Package ‘SparseDC’

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Type Package

Title Implementation of SparseDC Algorithm

Version 0.1.17

Description Implements the algorithm described in Barron, M., Zhang, S. and Li, J. 2017, `A sparse differential clustering algorithm for tracing cell type changes via single-cell RNA-sequencing data`, Nucleic Acids Research, gkx1113, <doi:10.1093/nar/gkx1113>. This algorithm clusters samples from two different populations, links the clusters across the conditions and identifies marker genes for these changes. The package was designed for scRNA-Seq data but is also applicable to many other data types, just replace cells with samples and genes with variables. The package also contains functions for estimating the parameters for SparseDC as outlined in the paper. We recommend that users further select their marker genes using the magnitude of the cluster centers.

Depends R (>= 3.1.0)

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Description

The cell type of each of the cells in the Biase data.

Usage

cell_type_biase

Format

An R.Data object containing a vector with the cell type of each of the cells in the Biase Data.

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Description

The condition for each sample in the Biase data. To be used when splitting the data to demonstrate SparseDC.

Usage

condition_biase

Format

An R.Data object containing a vector with the condition of the 49 cells in the Biase data.
Description

This dataset was created by Biase et al. to study cell fat inclination in mouse embryos. It contains FPKM gene expression measurements for 49 cells and 16,514 genes. There are three cell types in the dataset, zygote, two-cell embryo, and four-cell embryo cells.

Usage
data_biase

Format

An R.Data object storing FPKM gene expression measurements for each of the samples.

generate_uni_dat

Uniform data generator For use with the gap statistic. Generates datasets drawn from the reference distribution where each reference feature is generated uniformly over the range of observed values for that feature.

Description

Uniform data generator For use with the gap statistic. Generates datasets drawn from the reference distribution where each reference feature is generated uniformly over the range of observed values for that feature.

Usage
generate_uni_dat(data)

Arguments

data A dataset with rows as features and columns as samples.

Value

A dataset drawn from the reference distribution for use internally with the gap statistic.
Description

Calculates the lambda 1 value for the sparseDC algorithm. The lambda 1 value controls the number of marker genes selected for each cluster in the output from SparseDC. It is calculated as the value of lambda 1 that results in no marker genes being selected when there are no meaningful clusters present in the data. Please see the original manuscript for further details.

Usage

lambda1_calculator(pdat1, pdat2, ncluster, alpha1 = 0.5, nboot1 = 1000)

Arguments

pdat1 The centered data from condition 1, columns should be samples (cells) and rows should be features (genes).
pdat2 The centered data from condition 2, columns should be samples (cells) and rows should be features (genes). The number of genes should be the same as in pdat1.
ncluster The number of clusters present in the data.
alpha1 The quantile of the bootstrapped lambda 1 values to use, range is (0,1). The default value is 0.5, the median of the calculated lambda 1 values.
nboot1 The number of bootstrap repetitions used for estimating lambda 1, the default value is 1000.

Value

The calculated value of lambda 1 to use in the main SparseDC algorithm.

See Also

lambda2_calculator for how to calculate the lambda 2 parameter. sparsedc_cluster for the main sparse differential clustering function.

Examples

set.seed(10)
# Select small dataset for example
data_test <- data_biase[1:100,]
# Split data into conditions A and B
data_A <- data_test[, which(condition_biase == "A")]
data_B <- data_test[, which(condition_biase == "B")]
# Pre-process the data
pre_data <- pre_proc_data(data_A, data_B, norm = FALSE, log = TRUE, center = TRUE)
lambda2_calculator

# Calculate the lambda 1 value
lambda1_calculator(pdat1 = pre_data[[1]], pdat2 = pre_data[[2]], ncluster=3,
alpha1 = 0.5, nboot1 = 1000)

# Can also run

# Pre-process the data
pre_data <- pre_proc_data(data_A, data_B, norm = FALSE, log = TRUE,
center = TRUE)
pdata_A <- pre_data[[1]]
pdata_B <- pre_data[[2]]
# Calculate the lambda 1 value
lambda1_calculator(pdat1 = pdata_A, pdat2 = pdata_B, ncluster=3,
alpha1 = 0.5, nboot1 = 1000)

lambda2_calculator

Lambda 2 Calculator.

Description

Calculates the lambda 2 values for use in the main SparseDC algorithm, the lambda 2 value controls
the number of genes that show condition-dependent expression within each cell type. That is it con-
trols the number of different mean values across the conditions for each cell type. It is calculated by
estimating the value of lambda 2 that would result in no difference in mean values across conditions
when there are no meaningful differences across between the conditions. For further details please
see the original manuscript.

Usage

lambda2_calculator(pdat1, pdat2, ncluster, alpha2 = 0.5, nboot2 = 1000)

Arguments

pdat1 The centered data from condition 1, columns should be samples (cells) and rows
should be features (genes).
pdat2 The centered data from condition 2, columns should be samples (cells) and rows
should be features (genes). The number of genes should be the same as pdat1.
nccluster The number of clusters present in the data.
alpha2 The quantile of the bootstrapped lambda 2 values to use, range is (0,1). The
default value is 0.5, the median of the calculated lambda 2 values.
nboot2 The number of bootstrap repetitions for estimating lambda 2, the default value
is 1000.

Value

The calculated value of lambda 2 to use in the main SparseDC algorithm.
See Also

lambda1_calculator sparsedc_cluster

Examples

```r
set.seed(10)
# Select small dataset for example
data_test <- data_biase[1:100,]
# Split data into conditions A and B
data_A <- data_test[, which(condition_biase == "A")]
data_B <- data_test[, which(condition_biase == "B")]
# Pre-process the data
pre_data <- pre_proc_data(data_A, data_B, norm = FALSE, log = TRUE,
center = TRUE)
# Calculate the lambda 2 value
lambda2_calculator(pdat1 = pre_data[[1]], pdat2 = pre_data[[2]], ncluster = 3,
alpha2 = 0.5, nboot2 = 1000)
# Can also run
pdata_A <- pre_data[[1]]
pdata_B <- pre_data[[2]]
lambda2_calculator(pdat1 = pdata_A, pdat2 = pdata_B, ncluster = 3,
alpha2 = 0.5, nboot2 = 1000)
```

---

**pre_proc_data**  
*Pre-process Data*

**Description**

This function pre-process the data so that SparseDC can be applied. SparseDC requires data that have been normalized for sequencing depth, log-transformed and centralized on a gene-by-gene basis. For the sequencing depth normalization we recommend that users use one of the many methods developed for normalizing scRNA-Seq data prior to using SparseDC and so can set `norm = FALSE`. However, here we normalize the data by dividing by the total number of reads. This function log transforms the data by applying \( \log(x + 1) \) to each of the data sets. By far the most important pre-processing step for SparseDC is the centralization of the data. Having centralized data is a core component of the SparseDC algorithm and is necessary for both accurate clustering of the cells and identifying marker genes. We therefore recommend that all users centralize their data using this function and that only experienced users set `center = FALSE`.

**Usage**

```
pre_proc_data(dat1, dat2, norm = TRUE, log = TRUE, center = TRUE)
```
**Arguments**

- **dat1**
  - The data for the first condition with samples (cells) as columns and features (genes) as rows.

- **dat2**
  - The data for the second condition with samples (cells) as columns and features (genes) as rows.

- **norm**
  - This parameter controls whether the data is normalized for sequencing depth by dividing each column by the total number of reads for that sample. We recommend that users use one of the many methods for normalizing scRNA-Seq data and set this as **FALSE**. The default value is **TRUE**.

- **log**
  - This parameter controls whether the data is transformed using $\log(x + 1)$. The default value is **TRUE**.

- **center**
  - This parameter controls whether the data is centered on a gene by gene basis. We recommend all users center their data prior to applying SparseDC and only experienced users should set this as **FALSE**. The default value is **TRUE**.

**Value**

This function returns the two pre-processed datasets stored as a list.

**Examples**

```r
set.seed(10)
# Select small dataset for example
data_test <- data_biase[1:100,]
# Split data into condition A and B
data_A <- data_test[, which(condition_biase == "A")]
data_B <- data_test[, which(condition_biase == "B")]
# Pre-process the data
pre_data <- pre_proc_data(data_A, data_B, norm = FALSE, log = TRUE, center = TRUE)
# Extract Data
pdata_A <- pre_data[[1]]
pdata_B <- pre_data[[2]]
```

**sim_data**

*Data Simulator*

**Description**

Simulates two condition data for a range of conditions depending on the parameters used.

**Usage**

```r
sim_data(genes, cells, sig.genes, sig.genes.s, clus.t1, clus.t2, same.sig = FALSE, u.l = 1, u.h = 2)
```
Arguments

- **genes**: The number of genes to be simulated.
- **cells**: The number of cells to be simulated per condition.
- **sig.genes**: The number of marker genes for each cluster.
- **sig.genes.s**: The number of marker genes shared across conditions for each cluster. Should be less than or equal to **sig.genes**.
- **clus.t1**: A vector of clusters present in the first condition. Start at 1, e.g., `c(1,2,3,4)`.
- **clus.t2**: A vector of clusters present in the second condition. Does not have to match **clus.t1**, e.g., `c(3,4,5)`.
- **same.sig**: TRUE or FALSE. Should each cluster have a unique set of marker genes. Default is FALSE.
- **u.l**: Lower bound for the cluster gene means, default is 1.
- **u.h**: Upper bound for the cluster gene means, default is 2.

Value

A list containing the two simulated data matrices, `dat.1` and `dat.2`, true clusters for the cells in the first and second conditions, `clusters1` and `clusters2`, a matrix indicating marker genes for the first and second condition, `sig.gene.mat.1` and `sig.gene.mat.2`, the base mean values for each gene `gene.means` and the cluster-specific additions for each gene `clus.gene.means`.

Examples

```r
set.seed(10)
genes <- 1000  # Simulate 1,000 genes
cells <- 100    # Simulate 100 cells per condition
clus.t1 <- c(1,2,3)  # Generate 3 clusters present in condition A
clus.t2 <- c(1,2,3)  # Generate 3 clusters present in condition B
sig.genes  <- 30   # Generate 30 marker genes per cluster
sig.genes.s <- 15   # Let half of the 30 marker genes be shared.
temp_sim_dat <- sim_data(genes, cells, sig.genes, sig.genes.s, clus.t1, clus.t2)
```

---

**sparsedc_cluster**

**Sparse Differential Clustering**

Description

The main SparseDC function. This function clusters the samples from the two conditions and links the clusters across the conditions. It also identifies marker genes for each of the clusters. There are three types of marker gene which SparseDC identifies. Please see the original manuscript for further details.
Usage

sparsedc_cluster(pdat1, pdat2, ncluster, lambda1, lambda2, nitter = 20,
    nstarts = 50, init_iter = 5)

Arguments

pdat1 The centered data from condition 1, columns should be samples (cells) and rows
    should be features (genes).

pdat2 The centered data from condition 2, columns should be samples (cells) and rows
    should be features (genes). The number of genes should be the same as
    pdat1.

ncluster The number of clusters present in the data.

lambda1 The lambda 1 value to use in the SparseDC function. This value controls the
    number of marker genes detected for each of the clusters in the final result. This
    can be calculated using the "lambda1_calculator" function or supplied by the
    user.

lambda2 The lambda 2 value to use in the SparseDC function. This value controls the
    number of genes that show condition-dependent expression within each cell
    type. This can be calculated using the "lambda2_calculator" function or sup-
    plied by the user.

nitter The max number of iterations for each of the start values, the default value is 20.

nstarts The number of start values to use for SparseDC. The default value is 50.

init_iter The number of iterations used to generate the starting center values.

Value

A list containing the clustering solution, cluster centers and the score of each of the starts.

See Also

lambda1_calculator lambda2_calculator update_c update_mu

Examples

```r
set.seed(10)
# Select small dataset for example
data_test <- data_biase[1:100,]
# Split data into conditions 1 and 2
data_1 <- data_test[, which(condition_biase == "A")]
data_2 <- data_test[, which(condition_biase == "B")]
# Preprocess data (log transform and center)
pre_data <- pre_proc_data(data_1, data_2, norm = FALSE, log = TRUE, center = TRUE)
# Calculate lambda 1 parameter
lambda1 <- lambda1_calculator(pdat1 = pre_data[[1]], pdat2 = pre_data[[2]],
    ncluster=3, alpha1 = 0.5, nboot1 = 1000)
# Calculate lambda 2 parameter
```
lambda2 <- lambda2_calculator(pdat1 = pre_data[[1]], pdat2 = pre_data[[2]],
ncluster = 3, alpha2 = 0.5, nboot2 = 1000)
# Run sparse DC
sdc_res <- sparsedc_cluster(pdat1 = pre_data[[1]], pdat2 = pre_data[[2]],
ncluster = 3, lambda1 = lambda1, lambda2 = lambda2, nitter = 20, nstarts =50)
# Extract results
clusters_1 <- sdc_res$clusters1 # Clusters for condition 1 data
clusters_2 <- sdc_res$clusters2 # Clusters for condition 2 data
centers_1 <- sdc_res$centers1 # Centers for condition 1 data
centers_2 <- sdc_res$centers2 # Centers for condition 2 data
# View clusters
summary(as.factor(clusters_1))
summary(as.factor(clusters_2))
# View Marker genes
gene_names <- row.names(data_test)
m_gene_c1_up1 <- gene_names[which(centers_1[,1] > 0)]
m_gene_c1_up2 <- gene_names[which(centers_2[,1] > 0)]
m_gene_c1_down1 <- gene_names[which(centers_1[,1] < 0)]
m_gene_c1_down2 <- gene_names[which(centers_2[,1] < 0)]
m_gene_c2_cond <- gene_names[which(centers_1[,2] != centers_2[,2])]
# Can also run
pre_data <- pre_proc_data(data_1, data_2, norm = FALSE, log = TRUE,
center = TRUE)
pdata_A <- pre_data[[1]]
pdata_B <- pre_data[[2]]
lambda1 <- lambda1_calculator(pdat1 = pdata_A, pdat2 = pdata_B,
ncluster=3, alpha1 = 0.5, nboot1 = 1000)
lambda2 <- lambda2_calculator(pdat1 = pdata_A, pdat2 = pdata_B,
ncluster = 3, alpha2 = 0.5, nboot2 = 1000)
# Run sparse DC
sdc_res <- sparsedc_cluster(pdat1 = pdata_A, pdat2 = pdata_B, ncluster = 3,
lambda1 = lambda1, lambda2 = lambda2, nitter = 20, nstarts =50)

---

**sparsedc_gap**  
*Gap Statistic Calculator*

**Description**

This function calculates the gap statistic for SparseDC. For use when the number of clusters in the data is unknown. We recommend using alternate methods to infer the number of clusters in the data.

**Usage**

```r
sparsedc_gap(pdat1, pdat2, min_clus, max_clus, nboots = 200, nitter = 20,
nstarts = 10, l1_boot = 50, l2_boot = 50)
```
Arguments

- **pdat1**: The centered data from condition 1, columns should be samples (cells) and rows should be features (genes).
- **pdat2**: The centered data from condition 2, columns should be samples (cells) and rows should be features (genes). The number of genes should be the same as \( \text{pdat1} \) as in \( \text{pdat1} \).
- **min_clus**: The minimum number of clusters to try, minimum value is 2.
- **max_clus**: The maximum number of clusters to try.
- **nboots**: The number of bootstrap repetitions to use, default = 200.
- **nitter**: The max number of iterations for each of the start values, the default value is 20.
- **nstarts**: The number of start values to use for SparseDC. The default value is 10.
- **l1_boot**: The number of bootstrap repetitions used for estimating lambda 1.
- **l2_boot**: The number of bootstrap repetitions used for estimating lambda 2.

Value

A list containing the optimal number of clusters, as well as gap statistics and the calculated standard error for each number of clusters.

Examples

```r
# load a small dataset
data_test <- data_biase[1:50,]
# Split data into conditions 1 and 2
data_1 <- data_test[, which(condition_biase == "A")]
data_2 <- data_test[, which(condition_biase == "B")]
# Preprocess data (log transform and center)
pre_data <- pre_proc_data(data_1, data_2, norm = FALSE, log = TRUE, center = TRUE)
# Run with one bootstrap sample for example
gap_stat <- sparsedc_gap(pre_data[[1]], pre_data[[2]],
                        min_clus <- 2, max_clus <- 3, nboots <- 2)
```

---

**S_func**

The soft thresholding operator

Description

Function to solve the soft thresholding problem

Usage

\[ \text{S_func}(x, a) \]
Arguments

- x: The data value
- a: The lambda value

Value

The solution to the soft thresholding operator.

---

**update_c**  
*Update Clusters*

**Description**

Updates the cluster membership for each iteration of SparseDC. Runs inside `sparse_dc_fun`.

**Usage**

```r
update_c(mu_1, mu_2, pdat1, pdat2, ncluster)
```

**Arguments**

- **mu_1**: The center values for each cluster in condition 1.
- **mu_2**: The center values for each cluster in condition 2.
- **pdat1**: The centered data from condition 1, columns should be samples (cells) and rows should be features (genes).
- **pdat2**: The centered data from condition 2, columns should be samples (cells) and rows should be features (genes). The number of genes should be the same as in pdat1.
- **ncluster**: The number of clusters present in the data.

**Value**

A list containing the cluster membership for condition 1 and condition 2.
**update_mu**

**Update the Center Values**

**Description**

This function updates the center values for each cluster for each iteration of SparseDC. This function runs inside `sparse_dc_fun`.

**Usage**

```r
update_mu(C_1, C_2, pdat1, pdat2, ncluster, lambda1, lambda2)
```

**Arguments**

- `C_1` The cluster membership for samples in condition 1
- `C_2` The cluster membership for samples in condition 2
- `pdat1` The centered data from condition 1, columns should be samples (cells) and rows should be features (genes).
- `pdat2` The centered data from condition 2, columns should be samples (cells) and rows should be features (genes). The number of genes should be the same as in `pdat1`.
- `ncluster` The number of clusters present in the data.
- `lambda1` The lambda 1 value to use in the SparseDC function. This value controls the number of marker genes detected for each of the clusters in the final result. This can be calculated using the "lambda1_calculator" function or supplied by the user.
- `lambda2` The lambda 2 value to use in the SparseDC function. This value controls the number of genes that show condition-dependent expression within each cell type. This can be calculated using the "lambda2_calculator" function or supplied by the user.

**Value**

Returns a list containing the center values for each of the clusters in condition 1 and 2.
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