

# Package ‘proDA’

August 28, 2025

**Type** Package

**Title** Differential Abundance Analysis of Label-Free Mass Spectrometry Data

**Version** 1.22.1

**Description** Account for missing values in label-free mass spectrometry data without imputation. The package implements a probabilistic dropout model that ensures that the information from observed and missing values are properly combined. It adds empirical Bayesian priors to increase power to detect differentially abundant proteins.

**License** GPL-3

**Encoding** UTF-8

**LazyData** false

**RoxygenNote** 7.1.0

**Suggests** testthat (>= 2.1.0), MSnbase, dplyr, stringr, readr, tidyr, tibble, limma, DEP, numDeriv, pheatmap, knitr, rmarkdown, BiocStyle

**Imports** stats, utils, methods, BiocGenerics, SummarizedExperiment, S4Vectors, extraDistr

**URL** <https://github.com/const-ae/proDA>

**BugReports** <https://github.com/const-ae/proDA/issues>

**biocViews** Proteomics, MassSpectrometry, DifferentialExpression, Bayesian, Regression, Software, Normalization, QualityControl

**VignetteBuilder** knitr

**git\_url** <https://git.bioconductor.org/packages/proDA>

**git\_branch** RELEASE\_3\_21

**git\_last\_commit** 6954666

**git\_last\_commit\_date** 2025-05-08

**Repository** Bioconductor 3.21

**Date/Publication** 2025-08-27

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## Description

The 'proDAFit' object overwrites the dollar function to make it easy to call functions to access values inside the object. This has the advantage that it is very easy to discover the relevant methods but nonetheless have an isolated implementation. Unlike the ``@`` operator which directly accesses the underlying implementation, the ``$`` operator only exposes a limited set of functions

- abundances
- hyper\_parameters
- feature\_parameters
- coefficients
- convergence
- design
- reference\_level
- result\_names
- coefficient\_variance\_matrices
- colData
- rowData

## Usage

```
## S3 method for class 'proDAFit'  
.DollarNames(x, pattern = "")  
  
## S4 method for signature 'proDAFit'  
x$name  
  
## S4 replacement method for signature 'proDAFit'  
x$name <- value
```

## Arguments

|         |                                                                             |
|---------|-----------------------------------------------------------------------------|
| x       | an object of class 'proDAFit' produced by <code>proDA()</code>              |
| pattern | the regex pattern that is provided by the IDE                               |
| name    | one of the functions listed above                                           |
| value   | <b>Warning:</b> modifying the content of a 'proDAFit' object is not allowed |

## Value

whatever the function called name returns.

## See Also

[accessor\\_methods](#) for more documentation on the accessor functions.

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)

# The two styles are identical
design(fit)
fit$design

# More functions
fit$abundances
```

---

abundances

*Get the abundance matrix*


---

**Description**

Get the abundance matrix

**Usage**

```
abundances(object, ...)
```

**Arguments**

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object to get from                                   |
| ...    | additional arguments used by the concrete implementation |

**Value**

the original matrix that was fitted

**See Also**

[accessor\\_methods](#) for the implementation for a 'proDAFit' object

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
abundances(fit)
```

---

|                  |                                                                     |
|------------------|---------------------------------------------------------------------|
| accessor_methods | <i>Get different features and elements of the 'proDAFit' object</i> |
|------------------|---------------------------------------------------------------------|

---

## Description

The functions listed below can all be accessed using the fluent dollar notation (ie. `fit$abundances[1:3, 1:3]`) without any additional parentheses.

## Usage

```
## S4 method for signature 'proDAFit'  
abundances(object)
```

```
## S4 method for signature 'proDAFit'  
design(object, formula = FALSE)
```

```
## S4 method for signature 'proDAFit'  
hyper_parameters(object)
```

```
## S4 method for signature 'proDAFit'  
feature_parameters(object)
```

```
## S4 method for signature 'proDAFit'  
coefficients(object)
```

```
## S4 method for signature 'proDAFit'  
coefficient_variance_matrices(object)
```

```
## S4 method for signature 'proDAFit'  
reference_level(object)
```

```
## S4 method for signature 'proDAFit'  
convergence(object)
```

## Arguments

|         |                                                                                                                                                 |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| object  | the 'proDAFit' object                                                                                                                           |
| formula | specific argument for the design function to get the formula that was used to create the linear model. If no formula was used NULL is returned. |

## Value

See the documentation of the generics to find out what each method returns

---

|              |                                                                            |
|--------------|----------------------------------------------------------------------------|
| as_replicate | <i>Get numeric vector with the count of the replicate for each element</i> |
|--------------|----------------------------------------------------------------------------|

---

**Description**

For a vector with repeated values return a vector where each element is the count how often the element was observed previously

**Usage**

```
as_replicate(x)
```

**Arguments**

|   |                                 |
|---|---------------------------------|
| x | a vector with repeated elements |
|---|---------------------------------|

**Value**

numeric vector

**See Also**

[order](#), [rank](#)

**Examples**

```
x <- c("a", "b", "a", "b", "b", "d")
all(proDA:::as_replicate(x) == c(1,1,2,2,3,1))
```

---

|              |                             |
|--------------|-----------------------------|
| coefficients | <i>Get the coefficients</i> |
|--------------|-----------------------------|

---

**Description**

Get the coefficients

**Usage**

```
coefficients(object, ...)
```

**Arguments**

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object to get from                                   |
| ...    | additional arguments used by the concrete implementation |

**Value**

a numeric matrix of size 'nrow(fit) \* p'

**See Also**

[accessor\\_methods](#) for the implementation for a 'proDAFit' object

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
coefficients(fit)
```

---

coefficient\_variance\_matrices

*Get the coefficients*

---

**Description**

Get the coefficients

**Usage**

```
coefficient_variance_matrices(object, ...)
```

**Arguments**

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object to get from                                   |
| ...    | additional arguments used by the concrete implementation |

**Value**

a list with as many entries as rows in the data. Each element is a p\*p matrix

**See Also**

[accessor\\_methods](#) for the implementation for a 'proDAFit' object

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
coefficient_variance_matrices(fit)
```

---

|             |                                        |
|-------------|----------------------------------------|
| convergence | <i>Get the convergence information</i> |
|-------------|----------------------------------------|

---

**Description**

Get the convergence information

**Usage**

```
convergence(object, ...)
```

**Arguments**

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object to get from                                   |
| ...    | additional arguments used by the concrete implementation |

**Value**

a list with information on the convergence

**See Also**

[accessor\\_methods](#) for the implementation for a 'proDAFit' object

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
convergence(fit)
```

---

|             |                                                           |
|-------------|-----------------------------------------------------------|
| distance_sq | <i>Square distance between two Gaussian distributions</i> |
|-------------|-----------------------------------------------------------|

---

**Description**

The function takes the mean and the diagonal of the covariance matrix as vector and calculates the mean and variance of their distance distribution. The formulas are based on [1] page 53.

**Usage**

```
distance_sq(mu1, sigma1, mu2, sigma2)
```

**Value**

a list with elements 'mean' and 'var'

1. Mathai, A. & Provost, S. Quadratic Forms in Random Variables. (1992).

---

|             |                                                       |
|-------------|-------------------------------------------------------|
| dist_approx | <i>Calculate an approximate distance for 'object'</i> |
|-------------|-------------------------------------------------------|

---

**Description**

Calculate an approximate distance for 'object'

**Usage**

```
dist_approx(object, ...)
```

**Arguments**

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object for which the distance is approximated        |
| ...    | additional arguments used by the concrete implementation |

**Value**

a list with two elements: 'mean' and 'sd' both are formally of class "dist"

**See Also**

[dist](#) for the base R function and [dist\\_approx\(\)](#) concrete implementation for 'proDAFit' objects

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
dist_approx(fit)
```

---

|                  |                                              |
|------------------|----------------------------------------------|
| dist_approx_impl | <i>Distance method for 'proDAFit' object</i> |
|------------------|----------------------------------------------|

---

**Description**

The method calculates either the euclidean distance between samples or proteins taking into account the missing values and the associated uncertainty. Because with missing value no single deterministic distance can be calculated two objects are returned: the mean and the associated standard deviation of the distance estimates.

**Usage**

```
## S4 method for signature 'proDAFit'
dist_approx(object, by_sample = TRUE, blind = TRUE)

## S4 method for signature 'SummarizedExperiment'
dist_approx(object, by_sample = TRUE, blind = TRUE, ...)

## S4 method for signature 'ANY'
dist_approx(object, by_sample = TRUE, blind = TRUE, ...)
```

**Arguments**

|           |                                                                                                                                                                 |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| object    | the 'proDAFit' object for which we calculate the distance or a matrix like object for which 'proDAFit' is created internally                                    |
| by_sample | a boolean that indicates if the distances is calculated between the samples ('by_sample = TRUE') or between the proteins ('by_sample = FALSE'). Default: 'TRUE' |
| blind     | fit an intercept model for the missing values to make sure that the results are not biased for the expected result. Default: 'TRUE'                             |
| ...       | additional arguments to proDA() in case object is a SummarizedExperiment or a matrix                                                                            |

**Value**

a list with two elements: 'mean' and 'sd' both are formally of class "dist"

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
dist_approx(fit)
```

---

|                    |                                   |
|--------------------|-----------------------------------|
| feature_parameters | <i>Get the feature parameters</i> |
|--------------------|-----------------------------------|

---

**Description**

Get the feature parameters

**Usage**

```
feature_parameters(object, ...)
```

**Arguments**

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object to get from                                   |
| ...    | additional arguments used by the concrete implementation |

**Value**

a data.frame with information on each fit

**See Also**

[accessor\\_methods](#) for the implementation for a 'proDAFit' object

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
feature_parameters(fit)
```

---

generate\_synthetic\_data

*Generate a dataset according to the probabilistic dropout model*

---

**Description**

Generate a dataset according to the probabilistic dropout model

**Usage**

```
generate_synthetic_data(
  n_proteins,
  n_conditions = 2,
  n_replicates = 3,
  frac_changed = 0.1,
  dropout_curve_position = 18.5,
  dropout_curve_scale = -1.2,
  location_prior_mean = 20,
  location_prior_scale = 4,
  variance_prior_scale = 0.05,
  variance_prior_df = 2,
  effect_size = 2,
  return_summarized_experiment = FALSE
)
```

**Arguments**

|              |                                                                                                                                                       |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| n_proteins   | the number of rows in the dataset                                                                                                                     |
| n_conditions | the number of conditions. Default: 2                                                                                                                  |
| n_replicates | the number of replicates per condition. Can either be a single number or a vector with <code>length(n_replicates) == n_conditions</code> . Default: 3 |
| frac_changed | the fraction of proteins that actually differ between the conditions. Default: 0.1                                                                    |

**dropout\_curve\_position**  
the point where the chance to observe a value is 50%. Can be a single number or a vector of length(dropout\_curve\_position) == n\_conditions \* n\_replicates. Default: 18.5

**dropout\_curve\_scale**  
The width of the dropout curve. Negative numbers mean that lower intensities are more likely to be missing. Can be a single number or a vector of length(dropout\_curve\_position) == n\_conditions \* n\_replicates. Default: -1.2

**location\_prior\_mean, location\_prior\_scale**  
the position and the variance around which the individual condition means ( $t_{\mu}$ ) scatter. Default: 20 and 4

**variance\_prior\_scale, variance\_prior\_df**  
the scale and the degrees of freedom of the inverse Chi-squared distribution used as a prior for the variances. Default: 0.05 and 2

**effect\_size**  
the standard deviation that is used to draw different values for the frac\_changed part of the proteins. Default: 2

**return\_summarized\_experiment**  
a boolean indicator if the method should return a SummarizedExperiment object instead of a list. Default: FALSE

## Value

a list with the following elements

**Y** the intensity matrix including the missing values

**Z** the intensity matrix before dropping out values

**t\_mu** a matrix with n\_proteins rows and n\_conditions columns that contains the underlying means for each protein

**t\_sigma2** a vector with the true variances for each protein

**changed** a vector with boolean values if the protein is actually changed

**group** the group structure mapping samples to conditions

if return\_summarized\_experiment is FALSE. Otherwise returns a SummarizedExperiment with the same information.

## Examples

```
syn_data <- generate_synthetic_data(n_proteins = 10)
names(syn_data)
head(syn_data$Y)

# Returning a SummarizedExperiment
se <- generate_synthetic_data(n_proteins = 10, return_summarized_experiment = TRUE)
se
head(SummarizedExperiment::assay(se))
```

---

|                  |                                 |
|------------------|---------------------------------|
| hyper_parameters | <i>Get the hyper parameters</i> |
|------------------|---------------------------------|

---

**Description**

Get the hyper parameters

**Usage**

```
hyper_parameters(object, ...)
```

**Arguments**

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object to get from                                   |
| ...    | additional arguments used by the concrete implementation |

**Value**

a list with the values for each fitted hyper-parameter

**See Also**

[accessor\\_methods](#) for the implementation for a 'proDAFit' object

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
hyper_parameters(fit)
```

---

|           |                                |
|-----------|--------------------------------|
| invprobit | <i>Inverse probit function</i> |
|-----------|--------------------------------|

---

**Description**

Calculate the values of the sigmoidal function that is defined by the cumulative normal distribution function ([pnorm](#)). This method provides a convenient wrapper for the pnorm that automatically handles negative zeta and is more consistent in its naming.

**Usage**

```
invprobit(x, rho, zeta, log = FALSE, oneminus = FALSE)
```

**Arguments**

|          |                                                                                                                                           |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------|
| x        | numeric vector                                                                                                                            |
| rho      | numeric vector of length 1 or the same length as x. Specifies the inflection point of the inverse probit curve.                           |
| zeta     | numeric vector of length 1 or the same length as x. Specifies the scale of the curve at the inflection point of the inverse probit curve. |
| log      | boolean if the log of the result is returned                                                                                              |
| oneminus | boolean if one minus the result is returned                                                                                               |

**Value**

a numeric vector of length(x).

**Examples**

```
xg <- seq(-5, 5, length.out=101)
plot(xg, invprobit(xg, rho=-2, zeta=-0.3))
```

---

|                |                                                                      |
|----------------|----------------------------------------------------------------------|
| invprobit_fast | <i>Same thing as invprobit, but without the parameter validation</i> |
|----------------|----------------------------------------------------------------------|

---

**Description**

Same thing as invprobit, but without the parameter validation

**Usage**

```
invprobit_fast(x, rho, zeta, log = FALSE, oneminus = FALSE)
```

**Value**

a numeric vector of length(x)

---

|                      |                                                            |
|----------------------|------------------------------------------------------------|
| median_normalization | <i>Column wise median normalization of the data matrix</i> |
|----------------------|------------------------------------------------------------|

---

### Description

The method calculates for each sample the median change (i.e. the difference between the observed value and the row average) and subtracts it from each row. Missing values are ignored in the procedure. The method is based on the assumption that a majority of the rows did not change.

### Usage

```
median_normalization(X, spike_in_rows = NULL)
```

### Arguments

|               |                                                                                                                                            |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| X             | a matrix or SummarizedExperiment of proteins and samples                                                                                   |
| spike_in_rows | a numeric or boolean vector that is used to to normalize the intensities across samples. Default: NULL which means that all rows are used. |

### Value

the normalized matrix

### Examples

```
syn_data <- generate_synthetic_data(n_proteins = 10)
normalized_data <- median_normalization(syn_data$Y)
normalized_data

# If we assume that the first 5 proteins are spike-ins
normalized_data2 <- median_normalization(syn_data$Y, spike_in_rows = 1:5)
```

---

|          |                                                            |
|----------|------------------------------------------------------------|
| mply_dbl | <i>apply function that always returns a numeric matrix</i> |
|----------|------------------------------------------------------------|

---

### Description

The function is modeled after 'vapply', but always returns a matrix with one row for each iteration. You need to provide the number of elements each function call produces beforehand (i.e. the number of resulting columns). For a more flexible version where you don't need to provide the number of columns see [msply\\_dbl](#)

**Usage**

```
mapply_dbl(x, FUN, ncol = 1, ...)
```

```
msply_dbl(x, FUN, ...)
```

**Arguments**

|      |                                                                                                  |
|------|--------------------------------------------------------------------------------------------------|
| x    | a vector that will be passed to ‘vapply’ or a matrix that will be passed to apply with MARGIN=1. |
| FUN  | the function that returns a vector of length ncol                                                |
| ncol | the length of the vector returned by ‘FUN’.                                                      |
| ...  | additional arguments to FUN                                                                      |

**Value**

a matrix of size length(x) x ncol

**Functions**

- mply\_dbl: apply function that always returns a numeric matrix
- msply\_dbl: flexible version that automatically infers the number of columns

**Examples**

```
# Behaves similar to sapply(), but it always returns a matrix
t(sapply(1:5, function(i) c(i - i/3, i, i + i/3)))
proDA::mapply_dbl(1:5, function(i) c(i - i/3, i, i + i/3), ncol=3)
```

```
# Which can avoid some bad surprises
t(sapply(1:5, identity))
proDA::mapply_dbl(1:5, identity)
```

```
# Works also with matrix input
mat <- matrix(1:20, ncol=4)
mat
proDA::msply_dbl(mat, function(i) rep(i, each=2))
```

## Description

The function works similar to the classical `lm` but with special handling of NA's. Whereas `lm` usually just ignores response value that are missing, `pd_lm` applies a probabilistic dropout model, that assumes that missing values occur because of the dropout curve. The dropout curve describes for each position the chance that that a value is missed. A negative `dropout_curve_scale` means that the lower the intensity was, the more likely it is to miss the value.

## Usage

```
pd_lm(
  formula,
  data = NULL,
  subset = NULL,
  dropout_curve_position,
  dropout_curve_scale,
  location_prior_mean = NULL,
  location_prior_scale = NULL,
  variance_prior_scale = NULL,
  variance_prior_df = NULL,
  location_prior_df = 3,
  method = c("analytic_hessian", "analytic_grad", "numeric"),
  verbose = FALSE
)
```

## Arguments

|                                                        |                                                                                                                                                                                                              |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>formula</code>                                   | a formula that specifies a linear model                                                                                                                                                                      |
| <code>data</code>                                      | an optional data.frame whose columns can be used to specify the formula                                                                                                                                      |
| <code>subset</code>                                    | an optional selection vector for data to subset it                                                                                                                                                           |
| <code>dropout_curve_position</code>                    | the value where the chance to observe a value is 50%. Can either be a single value that is repeated for each row or a vector with one element for each row. Not optional.                                    |
| <code>dropout_curve_scale</code>                       | the width of the dropout curve. Smaller values mean that the sigmoidal curve is steeper. Can either be a single value that is repeated for each row or a vector with one element for each row. Not optional. |
| <code>location_prior_mean, location_prior_scale</code> | the optional mean and variance of the prior around which the predictions are supposed to scatter. If no value is provided no location regularization is applied.                                             |
| <code>variance_prior_scale, variance_prior_df</code>   | the optional scale and degrees of freedom of the variance prior. If no value is provided no variance regularization is applied.                                                                              |
| <code>location_prior_df</code>                         | The degrees of freedom for the t-distribution of the location prior. If it is large (> 30) the prior is approximately Normal. Default: 3                                                                     |

**method** one of 'analytic\_hessian', 'analytic\_gradient', or 'numeric'. If 'analytic\_hessian' the `nlminb` optimization routine is used, with the hand derived first and second derivative. Otherwise, `optim` either with or without the first derivative is used.

**verbose** boolean that signals if the method prints informative messages. Default: FALSE.

## Value

a list with the following entries

**coefficients** a named vector with the fitted values

**coef\_variance\_matrix** a p\*p matrix with the variance associated with each coefficient estimate

**n\_approx** the estimated "size" of the data set (n\_hat - variance\_prior\_df)

**df** the estimated degrees of freedom (n\_hat - p)

**s2** the estimated unbiased variance

**n\_obs** the number of response values that were not 'NA'

## Examples

```
# Without missing values
y <- rnorm(5, mean=20)
lm(y ~ 1)
pd_lm(y ~ 1,
      dropout_curve_position = NA,
      dropout_curve_scale = NA)
```

```
# With some missing values
y <- c(23, 21.4, NA)
lm(y ~ 1)
pd_lm(y ~ 1,
      dropout_curve_position = 19,
      dropout_curve_scale = -1)
```

```
# With only missing values
y <- c(NA, NA, NA)
# lm(y ~ 1) # Fails
pd_lm(y ~ 1,
      dropout_curve_position = 19,
      dropout_curve_scale = -1,
      location_prior_mean = 21,
      location_prior_scale = 3,
      variance_prior_scale = 0.1,
      variance_prior_df = 2)
```

---

pd\_lm.fit

*The work horse for fitting the probabilistic dropout model*


---

## Description

If there is no location and variance moderation and no missing values, the model is fitted with ‘lm’.

## Usage

```
pd_lm.fit(
  y,
  X,
  dropout_curve_position,
  dropout_curve_scale,
  location_prior_mean = NULL,
  location_prior_scale = NULL,
  variance_prior_scale = NULL,
  variance_prior_df = NULL,
  location_prior_df = 3,
  method = c("analytic_hessian", "analytic_grad", "numeric"),
  verbose = FALSE
)
```

## Value

a list with the following entries

**coefficients** a named vector with the fitted values

**n\_approx** the estimated "size" of the data set (n\_hat - variance\_prior\_df)

**df** the estimated degrees of freedom (n\_hat - p)

**s2** the estimated unbiased variance

**n\_obs** the number of response values that were not ‘NA’

---

pd\_row\_t\_test

*Row-wise tests of difference using the probabilistic dropout model*


---

## Description

This is a helper function that combines the call of proDA() and test\_diff(). If you need more flexibility use those functions.

**Usage**

```

pd_row_t_test(
  X,
  Y,
  moderate_location = TRUE,
  moderate_variance = TRUE,
  alternative = c("two.sided", "greater", "less"),
  pval_adjust_method = "BH",
  location_prior_df = 3,
  max_iter = 20,
  epsilon = 0.001,
  return_fit = FALSE,
  verbose = FALSE
)

pd_row_f_test(
  X,
  ...,
  groups = NULL,
  moderate_location = TRUE,
  moderate_variance = TRUE,
  pval_adjust_method = "BH",
  location_prior_df = 3,
  max_iter = 20,
  epsilon = 0.001,
  return_fit = FALSE,
  verbose = FALSE
)

```

**Arguments**

|                    |                                                                                                                                                                        |
|--------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| X, Y, ...          | the matrices for condition 1, 2 and so on. They must have the same number of rows.                                                                                     |
| moderate_location  | boolean values to indicate if the location and the variances are moderated. Default: TRUE                                                                              |
| moderate_variance  | boolean values to indicate if the location and the variances are moderated. Default: TRUE                                                                              |
| alternative        | a string that decides how the hypothesis test is done. This parameter is only relevant for the Wald-test specified using the 'contrast' argument. Default: "two.sided" |
| pval_adjust_method | a string the indicates the method that is used to adjust the p-value for the multiple testing. It must match the options in <a href="#">p.adjust</a> . Default: "BH"   |
| location_prior_df  | the number of degrees of freedom used for the location prior. A large number (> 30) means that the prior is approximately Normal. Default: 3                           |

|            |                                                                                                                                                                                                      |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| max_iter   | the maximum of iterations <code>proDA()</code> tries to converge to the hyper-parameter estimates. Default: 20                                                                                       |
| epsilon    | if the remaining error is smaller than epsilon the model has converged. Default: 1e-3                                                                                                                |
| return_fit | boolean that signals that in addition to the data.frame with the hypothesis test results, the fit from <code>proDA()</code> is returned. Default: FALSE                                              |
| verbose    | boolean that signals if the method prints messages during the fitting. Default: FALSE                                                                                                                |
| groups     | a factor or character vector with that assigns the columns of X to different conditions. This parameter is only applicable for the F-test and must be specified if only a single matrix is provided. |

### Details

The `pd_row_t_test` is not actually doing a t-test, but rather a Wald test. But, as the two are closely related and term t-test is more widely understood, we choose to use that name.

### Value

If `return_fit == FALSE` a data.frame is returned with the content that is described in [test\\_diff](#).

If `return_fit == TRUE` a list is returned with two elements: fit with a reference to the object returned from `proDA()` and a `test_result()` with the data.frame returned from `test_diff()`.

### See Also

[proDA](#) and [test\\_diff](#) for more flexible versions. The function was inspired by the [rowFtests](#) function in the `genefilter` package.

### Examples

```
data1 <- matrix(rnorm(10 * 3), nrow=10)
data2 <- matrix(rnorm(10 * 4), nrow=10)
data3 <- matrix(rnorm(10 * 2), nrow=10)

# Comparing two datasets
pd_row_t_test(data1, data2)

# Comparing multiple datasets
pd_row_f_test(data1, data2, data3)

# Alternative
data_comb <- cbind(data1, data2, data3)
pd_row_f_test(data_comb,
  groups = c(rep("A",3), rep("B", 4), rep("C", 2)))

# t.test, lm, pd_row_t_test, and pd_row_f_test are
# approximately equivalent on fully observed data
set.seed(1)
x <- rnorm(5)
```

```

y <- rnorm(5, mean=0.3)

t.test(x, y)
summary(lm(c(x, y) ~ cond,
            data = data.frame(cond = c(rep("x", 5),
                                       rep("y", 5)))))$coefficients[2,]

pd_row_t_test(matrix(x, nrow=1), matrix(y, nrow=1),
               moderate_location = FALSE,
               moderate_variance = FALSE)
pd_row_f_test(matrix(x, nrow=1), matrix(y, nrow=1),
               moderate_location = FALSE,
               moderate_variance = FALSE)

```

---

predict,proDAFit-method

*Predict the parameters or values of additional proteins*


---

## Description

This function can either predict the abundance matrix for proteins (type = "response") without missing values according to the linear probabilistic dropout model, fitted with proDA(). Or, it can predict the feature parameters for additional proteins given their abundances including missing values after estimating the hyper-parameters on a dataset with the same sample structure (type = "feature\_parameters").

## Usage

```

## S4 method for signature 'proDAFit'
predict(
  object,
  newdata,
  newdesign,
  type = c("response", "feature_parameters"),
  ...
)

```

## Arguments

|           |                                                                                                      |
|-----------|------------------------------------------------------------------------------------------------------|
| object    | an 'proDAFit' object that is produced by proDA().                                                    |
| newdata   | a matrix or a SummarizedExperiment which contains the new abundances for which values are predicted. |
| newdesign | a formula or design matrix that specifies the new structure that will be fitted                      |
| type      | either "response" or "feature_parameters". Default: "response"                                       |
| ...       | additional parameters for the construction of the 'proDAFit' object.                                 |

## Details

**Note:** this method behaves a little different from what one might expect from the classical `predict.lm()` function, because `object` is not just a single set of coefficients for one fit, but many fits (ie. one for each protein) with some more hyper-parameters. The classical `predict` function predicts the response for new samples. This function does not support this, instead it is useful for getting a matrix without missing values for additional proteins.

## Value

If `type = "response"` a matrix with the same dimensions as `object`. Or, if `type = "feature_parameters"` a 'proDAFit' object with the same hyper-parameters and column data as `object`, but new fitted `rowData()`.

---

proDA

*Main function to fit the probabilistic dropout model*

---

## Description

The function fits a linear probabilistic dropout model and infers the hyper-parameters for the location prior, the variance prior, and the dropout curves. In addition it infers for each protein the coefficients that best explain the observed data and the associated uncertainty.

## Usage

```
proDA(
  data,
  design = ~1,
  col_data = NULL,
  reference_level = NULL,
  data_is_log_transformed = TRUE,
  moderate_location = TRUE,
  moderate_variance = TRUE,
  location_prior_df = 3,
  n_subsample = nrow(data),
  max_iter = 20,
  epsilon = 0.001,
  verbose = FALSE,
  ...
)
```

## Arguments

|                   |                                                                                                                                                                                                                                                                                 |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>data</code> | a matrix like object ( <code>matrix()</code> , <code>SummarizedExperiment()</code> , or anything that can be cast to <code>SummarizedExperiment()</code> (eg. 'MSnSet', 'eSet', ...)) with one column per sample and one row per protein. Missing values should be coded as NA. |
|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| design                               | a specification of the experimental design that is used to fit the linear model. It can be a <code>model.matrix()</code> with one row for each sample and one column for each coefficient. It can also be a formula with the entries referring to global objects, columns in the <code>col_data</code> argument or columns in the <code>colData(data)</code> if data is a <code>SummarizedExperiment</code> . Thirdly, it can be a vector that for each sample specifies the condition of that sample. Default: <code>~ 1</code> , which means that all samples are treated as if they are in the same condition. |
| col_data                             | a data.frame with one row for each sample in data. Default: NULL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| reference_level                      | a string that specifies which level in a factor coefficient is used for the intercept. Default: NULL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| data_is_log_transformed              | the raw intensities from mass spectrometry experiments have a linear mean-variance relation. This is undesirable and can be removed by working on the log scale. The easiest way to find out if the data is already log- transformed is to see if the intensities are in the range of '0' to '100' in which case they are transformed or if they rather are between '1e5' to '1e12', in which case they are not. Default: TRUE                                                                                                                                                                                    |
| moderate_location, moderate_variance | boolean values to indicate if the location and the variances are moderated. Default: TRUE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| location_prior_df                    | the number of degrees of freedom used for the location prior. A large number (> 30) means that the prior is approximately Normal. Default: 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| n_subsample                          | the number of proteins that are used to estimate the hyper-parameter. Reducing this number can speed up the fitting, but also mean that the final estimate is less precise. By default all proteins are used. Default: <code>nrow(data)</code>                                                                                                                                                                                                                                                                                                                                                                    |
| max_iter                             | the maximum of iterations <code>proDA()</code> tries to converge to the hyper-parameter estimates. Default: 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| epsilon                              | if the remaining error is smaller than <code>epsilon</code> the model has converged. Default: <code>1e-3</code>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| verbose                              | boolean that signals if the method prints messages during the fitting. Default: FALSE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| ...                                  | additional parameters for the construction of the 'proDAFit' object                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

## Details

By default, the method is moderating the locations and the variance of each protein estimate. The variance moderation is fairly standard in high-throughput experiments and can boost the power to detect differentially abundant proteins. The location moderation is important to handle the edge case where in one condition a protein is not observed in any sample. In addition it can help to get more precise estimates of the difference between conditions. Unlike 'DESeq2', which moderates the coefficient estimates (ie. the "betas") to be centered around zero, 'proDA' penalizes predicted intensities that strain far from the other observed intensities.

**Value**

An object of class 'proDAFit'. The object contains information on the hyper-parameters and feature parameters, the convergence, the experimental design etc. Internally, it is a sub-class of SummarizedExperiment which means the object is subsettable. The '\$'-operator is overloaded for this object to make it easy to discover applicable functions.

**Examples**

```
# Quick start

# Import the proDA package if you haven't already done so
# library(proDA)
set.seed(1)
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
fit
result_names(fit)
test_diff(fit, Condition_1 - Condition_2)

# SummarizedExperiment
se <- generate_synthetic_data(n_proteins = 10,
                             return_summarized_experiment = TRUE)
se
proDA(se, design = ~ group)

# Design using model.matrix()
data_mat <- matrix(rnorm(5 * 10), nrow=10)
colnames(data_mat) <- paste0("sample", 1:5)
annotation_df <- data.frame(names = paste0("sample", 1:5),
                             condition = c("A", "A", "A", "B", "B"),
                             age = rnorm(5, mean=40, sd=10))

design_mat <- model.matrix(~ condition + age,
                          data=annotation_df)

design_mat
proDA(data_mat, design_mat, col_data = annotation_df)
```

---

proDAFit-class

*proDA Class Definition*


---

**Description**

proDA Class Definition

---

|               |                                                                                         |
|---------------|-----------------------------------------------------------------------------------------|
| proDA_package | <i>proDA: Identify differentially abundant proteins in label-free mass spectrometry</i> |
|---------------|-----------------------------------------------------------------------------------------|

---

### Description

Account for missing values in label-free mass spectrometry data without imputation. The package implements a probabilistic dropout model that ensures that the information from observed and missing values are properly combined. It adds empirical Bayesian priors to increase power to detect differentially abundant proteins.

---

|                 |                                |
|-----------------|--------------------------------|
| reference_level | <i>Get the reference level</i> |
|-----------------|--------------------------------|

---

### Description

Get the reference level

### Usage

```
reference_level(object, ...)
```

### Arguments

|        |                                                          |
|--------|----------------------------------------------------------|
| object | the object to get from                                   |
| ...    | additional arguments used by the concrete implementation |

### Value

a string

### See Also

[accessor\\_methods](#) for the implementation for a 'proDAFit' object

### Examples

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups, reference_level = "Condition_1")
reference_level(fit)
```

---

|              |                             |
|--------------|-----------------------------|
| result_names | <i>Get the result_names</i> |
|--------------|-----------------------------|

---

**Description**

Get the result\_names

**Usage**

```
result_names(fit, ...)
```

**Arguments**

|     |                                                          |
|-----|----------------------------------------------------------|
| fit | the fit to get the result_names from                     |
| ... | additional arguments used by the concrete implementation |

**Value**

a character vector

**Examples**

```
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
result_names(fit)
```

---

|           |                                                  |
|-----------|--------------------------------------------------|
| test_diff | <i>Identify differentially abundant proteins</i> |
|-----------|--------------------------------------------------|

---

**Description**

The ‘test\_diff()’ function is used to test coefficients of a ‘proDAFit’ object. It provides a Wald test to test individual coefficients and a likelihood ratio F-test to compare the original model with a reduced model. The result\_names method provides a quick overview which coefficients are available for testing.

**Usage**

```
test_diff(
  fit,
  contrast,
  reduced_model = ~1,
  alternative = c("two.sided", "greater", "less"),
  pval_adjust_method = "BH",
  sort_by = NULL,
```

```

    decreasing = FALSE,
    n_max = Inf,
    verbose = FALSE
)

## S4 method for signature 'proDAFit'
result_names(fit)

```

## Arguments

|                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <code>fit</code>                | an object of class 'proDAFit'. Usually, this is produced by calling <code>proDA()</code>                                                                                                                                                                                                                                                                                                                                                                                                               |
| <code>contrast</code>           | an expression or a string specifying which contrast is tested. It can be a single coefficient (to see the available options use <code>result_names(fit)</code> ) or any linear combination of them. The contrast is always compared against zero. Thus, to find out if two coefficients differ use <code>coef1 - coef2</code> . Remember if the coefficient is not a valid identifier in R, to escape it using back ticks. For example if you test the interaction of A and B use <code>`A:B`</code> . |
| <code>reduced_model</code>      | If you don't want to test an individual coefficient, you can specify a reduced model and compare it with the original model using an F-test. This is useful to find out how a set of parameters affect the goodness of the fit. If neither a contrast, nor a <code>reduced_model</code> is specified, by default a comparison with an intercept model (ie. just the average across conditions) is done. Default: <code>~ 1</code> .                                                                    |
| <code>alternative</code>        | a string that decides how the hypothesis test is done. This parameter is only relevant for the Wald-test specified using the 'contrast' argument. Default: <code>"two.sided"</code>                                                                                                                                                                                                                                                                                                                    |
| <code>pval_adjust_method</code> | a string that indicates the method that is used to adjust the p-value for the multiple testing. It must match the options in <code>p.adjust</code> . Default: <code>"BH"</code>                                                                                                                                                                                                                                                                                                                        |
| <code>sort_by</code>            | a string that specifies the column that is used to sort the resulting data.frame. Default: <code>NULL</code> which means the result is sorted by the order of the input matrix.                                                                                                                                                                                                                                                                                                                        |
| <code>decreasing</code>         | a boolean to indicate if the order is reversed. Default: <code>FALSE</code>                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <code>n_max</code>              | the maximum number of rows returned by the method. Default: <code>Inf</code>                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <code>verbose</code>            | boolean that signals if the method prints informative messages. Default: <code>FALSE</code> .                                                                                                                                                                                                                                                                                                                                                                                                          |

## Details

To test if coefficient is different from zero with a Wald test use the `contrast` function argument. To test if two models differ with an F-test use the `reduced_model` argument. Depending on the test that is conducted, the functions returns slightly different data.frames.

The function is designed to follow the principles of the base R test functions (ie. `t.test` and `wilcox.test`) and the functions designed for collecting the results of high-throughput testing (ie. `limma::topTable` and `DESeq2::results`).

## Value

The `'result_names()'` function returns a character vector.

The `'test_diff()'` function returns a `data.frame` with one row per protein with the key parameters of the statistical test. Depending what kind of test (Wald or F test) the content of the `'data.frame'` differs.

The Wald test, which can be considered equivalent to a t-test, returns a `'data.frame'` with the following columns:

- name** the name of the protein, extracted from the rowname of the input matrix
- pval** the p-value of the statistical test
- adj\_pval** the multiple testing adjusted p-value
- diff** the difference that particular coefficient makes. In differential expression analysis this value is also called log fold change, which is equivalent to the difference on the log scale.
- t\_statistic** the diff divided by the standard error se
- se** the standard error associated with the diff
- df** the degrees of freedom, which describe the amount of available information for estimating the se. They are the sum of the number of samples the protein was observed in, the amount of information contained in the missing values, and the degrees of freedom of the variance prior.
- avg\_abundance** the estimate of the average abundance of the protein across all samples.
- n\_approx** the approximated information available for estimating the protein features, expressed as multiple of the information contained in one observed value.
- n\_obs** the number of samples a protein was observed in

The F-test returns a `'data.frame'` with the following columns

- name** the name of the protein, extracted from the rowname of the input matrix
- pval** the p-value of the statistical test
- adj\_pval** the multiple testing adjusted p-value
- f\_statistic** the ratio of difference of normalized deviances from original model and the reduced model, divided by the standard deviation.
- df1** the difference of the number of coefficients in the original model and the number of coefficients in the reduced model
- df2** the degrees of freedom, which describe the amount of available information for estimating the se. They are the sum of the number of samples the protein was observed in, the amount of information contained in the missing values, and the degrees of freedom of the variance prior.
- avg\_abundance** the estimate of the average abundance of the protein across all samples.
- n\_approx** the information available for estimating the protein features, expressed as multiple of the information contained in one observed value.
- n\_obs** the number of samples a protein was observed in

## See Also

The contrast argument is inspired by `limma::makeContrasts`.

**Examples**

```
# "t-test"
syn_data <- generate_synthetic_data(n_proteins = 10)
fit <- proDA(syn_data$Y, design = syn_data$groups)
result_names(fit)
test_diff(fit, Condition_1 - Condition_2)

suppressPackageStartupMessages(library(SummarizedExperiment))
se <- generate_synthetic_data(n_proteins = 10,
                             n_conditions = 3,
                             return_summarized_experiment = TRUE)
colData(se)$age <- rnorm(9, mean=45, sd=5)
colData(se)
fit <- proDA(se, design = ~ group + age)
result_names(fit)
test_diff(fit, "groupCondition_2",
          n_max = 3, sort_by = "pval")

# F-test
test_diff(fit, reduced_model = ~ group)
```

---

%zero\_dom\_mat\_mult%      *Helper function that makes sure that  $NA * 0 = 0$  in matrix multiply*

---

**Description**

Helper function that makes sure that  $NA * 0 = 0$  in matrix multiply

**Usage**

```
X %zero_dom_mat_mult% Y
```

**Arguments**

|   |                        |
|---|------------------------|
| X | a matrix of size ‘n*m’ |
| Y | a matrix of size ‘m*p’ |

**Value**

a matrix of size ‘n\*p’

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