW, Finn SP, Fiorentino M, Loda M, Lotan TL, Parmigiani G+, Mucci LA+ (+ equal contribution). Extent, impact, and mitigation of batch effects in tumor biomarker studies using tissue microarrays. eLife 2021;10:e71265. doi: <https://doi.org/10.7554/elife.71265>

See Also

<https://stopsack.github.io/batchtma/>

diagnose_models *Model diagnostics after batch adjustment*

Description

After `adjust_batch` has performed adjustment for batch effects, `diagnose_models` provides an overview of parameters and adjustment models. Information is only available about the most recent run of `adjust_batch` on a dataset.

Usage

```
diagnose_models(data)
```

Arguments

`data` Batch-adjusted dataset (in which `adjust_batch` has stored information on batch adjustment in the attribute `.batchtma`)

Value

List:

- `adjust_method` Method used for batch adjustment (see `adjust_batch`).
- `markers` Variables of biomarkers for adjustment
- `suffix` Suffix appended to variable names
- `batchvar` Variable indicating batch
- `confounders` Confounders, i.e. determinants of biomarker levels that differ between batches. Returned only if used by the model.
- `adjust_parameters` Tibble of parameters used to obtain adjust biomarker levels. Parameters differ between methods:
 - `simple`, `standardize`, and `ipw`: Estimated adjustment parameters are a tibble with one `batchmean` per marker and `.batchvar`.
 - `quantreg` returns a tibble with numerous values per marker and `.batchvar`: unadjusted (`un_...`) and adjusted (`ad_...`) estimates of the lower (`..._lo`) and upper quantile (`..._hi`) and interquantile range (`..._iq`), plus the lower (`all_lo`) and upper quantiles (`all_hi`) across all batches.
 - `quantnorm` does not explicitly estimate parameters.
- `model_fits` List of model fit objects, one per biomarker. Models differ between methods:
 - `standardize`: Linear regression model for the biomarker with `.batchvar` and `confounders` as predictors, from which marginal predictions of batch means for each batch are obtained.
 - `ipw`: Logistic (2 batches) or multinomial models for assignment to a specific batch with `.batchvar` as the response and `confounders` as the predictors, used to generate stabilized inverse-probability weights that are then used in a linear regression model to estimate marginally standardized batch means.

- quantreg: Quantile regression with the marker as the response variable and .batchvar and confounders as predictors.
- simple and quantnorm do not fit any regression models.

Examples

```
# Data frame with two batches
# Batch 2 has higher values of biomarker and confounder
df <- data.frame(
  tma = rep(1:2, times = 10),
  biomarker = rep(1:2, times = 10) +
    runif(max = 5, n = 20),
  confounder = rep(0:1, times = 10) +
    runif(max = 10, n = 20)
)

# Adjust for batch effects
df2 <- adjust_batch(
  data = df,
  markers = biomarker,
  batch = tma,
  method = quantreg,
  confounders = confounder
)

# Show overview of model diagnostics:
diagnose_models(data = df2)

# Obtain first fitted regression model:
fit <- diagnose_models(data = df2)$model_fits[[1]][[1]]

# Obtain residuals for this model:
residuals(fit)
```

plot_batch

Plot biomarkers by batch

Description

To provide a simple visualization of potential batch effects, plot_batch generates a Tukey box plot overlaid by a jittered dot plot, inspired by the Stata plugin stripplot.

Boxes span from the 1st to the 3rd quartile; thick lines indicate medians; whiskers span up to 1.5 times the interquartile range; and asterisks indicate means.

Usage

```
plot_batch(
  data,
  marker,
```

```

    batch,
    color = NULL,
    maxlevels = 15,
    title = NULL,
    ...
  )

```

Arguments

data	Dataset.
marker	Variable indicating the biomarker.
batch	Variable indicating the batch.
color	Optional: third variable to use for symbol color and shape. For example, color can be used to show differences in a confounder.
maxlevels	Optional: Maximum number of levels for color parameter to accept as a discrete variable, rather than a continuous variable. Defaults to 15.
title	Optional: character string that specifies plot title
...	Optional: Passed on to <code>ggplot</code> .

Value

ggplot2 object, which can be further modified using standard ggplot2 functions. See examples.

References

Cox NJ (2003). STRIPLOT: Stata module for strip plots (one-way dot plots). Statistical Software Components S433401, Boston College Department of Economics, revised 11 Oct 2020.

Manimaran S, Selby HM, Okrah K, Ruberman C, Leek JT, Quackenbush J, Haibe-Kains B, Bravo HC, Johnson WE (2016). BatchQC: interactive software for evaluating sample and batch effects in genomic data. *Bioinformatics*. doi:10.1093/bioinformatics/btw538

See Also

More powerful visualizations of batch effects exist in the BatchQC package:

<https://bioconductor.org/packages/release/bioc/html/BatchQC.html>

Examples

```

# Define example data
df <- data.frame(
  tma = rep(1:2, times = 10),
  biomarker = rep(1:2, times = 10) +
    runif(max = 5, n = 20),
  confounder = rep(0:1, times = 10) +
    runif(max = 10, n = 20)
)

# Visualize batch effects:

```

```
plot_batch(  
  data = df,  
  marker = biomarker,  
  batch = tma,  
  color = confounder  
)  
  
# Label y-axis, changing graph like other ggplots:  
plot_batch(  
  data = df,  
  marker = biomarker,  
  batch = tma,  
  color = confounder  
) +  
  ggplot2::labs(y = "Biomarker (variable 'noisy')")
```

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