

Package ‘ISLET’

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Type Package

Title Individual-Specific ceLl typE referencing Tool

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Description ISLET is a method to conduct signal deconvolution for general -omics data. It can estimate the individual-specific and cell-type-specific reference panels, when there are multiple samples observed from each subject. It takes the input of the observed mixture data (feature by sample matrix), and the cell type mixture proportions (sample by cell type matrix), and the sample-to-subject information. It can solve for the reference panel on the individual-basis. It can also conduct test to identify cell-type-specific differential expression (csDE) genes.

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Depends R(>= 4.1.0), Matrix, parallel, BiocParallel,
SummarizedExperiment, BiocGenerics

Imports stats, methods

Suggests BiocStyle, knitr, rmarkdown, htmltools, RUnit

Collate utils.R dataprep.R dataprep_slope.R islet.est.R islet.solve.R
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caseEst	<i>ISLET reference estimation results extraction</i>
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Description

This function, `caseEst`, extracts the estimated reference panels from the case group. It takes one `outputSol` objects as the input, and produce a list of matrices containing the estimated reference panels. The length of the list is equal to the number of cell types. For each matrix, it contains the gene by subject reference panel for that specific cell type.

Usage

```
caseEst(res.sol)
```

Arguments

`res.sol` A `outputSol` objects from `isletSolve` step.

Details

This is the accessor function help to extract the estimated reference panels from `isletSolve` step.

Value

A list of matrices containing the estimated reference panels. The length of the list is equal to the number of cell types. For each matrix, it contains the gene by subject reference panel for that specific cell type.

Author(s)

Hao Feng <hxf155@case.edu>

Examples

```
data(GE600)

study123input <- dataPrep(dat_se=GE600_se)
res.sol <- isletSolve(input=study123input)
caseVal <- caseEst(res.sol)
```

`ctrlEst`*ISLET reference estimation results extraction*

Description

This function, `ctrlEst`, extracts the estimated reference panels from the control group. It takes one `outputSol` objects as the input, and produce a list of matrices containing the estimated reference panels. The length of the list is equal to the number of cell types. For each matrix, it contains the gene by subject reference panel for that specific cell type.

Usage

```
ctrlEst(res.sol)
```

Arguments

`res.sol` A `outputSol` objects from `isletSolve` step.

Details

This is the accessor function help to extract the estimated reference panels from `isletSolve` step.

Value

A list of matrices containing the estimated reference panels. The length of the list is equal to the number of cell types. For each matrix, it contains the gene by subject reference panel for that specific cell type.

Author(s)

Hao Feng <hxf155@case.edu>

Examples

```
data(GE600)

study123input <- dataPrep(dat_se=GE600_se)
res.sol <- isletSolve(input=study123input)
caseVal <- ctrlEst(res.sol)
```

`dataPrep`*Data preparation step utility function before using ISLET*

Description

This function, `dataPrep`, is a necessary step to make your data ready and acceptable to ISLET. It takes one `SummarizedExperiment` objects listed below as the input, and produce a list ready to be feed into ISLET downstream deconvolution (function `isletSolve`) and/or cell type-specific differentially expressed gene testing (function `isletTest`).

Usage

```
dataPrep(dat_se)
```

Arguments

<code>dat_se</code>	A <code>SummarizedExperiment</code> object containing both case group and control. It should contain the observed feature by sample matrix, group label (case or ctrl) for each sample, subject IDs for each sample, and cell type proportions for each sample. The feature by sample matrix is stored in the <code>assay</code> , while the remaining components are stored in the <code>colData</code> slot. In the <code>colData</code> slot, the group label should be stored in the first column, subject IDs should be stroed in the second column, and the cell type proportions take the remaining columns. Subject IDs need to be sorted before using the <code>dataPrep</code> function.
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Details

This is the initial step for using ISLET, to prepare your data input ready for downstream deconvolution (function `isletSolve`) and/or differentially expressed gene testing (function `isletTest`). The input data must follow requirements listed above.

Value

`dataPrep` returns a S4 object, containing elements ready to serve as the input for downstream deconvolution (function `isletSolve`) and/or differentially expressed gene testing (function `isletTest`).

Author(s)

Hao Feng <hxf155@case.edu>

Examples

```
data(GE600)
ls()
## [1] "GE600_se"

study123input <- dataPrep(dat_se=GE600_se)
```

dataPrepSlope	<i>Data preparation function specifically for slope effect testing</i>
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Description

This function, `dataPrepSlope`, is a necessary step to make your data ready and acceptable to ISLET slope effect testing. It takes one `SummarizedExperiment` objects containing both case and control group as the input, and produce a list ready to be feed into ISLET downstream deconvolution (function `isletSolve`) and/or differentially expressed gene testing (function `isletTest`).

Usage

```
dataPrepSlope(dat_se)
```

Arguments

<code>dat_se</code>	A <code>SummarizedExperiment</code> object containing both case and control group. It should contain the observed feature by sample matrix, group label (case or ctrl) for each sample, subject IDs for each sample, a slope variable for each sample, and cell type proportions for each sample. The feature by sample matrix is stored in the <code>assay</code> , while the remaining components are stored in the <code>colData</code> slot. In the <code>colData</code> slot, the group label (case or ctrl) take the first column, subject IDs take the second column, the slope variable takes the third column, and the cell type proportions take the remaining columns. Subject IDs need to be sorted before using the <code>dataPrepSlope</code> function.
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Details

This is the initial step for using ISLET, to prepare your data input ready for downstream cell-type-specific differentially expressed gene testing (function `isletTest`) with respect to the slope variable. The input data matrices must follow requirements listed above, and samples/subjects must be ordered and match across matrices.

Value

`dataPrepSlope` returns a S4 object, containing elements ready to serve as the input for cell-type-specific differentially expressed gene testing (function `isletTest`).

Author(s)

Hao Feng <hxf155@case.edu>

Examples

```
data(GE600age)
ls()
## [1] "GE600age_se"
```

```
#(1) Data preparation
study456input <- dataPrepSlope(dat_se=GE600age_se)

#(2) [Downstream] Test for slope effect(i.e. age) difference in csDE testing
#result.test <- isletTest(input=study456input)
```

 GE600

ISLET deconvolution example raw input data

Description

GE600 contains the raw example datasets for ISLET. It has the gene expression values for 10 genes by 520 sample, with 83 cases and 89 controls, and multiple repeated measurements (i.e. time points) per subject. Data were combined by case/control status, into one single SummarizedExperiment object. These raw example datasets will need to be converted by the dataPrep function, and then they will be ready for downstream deconvolution (function isletSolve) and/or differentially expressed gene testing (function isletTest).

Usage

```
data(GE600)
```

Format

One SummarizedExperiment object containing the following elements:

counts A gene expression value data frame of 10 genes by 520 sample, with 83 cases and 89 controls, and multiple repeated measurements (i.e. time points) per subject.

colData Sample meta-data. The first column is the group status (i.e. case/ctrl), the second column is the subject ID, shows the relationship between the samples IDs and their subject IDs. The remaining 6 columns (i.e. column 3-8) are the cell type proportions of all samples by their 6 cell types.

Examples

```
data(GE600)
ls()
## [1] "GE600_se"

#show GE600_se details
GE600_se
#An object of class "SummarizedExperiment"

#Then, we can proceed to data preparation step, function 'dataPrep' for ISLET.
##The rest of the deconvolution/csDE analysis will then follow.
```

Description

GE600age contains the example input datasets for ISLET's slope testing function. It has the gene expression values for 10 genes by 520 sample, with 83 cases and 89 controls, and multiple repeated measurements (i.e. time points) per subject. Temporal measures are at different age, with an age variable stored in the metadata. This is the main variable-of-interest in downstream testing. Data were combined by case/control status, into one SummarizedExperiment object. These example datasets will need to be converted by the dataPrep function, and then they will be ready for downstream deconvolution (function isletSolve) and/or differentially expressed gene testing (function isletTest).

Usage

```
data(GE600age)
```

Format

One SummarizedExperiment object containing the following elements:

counts A gene expression value data frame of 10 genes by 520 sample, with 83 cases and 89 controls, and multiple repeated measurements (i.e. time points) per subject.

colData Sample meta-data. The first column is the case/ctrl group status, the second column is the subject ID, shows the relationship between the samples IDs and their subject IDs. The third column is the age variable for each sample, which is the main variable in downstream testing. The remaining 6 columns (i.e. column 4-9) are the cell type proportions of all samples by their 6 cell types.

Examples

```
data(GE600age)
ls()
## [1] "GE600age_se"

#show GE600age_se details
GE600age_se
#An object of class "SummarizedExperiment"

#Then, we can proceed to data preparation step, function 'dataPrep' for ISLET.
##The rest of the csDE testing on age(slope) effect will then follow.
```

`isletSolve`*Solving individual-specific and cell-type-specific reference panels*

Description

This function, `isletSolve`, is a core function of ISLET. It takes the output from data preparation function `dataPrep`, and solve for individual-specific and cell-type-specific reference panels. It has parallel computing implemented to speed up the EM algorithm application.

Usage

```
isletSolve(input, BPPARAM=bpparam() )
```

Arguments

<code>input</code>	The list object output from data preparation function <code>dataPrep</code> .
<code>BPPARAM</code>	An instance of <code>BiocParallelParam</code> class, e.g. <code>MulticoreParam</code> , <code>SnowParam</code> , <code>SerialParam</code> , to facilitate parallel computing. If using Unix, <code>MulticoreParam</code> is recommended. Customized options within <code>BiocParallelParam</code> class is allowed. If not specified, the default back-end is <code>retrieve</code> .

Details

For both case group and control group, the deconvolution result is a list of length K , where K is the number of cell types. For each of the K elements, it is a matrix of dimension G by N . It stores the deconvoluted feature (G) by subject (N) values, for each of the K elements.

Value

<code>case.ind.ref</code>	A list of length K , where K is the number of cell types. For each of the K elements in this list, it is a feature by subject matrix containing all the feature values (i.e. gene expression values), for case group. It is one of the main products the individual-specific and cell-type-specific solve algorithm.
<code>ctrl.ind.ref</code>	A list of length K , where K is the number of cell types. For each of the K elements in this list, it is a feature by subject matrix containing all the feature values (i.e. gene expression values), for control group. It is one of the main products the individual-specific and cell-type-specific solve algorithm.
<code>mLLK</code>	A scalar. The log-likelihood from the current model. It can be useful for testing purpose such as Likelihood Ratio Test.

Author(s)

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Examples

```
data(GE600)
ls()
## [1] "GE600_se"

#(1) Data preparation
study123input <- dataPrep(dat_se=GE600_se)

#(2) Individual-specific and cell-type-specific deconvolution
result <- isletSolve(input=study123input)
```

isletTest

Testing for cell-type-specific Differential Expression (csDE) genes

Description

This function, `isletTest`, can take the output from data preparation function `dataPrep`, and test for csDE genes. It uses Likelihood Ratio Test (LRT), iterating all cell types. The output is a matrix of p-values from LRT. It has parallel computing implemented to speed up the EM algorithm application.

Usage

```
isletTest(input, BPPARAM=bpparam() )
```

Arguments

<code>input</code>	The list object output from data preparation function <code>dataPrep</code> .
<code>BPPARAM</code>	An instance of <code>BiocParallelParam</code> class, e.g. <code>MulticoreParam</code> , <code>SnowParam</code> , <code>SerialParam</code> , to facilitate parallel computing. If using Unix, <code>MulticoreParam</code> is recommended. Customized options within <code>BiocParallelParam</code> class is allowed. If not specified, the default back-end is retrieve.

Details

This function implement a LRT, and run individually for each cell type, and then aggregate the results together into a matrix.

Value

A p-value matrix, in the dimension of feature by cell type. Each element is the LRT p-value, by contrasting case group and control group, for one feature in one cell type.

Author(s)

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Examples

```
data(GE600)
ls()
## [1] "GE600_se"

#(1) Data preparation
study123input <- dataPrep(dat_se=GE600_se)

#(2) [optional for csDE genes testing] Individual-specific and cell-type-specific deconvolution
#result.solve <- isletSolve(input=study123input)

#(3) Test for csDE genes
result.test <- isletTest(input=study123input)
```

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