

Package ‘sctransform’

December 16, 2020

Type Package

Title Variance Stabilizing Transformations for Single Cell UMI Data

Version 0.3.2

Description A normalization method for single-cell UMI count data using a variance stabilizing transformation. The transformation is based on a negative binomial regression model with regularized parameters. As part of the same regression framework, this package also provides functions for batch correction, and data correction. See Hafemeister and Satija 2019 <doi:10.1186/s13059-019-1874-1> for more details.

URL <https://github.com/ChristophH/sctransform>

BugReports <https://github.com/ChristophH/sctransform/issues>

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Encoding UTF-8

LazyData true

Depends R (>= 3.1.0)

LinkingTo RcppArmadillo, Rcpp (>= 0.11.0)

SystemRequirements C++11

Imports MASS, Matrix, methods, future.apply, future, ggplot2, reshape2, gridExtra, matrixStats

Suggests irlba, testthat, knitr

Enhances glmGamPoi

RoxygenNote 7.1.1

NeedsCompilation yes

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Repository CRAN

Date/Publication 2020-12-16 14:40:03 UTC

R topics documented:

compare_expression	2
correct	3
correct_counts	4
diff_mean_test	5
generate	7
get_model_var	8
get_residuals	9
get_residual_var	10
is_outlier	11
pbmc	11
plot_model	12
plot_model_pars	13
robust_scale	14
robust_scale_binned	15
row_gmean	15
row_var	16
smooth_via_pca	16
vst	17

Index	21
--------------	-----------

compare_expression	<i>Compare gene expression between two groups</i>
--------------------	---

Description

Compare gene expression between two groups

Usage

```
compare_expression(
  x,
  umi,
  group,
  val1,
  val2,
  method = "LRT",
  bin_size = 256,
  cell_attr = x$cell_attr,
  y = x$y,
  min_cells = 5,
  weighted = TRUE,
  randomize = FALSE,
  verbosity = 2,
  verbose = NULL,
  show_progress = NULL
)
```

Arguments

x	A list that provides model parameters and optionally meta data; use output of vst function
umi	A matrix of UMI counts with genes as rows and cells as columns
group	A vector indicating the groups
val1	A vector indicating the values of the group vector to treat as group 1
val2	A vector indicating the values of the group vector to treat as group 2
method	Either 'LRT' for likelihood ratio test, or 't_test' for t-test
bin_size	Number of genes that are processed between updates of progress bar
cell_attr	Data frame of cell meta data
y	Only used if method = 't_test', this is the residual matrix; default is x\$y
min_cells	A gene has to be detected in at least this many cells in at least one of the groups being compared to be tested
weighted	Balance the groups by using the appropriate weights
randomize	Boolean indicating whether to shuffle group labels - only set to TRUE when testing methods
verbosity	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
verbose	Deprecated; use verbosity instead
show_progress	Deprecated; use verbosity instead

Value

Data frame of results

correct	<i>Correct data by setting all latent factors to their median values and reversing the regression model</i>
---------	---

Description

Correct data by setting all latent factors to their median values and reversing the regression model

Usage

```
correct(
  x,
  data = "y",
  cell_attr = x$cell_attr,
  as_is = FALSE,
  do_round = TRUE,
  do_pos = TRUE,
  verbosity = 2,
  verbose = NULL,
  show_progress = NULL
)
```

Arguments

x	A list that provides model parameters and optionally meta data; use output of vst function
data	The name of the entry in x that holds the data
cell_attr	Provide cell meta data holding latent data info
as_is	Use cell attributes as is and do not use the median; set to TRUE if you want to manually control the values of the latent factors; default is FALSE
do_round	Round the result to integers
do_pos	Set negative values in the result to zero
verbosity	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
verbose	Deprecated; use verbosity instead
show_progress	Deprecated; use verbosity instead

Value

Corrected data as UMI counts

Examples

```
vst_out <- vst(pbmc, return_cell_attr = TRUE)
umi_corrected <- correct(vst_out)
```

correct_counts	<i>Correct data by setting all latent factors to their median values and reversing the regression model</i>
----------------	---

Description

This version does not need a matrix of Pearson residuals. It takes the count matrix as input and calculates the residuals on the fly. The corrected UMI counts will be rounded to the nearest integer and negative values clipped to 0.

Usage

```
correct_counts(
  x,
  umi,
  cell_attr = x$cell_attr,
  verbosity = 2,
  verbose = NULL,
  show_progress = NULL
)
```

Arguments

x	A list that provides model parameters and optionally meta data; use output of vst function
umi	The count matrix
cell_attr	Provide cell meta data holding latent data info
verbosity	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
verbose	Deprecated; use verbosity instead
show_progress	Deprecated; use verbosity instead

Value

Corrected data as UMI counts

Examples

```
vst_out <- vst(pbmc, return_cell_attr = TRUE)
umi_corrected <- correct_counts(vst_out, pbmc)
```

diff_mean_test	<i>Non-parametric differential expression test for sparse non-negative data</i>
----------------	---

Description

Non-parametric differential expression test for sparse non-negative data

Usage

```
diff_mean_test(
  y,
  labels,
  R = 99,
  log2FC_th = log2(1.2),
  mean_th = 0.05,
  cells_th = 5,
  only_pos = FALSE,
  only_top_n = NULL,
  mean_type = "geometric",
  verbosity = 1
)
```

Arguments

y	A matrix of counts; must be (or inherit from) class dgCMatrix; genes are row, cells are columns
labels	A factor giving the group labels; must have exactly two levels
R	The number of random permutations used to derive the p-values; default is 99
log2FC_th	Threshold to remove genes from testing; absolute log2FC must be at least this large for a gene to be tested; default is $\log_2(1.2)$
mean_th	Threshold to remove genes from testing; gene mean must be at least this large for a gene to be tested; default is 0.05
cells_th	Threshold to remove genes from testing; gene must be detected (non-zero count) in at least this many cells in the group with higher mean; default is 5
only_pos	Test only genes with positive fold change (mean in group 1 > mean in group2); default is FALSE
only_top_n	Test only the this number of genes from both ends of the log2FC spectrum after all of the above filters have been applied; useful to get only the top markers; only used if set to a numeric value; default is NULL
mean_type	Which type of mean to use; if 'geometric' (default) the geometric mean is used; to avoid $\log(0)$ we use $\log_1 p$ to add 1 to all counts and log-transform, calculate the arithmetic mean, and then back-transform and subtract 1 using $\exp 1 m$; if this parameter is set to 'arithmetic' the data is used as is
verbosity	Integer controlling how many messages the function prints; 0 is silent, 1 (default) is not

Value

Data frame of results

Details

This model-free test is applied to each gene (row) individually but is optimized to make use of the efficient sparse data representation of the input. A permutation null distribution is used to assess the significance of the observed difference in mean between two groups.

The observed difference in mean is compared against a distribution obtained by random shuffling of the group labels. For each gene every random permutation yields a difference in mean and from the population of these background differences we estimate a mean and standard deviation for the null distribution. This mean and standard deviation are used to turn the observed difference in mean into a z-score and then into a p-value. Finally, all p-values (for the tested genes) are adjusted using the Benjamini & Hochberg method (fdr). The log2FC values in the output are $\log_2(\text{mean}_1 / \text{mean}_2)$. Empirical p-values are also calculated: $\text{emp_pval} = (b + 1) / (R + 1)$ where b is the number of times the absolute difference in mean from a random permutation is at least as large as the absolute value of the observed difference in mean, R is the number of random permutations. This is an upper bound of the real empirical p-value that would be obtained by enumerating all possible group label permutations.

Examples

```
clustering <- 1:ncol(pbmc) %% 2
vst_out <- vst(pbmc, return_corrected_umi = TRUE)
de_res <- diff_mean_test(y = vst_out$umi_corrected, labels = clustering)
```

generate

Generate data from regularized models.

Description

Generate data from regularized models. This generates data from the background, i.e. no residuals are added to the simulated data. The cell attributes for the generated cells are sampled from the input with replacement.

Usage

```
generate(
  vst_out,
  genes = rownames(vst_out$model_pars_fit),
  cell_attr = vst_out$cell_attr,
  n_cells = nrow(cell_attr)
)
```

Arguments

vst_out	A list that provides model parameters and optionally meta data; use output of vst function
genes	The gene names for which to generate data; default is rownames(vst_out\$model_pars_fit)
cell_attr	Provide cell meta data holding latent data info; default is vst_out\$cell_attr
n_cells	Number of cells to generate; default is nrow(cell_attr)

Value

Generated data as dgCMatrix

Examples

```
vst_out <- vst(pbmc, return_cell_attr = TRUE)
generated_data <- generate(vst_out)
```

`get_model_var`*Return average variance under negative binomial model*

Description

This is based on the formula $\text{var} = \mu + \mu^2 / \theta$

Usage

```
get_model_var(  
  vst_out,  
  cell_attr = vst_out$cell_attr,  
  use_nonreg = FALSE,  
  bin_size = 256,  
  verbosity = 2,  
  verbose = NULL,  
  show_progress = NULL  
)
```

Arguments

<code>vst_out</code>	The output of a vst run
<code>cell_attr</code>	Data frame of cell meta data
<code>use_nonreg</code>	Use the non-regularized parameter estimates; boolean; default is FALSE
<code>bin_size</code>	Number of genes to put in each bin (to show progress)
<code>verbosity</code>	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
<code>verbose</code>	Deprecated; use verbosity instead
<code>show_progress</code>	Deprecated; use verbosity instead

Value

A named vector of variances (the average across all cells), one entry per gene.

Examples

```
vst_out <- vst(pbmc, return_cell_attr = TRUE)  
res_var <- get_model_var(vst_out)
```

get_residuals	<i>Return Pearson or deviance residuals of regularized models</i>
---------------	---

Description

Return Pearson or deviance residuals of regularized models

Usage

```
get_residuals(
  vst_out,
  umi,
  residual_type = "pearson",
  res_clip_range = c(-sqrt(ncol(umi)), sqrt(ncol(umi))),
  min_variance = vst_out$arguments$min_variance,
  cell_attr = vst_out$cell_attr,
  bin_size = 256,
  verbosity = vst_out$arguments$verbosity,
  verbose = NULL,
  show_progress = NULL
)
```

Arguments

vst_out	The output of a vst run
umi	The UMI count matrix that will be used
residual_type	What type of residuals to return; can be 'pearson' or 'deviance'; default is 'pearson'
res_clip_range	Numeric of length two specifying the min and max values the results will be clipped to; default is c(-sqrt(ncol(umi)), sqrt(ncol(umi)))
min_variance	Lower bound for the estimated variance for any gene in any cell when calculating pearson residual; default is vst_out\$arguments\$min_variance
cell_attr	Data frame of cell meta data
bin_size	Number of genes to put in each bin (to show progress)
verbosity	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
verbose	Deprecated; use verbosity instead
show_progress	Deprecated; use verbosity instead

Value

A matrix of residuals

Examples

```
vst_out <- vst(pbmc, return_cell_attr = TRUE)
pearson_res <- get_residuals(vst_out, pbmc)
deviance_res <- get_residuals(vst_out, pbmc, residual_type = 'deviance')
```

get_residual_var *Return variance of residuals of regularized models*

Description

This never creates the full residual matrix and can be used to determine highly variable genes.

Usage

```
get_residual_var(
  vst_out,
  umi,
  residual_type = "pearson",
  res_clip_range = c(-sqrt(ncol(umi)), sqrt(ncol(umi))),
  min_variance = vst_out$arguments$min_variance,
  cell_attr = vst_out$cell_attr,
  bin_size = 256,
  verbosity = vst_out$arguments$verbosity,
  verbose = NULL,
  show_progress = NULL
)
```

Arguments

vst_out	The output of a vst run
umi	The UMI count matrix that will be used
residual_type	What type of residuals to return; can be 'pearson' or 'deviance'; default is 'pearson'
res_clip_range	Numeric of length two specifying the min and max values the residuals will be clipped to; default is c(-sqrt(ncol(umi)), sqrt(ncol(umi)))
min_variance	Lower bound for the estimated variance for any gene in any cell when calculating pearson residual; default is vst_out\$arguments\$min_variance
cell_attr	Data frame of cell meta data
bin_size	Number of genes to put in each bin (to show progress)
verbosity	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
verbose	Deprecated; use verbosity instead
show_progress	Deprecated; use verbosity instead

Value

A vector of residual variances (after clipping)

Examples

```
vst_out <- vst(pbmc, return_cell_attr = TRUE)
res_var <- get_residual_var(vst_out, pbmc)
```

is_outlier	<i>Identify outliers</i>
------------	--------------------------

Description

Identify outliers

Usage

```
is_outlier(y, x, th = 10)
```

Arguments

y	Dependent variable
x	Independent variable
th	Outlier score threshold

Value

Boolean vector

pbmc	<i>Peripheral Blood Mononuclear Cells (PBMCs)</i>
------	---

Description

UMI counts for a subset of cells freely available from 10X Genomics

Usage

```
pbmc
```

Format

A sparse matrix (dgCMatrix, see Matrix package) of molecule counts. There are 914 rows (genes) and 283 columns (cells). This is a downsampled version of a 3K PBMC dataset available from 10x Genomics.

Source

<https://support.10xgenomics.com/single-cell-gene-expression/datasets/1.1.0/pbmc3k>

plot_model

Plot observed UMI counts and model

Description

Plot observed UMI counts and model

Usage

```
plot_model(
  x,
  umi,
  goi,
  x_var = x$arguments$latent_var[1],
  cell_attr = x$cell_attr,
  do_log = TRUE,
  show_fit = TRUE,
  show_nr = FALSE,
  plot_residual = FALSE,
  batches = NULL,
  as_poisson = FALSE,
  arrange_vertical = TRUE,
  show_density = FALSE,
  gg_cmds = NULL
)
```

Arguments

x	The output of a vst run
umi	UMI count matrix
goi	Vector of genes to plot
x_var	Cell attribute to use on x axis; will be taken from x\$arguments\$latent_var[1] by default
cell_attr	Cell attributes data frame; will be taken from x\$cell_attr by default
do_log	Log10 transform the UMI counts in plot
show_fit	Show the model fit

show_nr	Show the non-regularized model (if available)
plot_residual	Add panels for the Pearson residuals
batches	Manually specify a batch variable to break up the model plot in segments
as_poisson	Fix model parameter theta to Inf, effectively showing a Poisson model
arrange_vertical	Stack individual ggplot objects or place side by side
show_density	Draw 2D density lines over points
gg_cmds	Additional ggplot layer commands

Value

A ggplot object

Examples

```
vst_out <- vst(pbmc, return_cell_attr = TRUE)
plot_model(vst_out, pbmc, 'EMC4')
```

plot_model_pars	<i>Plot estimated and fitted model parameters</i>
-----------------	---

Description

Plot estimated and fitted model parameters

Usage

```
plot_model_pars(
  vst_out,
  show_theta = FALSE,
  show_var = FALSE,
  verbosity = 2,
  verbose = NULL,
  show_progress = NULL
)
```

Arguments

vst_out	The output of a vst run
show_theta	Whether to show the theta parameter; default is FALSE (only the overdispersion factor is shown)
show_var	Whether to show the average model variance; default is FALSE

verbosity	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
verbose	Deprecated; use verbosity instead
show_progress	Deprecated; use verbosity instead

Value

A ggplot object

Examples

```
vst_out <- vst(pbmc, return_gene_attr = TRUE)
plot_model_pars(vst_out)
```

robust_scale	<i>Robust scale using median and mad</i>
--------------	--

Description

Robust scale using median and mad

Usage

```
robust_scale(x)
```

Arguments

x	Numeric
---	---------

Value

Numeric

robust_scale_binned *Robust scale using median and mad per bin*

Description

Robust scale using median and mad per bin

Usage

```
robust_scale_binned(y, x, breaks)
```

Arguments

y	Numeric vector
x	Numeric vector
breaks	Numeric vector of breaks

Value

Numeric vector of scaled score

row_gmean *Geometric mean per row*

Description

Geometric mean per row

Usage

```
row_gmean(x, eps = 1)
```

Arguments

x	matrix of class <code>matrix</code> or <code>dgMatrix</code>
eps	small value to add to x to avoid <code>log(0)</code> ; default is 1

Value

geometric means

row_var	<i>Variance per row</i>
---------	-------------------------

Description

Variance per row

Usage

```
row_var(x)
```

Arguments

x matrix of class matrix or dgCMatix

Value

variances

smooth_via_pca	<i>Smooth data by PCA</i>
----------------	---------------------------

Description

Perform PCA, identify significant dimensions, and reverse the rotation using only significant dimensions.

Usage

```
smooth_via_pca(
  x,
  elbow_th = 0.025,
  dims_use = NULL,
  max_pc = 100,
  do_plot = FALSE,
  scale. = FALSE
)
```

Arguments

x	A data matrix with genes as rows and cells as columns
elbow_th	The fraction of PC sdev drop that is considered significant; low values will lead to more PCs being used
dims_use	Directly specify PCs to use, e.g. 1:10
max_pc	Maximum number of PCs computed

do_plot	Plot PC sdev and sdev drop
scale.	Boolean indicating whether genes should be divided by standard deviation after centering and prior to PCA

Value

Smoothed data

Examples

```
vst_out <- vst(pbmc)
y_smooth <- smooth_via_pca(vst_out$y, do_plot = TRUE)
```

vst

Variance stabilizing transformation for UMI count data

Description

Apply variance stabilizing transformation to UMI count data using a regularized Negative Binomial regression model. This will remove unwanted effects from UMI data and return Pearson residuals. Uses `future_lapply`; you can set the number of cores it will use to `n` with `plan(strategy = "multicore", workers = n)`. If `n_genes` is set, only a (somewhat-random) subset of genes is used for estimating the initial model parameters. For details see [doi: 10.1186/s13059-019-1874-1](https://doi.org/10.1186/s13059-019-1874-1).

Usage

```
vst(
  umi,
  cell_attr = NULL,
  latent_var = c("log_umi"),
  batch_var = NULL,
  latent_var_nonreg = NULL,
  n_genes = 2000,
  n_cells = NULL,
  method = "poisson",
  do_regularize = TRUE,
  theta_regularization = "od_factor",
  res_clip_range = c(-sqrt(ncol(umi)), sqrt(ncol(umi))),
  bin_size = 500,
  min_cells = 5,
  residual_type = "pearson",
  return_cell_attr = FALSE,
  return_gene_attr = TRUE,
  return_corrected_umi = FALSE,
```

```

min_variance = -Inf,
bw_adjust = 3,
gmean_eps = 1,
theta_estimation_fun = "theta.ml",
theta_given = NULL,
verbosity = 2,
verbose = NULL,
show_progress = NULL
)

```

Arguments

umi	A matrix of UMI counts with genes as rows and cells as columns
cell_attr	A data frame containing the dependent variables; if omitted a data frame with umi and gene will be generated
latent_var	The independent variables to regress out as a character vector; must match column names in cell_attr; default is c("log_umi")
batch_var	The dependent variables indicating which batch a cell belongs to; no batch interaction terms used if omitted
latent_var_nonreg	The non-regularized dependent variables to regress out as a character vector; must match column names in cell_attr; default is NULL
n_genes	Number of genes to use when estimating parameters (default uses 2000 genes, set to NULL to use all genes)
n_cells	Number of cells to use when estimating parameters (default uses all cells)
method	Method to use for initial parameter estimation; one of 'poisson', 'qpoisson', 'nb_fast', 'nb', 'nb_theta_given', 'glmGamPoi', 'offset', 'offset_shared_theta_estimate'; default is 'poisson'
do_regularize	Boolean that, if set to FALSE, will bypass parameter regularization and use all genes in first step (ignoring n_genes); default is FALSE
theta_regularization	Method to use to regularize theta; use 'log_theta' for the behavior prior to version 0.3; default is 'od_factor'
res_clip_range	Numeric of length two specifying the min and max values the results will be clipped to; default is c(-sqrt(ncol(umi)), sqrt(ncol(umi)))
bin_size	Number of genes to process simultaneously; this will determine how often the progress bars are updated and how much memory is being used; default is 500
min_cells	Only use genes that have been detected in at least this many cells; default is 5
residual_type	What type of residuals to return; can be 'pearson', 'deviance', or 'none'; default is 'pearson'
return_cell_attr	Make cell attributes part of the output; default is FALSE
return_gene_attr	Calculate gene attributes and make part of output; default is TRUE

return_corrected_umi	If set to TRUE output will contain corrected UMI matrix; see correct function
min_variance	Lower bound for the estimated variance for any gene in any cell when calculating pearson residual; default is -Inf
bw_adjust	Kernel bandwidth adjustment factor used during regularization; factor will be applied to output of bw.SJ; default is 3
gmean_eps	Small value added when calculating geometric mean of a gene to avoid log(0); default is 1
theta_estimation_fun	Character string indicating which method to use to estimate theta (when method = poisson); default is 'theta.ml', but 'theta.mm' seems to be a good and fast alternative
theta_given	If method is set to nb_theta_given, this should be a named numeric vector of fixed theta values for the genes; if method is offset, this should be a single value; default is NULL
verbosity	An integer specifying whether to show only messages (1), messages and progress bars (2) or nothing (0) while the function is running; default is 2
verbose	Deprecated; use verbosity instead
show_progress	Deprecated; use verbosity instead

Value

A list with components

y	Matrix of transformed data, i.e. Pearson residuals, or deviance residuals; empty if residual_type = 'none'
umi_corrected	Matrix of corrected UMI counts (optional)
model_str	Character representation of the model formula
model_pars	Matrix of estimated model parameters per gene (theta and regression coefficients)
model_pars_outliers	Vector indicating whether a gene was considered to be an outlier
model_pars_fit	Matrix of fitted / regularized model parameters
model_str_nonreg	Character representation of model for non-regularized variables
model_pars_nonreg	Model parameters for non-regularized variables
genes_log_gmean_step1	log-geometric mean of genes used in initial step of parameter estimation
cells_step1	Cells used in initial step of parameter estimation
arguments	List of function call arguments
cell_attr	Data frame of cell meta data (optional)
gene_attr	Data frame with gene attributes such as mean, detection rate, etc. (optional)
times	Time stamps at various points in the function

Details

In the first step of the algorithm, per-gene glm model parameters are learned. This step can be done on a subset of genes and/or cells to speed things up. If `method` is set to `'poisson'`, a poisson regression is done and the negative binomial theta parameter is estimated using the response residuals in `theta_estimation_fun`. If `method` is set to `'qpoisson'`, coefficients and overdispersion (ϕ) are estimated by quasi poisson regression and theta is estimated based on ϕ and the mean fitted value - this is currently the fastest method with results very similar to `'glmGamPoi'`. If `method` is set to `'nb_fast'`, coefficients and theta are estimated as in the `'poisson'` method, but coefficients are then re-estimated using a proper negative binomial model in a second call to `glm` with `family = MASS::negative.binomial(theta = theta)`. If `method` is set to `'nb'`, coefficients and theta are estimated by a single call to `MASS::glm.nb`. If `method` is set to `'glmGamPoi'`, coefficients and theta are estimated by a single call to `glmGamPoi::glm_gp`.

A special case is `method = 'offset'`. Here no regression parameters are learned, but instead an offset model is assumed. The latent variable is set to `log_umi` and a fixed slope of $\log(10)$ is used (offset). The intercept is given by $\log(\text{gene_mean}) - \log(\text{avg_cell_umi})$. See Lause et al. ([bioRxiv 2020.12.01.405886](https://doi.org/10.1101/2020.12.01.405886)) for details. Theta is set to 100 by default, but can be changed using the `theta_given` parameter (single numeric value). If the offset method is used, the following parameters are overwritten: `cell_attr <- NULL`, `latent_var <- c('log_umi')`, `batch_var <- NULL`, `latent_var_nonreg <- NULL`, `n_genes <- NULL`, `n_cells <- NULL`, `do_regularize <- FALSE`. Further, `method = 'offset_shared_theta_estima` exists where the 250 most highly expressed genes with detection rate of at least 0.5 are used to estimate a theta that is then shared across all genes. Thetas are estimated per individual gene using 5000 randomly selected cells. The final theta used for all genes is then the average.

Examples

```
vst_out <- vst(pbmc)
```

Index

* datasets

- pbmc, 11

- compare_expression, 2
- correct, 3
- correct_counts, 4

- diff_mean_test, 5

- generate, 7
- get_model_var, 8
- get_residual_var, 10
- get_residuals, 9

- is_outlier, 11

- pbmc, 11
- plot_model, 12
- plot_model_pars, 13

- robust_scale, 14
- robust_scale_binned, 15
- row_gmean, 15
- row_var, 16

- smooth_via_pca, 16

- vst, 17