# Package: cytoKernel (via r-universe)

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**Description** cytoKernel implements a kernel-based score test to identify differentially expressed features in high-dimensional biological experiments. This approach can be applied across many different high-dimensional biological data including gene expression data and dimensionally reduced cytometry-based marker expression data. In this R package, we implement functions that compute the feature-wise p values and their corresponding adjusted p values. Additionally, it also computes the feature-wise shrunk effect sizes and their corresponding shrunken effect size. Further, it calculates the percent of differentially expressed features and plots user-friendly heatmap of the top differentially expressed features on the rows and samples on the columns.

**biocViews** ImmunoOncology, Proteomics, SingleCell, Software, OneChannel, FlowCytometry, DifferentialExpression, GeneExpression, Clustering

**BugReports** https://github.com/Ghoshlab/cytoKernel/issues

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`cytoHDBMW` *Example of processed dimensionally reduced flow cytometry (marker median intensities) Bodenmiller_BCR_XL_flowSet() expression dataset from HDCytoData Bioconductor data package.*

---

## Description

The raw data (fcs files) were pre-processed using CATALYST, scuttle, scran Bioconductor packages and igraph CRAN package. The data processing package includes 4 steps and they are as follows: 1. Creating a SingleCellExperiment Object: the flowSet data object along with the metadata are converted into a SingleCellExperiment object using the CATALYST R/Bioconductor package. 2. Clustering: We apply Louvain algorithm using the R package igraph to cluster the expression values by the type markers (surface markers). 3. Median: Medians are calculated within a cluster for every signaling marker and subject. 4. Aggregating and converting the data: We convert the aggregated data into a SummarizedExperiment. The row meta-data indicates "cluster" corresponding to the cluster id for each protein marker. The colData represents the "sample_id", "condition", "patient_id", "ids" The remaining columns indicate median expression intensities for each of the 126 (14 markers * 9 clusters) cluster combination for each sample.

## Usage

```
data(cytoHDBMW)
```

## Format

SummarizedExperiment assay object containing 126 cluster-marker median expression intenities (features) of 8 subjects (samples).

## Details

The HDCytoData package is an extensible resource containing a set of publicly available high-dimensional flow cytometry and mass cytometry (CyTOF) benchmark datasets hosted on Bioconductor's ExperimentHub platform.

## References

Weber, M L, Soneson, Charlotte (2019). "HDCytoData: Collection of high-dimensional cytometry benchmark datasets in Bioconductor object formats." F1000Research, 8(v2), 1459.

## Examples

```
data(cytoHDBMW)
```

---

`CytoK` *CytoK*

---

## Description

This function applies a kernel-based score test for identifying differentially expressed features in high-throughput experiments, called the the CytoK procedure. This function also defines the CytoK class and constructor.

## Usage

```
CytoK(
  object,
  group_factor,
  lowerRho = 2,
  upperRho = 12,
  gridRho = 4,
  alpha = 0.05,
  featureVars = NULL
)
```

## Arguments

| | |
|---|---|
| object | an object which is a matrix or data.frame with features (e.g. cluster-marker combinations or genes) on the rows and samples as the columns. Alternatively, a user can provide a SummarizedExperiment object and the assay(object) will be used as input for the CytoK procedure. |
| group_factor | a group level binary categorical response associated with each sample or column in the object. The order of the group_factor must match the order of the columns in object. |
| lowerRho | (Optional) lower bound of the kernel parameter. |
| upperRho | (Optional) upper bound of the kernel parameter. |
| gridRho | (Optional) number of grid points in the interval [lowerRho, upperRho]. |
| alpha | (Optional) level of significance to control the False Discovery Rate (FDR). Default is 0.05. |
| featureVars | (Optional) Vector of the columns which identify features. If a 'SummarizedExperiment' is used for 'data', row variables will be used. |

## Details

CytoK (Kernel-based score test in biological feature differential analysis) is a nonlinear approach, which identifies differentially expressed features in high-dimensional biological experiments. This approach can be applied across many different high-dimensional biological data including Flow/Mass Cytometry data and other variety of gene expression data. The CytoK procedure employs a kernel-based score test to identify differentially expressed features. This procedure can be easily applied to a variety of measurement types since it uses a Gaussian distance based kernel.

This function computes the feature-wise p values and their corresponding adjusted p values. Additionally, it also computes the feature-wise shrunk effect sizes and their corresponding shrunk effect size sd's. Further, it calculates the percent of differentially expressed features. See the vignette for more details.

## Value

A object of the class CytoK that contains a data.frame of the CytoK features in the CytoKFeatures slot, a data.frame of the CytoK features in the CytoKFeaturesOrdered slot ordered by adjusted p values from low to high, a numeric value of the CytoK differentially expressed features CytoKDEfeatures slot, a data.frame or SummarizedExperiment original data objject in the CytoKData slot, a numeric value of the level of significance in the CytoKalpha slot and (optional) a vector of the columns which identify features in the CytoKfeatureVars slot.

## References

Liu D, Ghosh D, Lin X. Estimation and testing for the effect of a genetic pathway on a disease outcome using logistic kernel machine regression via logistic mixed models. BMC Bioinf. 2008; 9(1):292.

Zhan X, Ghosh D. Incorporating auxiliary information for improved prediction using combination of kernel machines. Stat Methodol. 2015; 22:47–57.

Zhan, X., Patterson, A.D. & Ghosh, D. Kernel approaches for differential expression analysis of mass spectrometry-based metabolomics data. BMC Bioinformatics 16, 77 (2015). https://doi.org/10.1186/s12859-015-0506-3

Matthew Stephens, False discovery rates: a new deal, Biostatistics, Volume 18, Issue 2, April 2017, Pages 275–294, https://doi.org/10.1093/biostatistics/kxw041

## Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
data("cytoHDBMW")
data_CytoK_HD <- CytoK(object=cytoHDBMW,
group_factor = rep(c(0, 1), c(4, 4)), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
```

---

`CytoK-class` *the CytoK class*

---

## Description

Objects of this class store needed information to work with a CytoK object

## Value

`CytoKFeatures` returns the data.frame with shrunk effect size, shrunk effect size sd, unadjusted p value and adjusted p value for each feature, `CytoKFeaturesOrdered` returns the data.frame with shrunk effect size, shrunk effect size sd, unadjusted p value and adjusted p value for each feature ordered by unadjusted p value from low to high, `CytoKDEfeatures` returns the percent of differentially expressed features based on alpha (level of significance), `CytoKData` returns the original data object, `CytoKalpha` returns the specified level of significance. Default is alpha=0.05. `CytoKFeatureVars` returns the value of featureVars. Default is NULL.

## Slots

`CytoKFeatures` CytoK features

`CytoKFeaturesOrdered` CytoK features ordered by adjusted p values

`CytoKDEfeatures` Percent of Differentially Expressed CytoK features

`CytoKData` Original data object passed to `CytoK`

`CytoKalpha` Value of `alpha` argument passed to `CytoK`

`CytoKFeatureVars` Value of `featureVars` passed to `CytoK`. NULL if `featureVars` is left blank

## Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
```

---

`CytoKalpha` *Generic function that returns the CytoK level of significance (alpha) Given a CytoK object, this function returns the CytoK alpha*

---

## Description

Accessors for the 'CytoKalpha' slot of a CytoK object.

## Usage

```
CytoKalpha(object)

## S4 method for signature 'CytoK'
CytoKalpha(object)
```

## Arguments

| | |
|---|---|
| `object` | an object of class `CytoK`. |

## Value

Value of `CytoKalpha` argument passed to `CytoK`

## Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
CytoKalpha(data_CytoK)
```

## CytoKData — *Generic function that returns the CytoK Data*

### Description

Given a CytoK object, this function returns the CytoK Data

Accessors for the 'CytoKData' slot of a CytoK object.

### Usage

```
CytoKData(object)

## S4 method for signature 'CytoK'
CytoKData(object)
```

### Arguments

| | |
|---|---|
| object | an object of class CytoK. |

### Value

Original data object passed to CytoK.

### Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
CytoKData(data_CytoK)
```

## CytoKDEData — *Differentially expressed data by cytoKernel*

### Description

Select CytoK object according to the differentially expressed features identified by cytoKernel. Features are filtered if their adjusted p values are greater than CytoKalpha.

### Usage

```
CytoKDEData(object, by = c("features"))
```

### Arguments

| | |
|---|---|
| object | a CytoK object from CytoK |
| by | String specifying which adjusted p values of the features to filter by. Default is "features". |

### Value

A list of data.frame's or a SummarizedExperiment. If a data.frame was originally input into the CytoK function, a list with two elements, DEdata, nonDEfeatures, will be returned. If a SummarizedExperiment was originally input, output will be a SummarizedExperiment with the filtered assay with one metadata object nonDEfeatures and four row meta-data EffectSize, EffectSizeSD, pvalue and padj.

### Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
CytoKDEData(data_CytoK, by = "features")
```

---

## CytoKDEfeatures *Generic function that returns the CytoK Differentially Expressed (DE) features Given a CytoK object, this function returns the CytoK DE features*

---

### Description

Accessors for the 'CytoKDEfeatures' slot of a CytoK object.

### Usage

```
CytoKDEfeatures(object)

## S4 method for signature 'CytoK'
CytoKDEfeatures(object)
```

### Arguments

| | |
|---|---|
| object | an object of class CytoK. |

### Value

The percent of differentially expressed features based on alpha (level of significance).

## Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
CytoKDEfeatures(data_CytoK)
```

---

`CytoKFeatures` *Generic function that returns the CytoK features*

---

## Description

Given a CytoK object, this function returns the CytoK features

Accessors for the 'CytoKFeatures' slot of a CytoK object.

## Usage

```
CytoKFeatures(object)

## S4 method for signature 'CytoK'
CytoKFeatures(object)
```

## Arguments

| | |
|---|---|
| `object` | an object of class `CytoK`. |

## Value

The data.frame with shrunk effect size, shrunk effect size sd, unadjusted p value and adjusted p value for each feature.

## Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
CytoKFeatures(data_CytoK)
```

## CytoKFeaturesOrdered *Generic function that returns the ordered CytoK features*

### Description

Given a CytoK object, this function returns the CytoK features ordered by adjusted p values

Accessors for the 'CytoKFeaturesOrdered' slot of a CytoK object.

### Usage

```
CytoKFeaturesOrdered(object)

## S4 method for signature 'CytoK'
CytoKFeaturesOrdered(object)
```

### Arguments

| | |
|---|---|
| object | an object of class CytoK. |

### Value

the data.frame with shrunk effect size, shrunk effect size sd, unadjusted p value and adjusted p value for each feature ordered by unadjusted p value from low to high.

### Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
CytoKFeaturesOrdered(data_CytoK)
```

## CytoKFeatureVars *Generic function that returns the CytoK Feature Vars*

### Description

Given a CytoK object, this function returns the CytoK Feature Vars

Accessors for the 'CytoKFeatureVars' slot of a CytoK object.

### Usage

```
CytoKFeatureVars(object)

## S4 method for signature 'CytoK'
CytoKFeatureVars(object)
```

### Arguments

| | |
|---|---|
| object | an object of class CytoK. |

### Value

Value of featureVars passed to CytoK. NULL if featureVars was left blank

### Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
CytoKFeatureVars(data_CytoK)
```

---

## CytoKProc *CytoKProc*

---

### Description

This function is a helper function that computes the shrunk effective size mean, shrunk effective size standard deviation (sd), p value and adjusted p value of each feature for the function CytoK.

### Usage

```
CytoKProc(object, group_factor, lowerRho = 2, upperRho = 12, gridRho = 4)
```

### Arguments

| | |
|---|---|
| object | an object which is a matrix or data.frame with features (e.g. cluster-marker combinations or genes) on the rows and samples (group factors) as the columns. Alternatively, a user can provide a SummarizedExperiment object and the assay(object) will be used as input for the CytoK procedure. |
| group_factor | a group level binary categorical response associated with each sample or column in the object. The order of the group_factor must match the order of the columns in object. |

| | |
|---|---|
| lowerRho | (Optional) lower bound of the kernel parameter. |
| upperRho | (Optional) upper bound of the kernel parameter. |
| gridRho | (Optional) number of grid points in the interval [lowerRho, upperRho]. |

## Value

A list of CytoK statistics including

| | |
|---|---|
| shrunkEffectSizeMean | the shrunk effective size posterior mean per feature |
| shrunkEffectSizeSD | the shrunk effective size posterior sd per feature |
| vec_pValue | the unadjusted p value per feature |
| AdjPvalue_features | the adjusted p value per feature using the Benjamini-Hochberg procedure. |

## Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoKProc <- CytoKProc(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4)
```

---

# data.frameORSummarizedExperiment-class *S4 Class union*

---

## Description

Class union allowing CytoKData slot to be a data.frame or Summarized Experiment

---

# plotCytoK *Heatmap of the differentially expressed data with features on the rows and samples (group factors) as the columns from* CytoK *and* CytoKDEData *function.*

---

## Description

This function plots a heatmap of the expression matrix with features (e.g., cluster-marker combinations) on the rows and samples (group factors) as the columns.

## Usage

```
plotCytoK(object, group_factor, topK, featureVars = NULL)
```

## Arguments

| | |
|---|---|
| object | a CytoK object from CytoK |
| group_factor | a group level binary categorical response associated with each sample or column in the object. The order of the group_factor must match the order of the columns in object. |
| topK | top K differentially expressed features. |
| featureVars | (Optional) Vector of the columns which identify features. If a 'SummarizedExperiment' is used for 'data', row variables will be used. |

## Value

A heatmap will be created showing the samples on the columns and features on the rows.

## Examples

```
data <- cbind(matrix(rnorm(1200,mean=2, sd=1.5),
nrow=200, ncol=6), matrix(rnorm(1200,mean=5, sd=1.9),
nrow=200, ncol=6))
data_CytoK <- CytoK(object=data,
group_factor = rep(c(0,1), each=6), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
data("cytoHDBMW")
data_CytoK_HD <- CytoK(object=cytoHDBMW,
group_factor = rep(c(0, 1), c(4, 4)), lowerRho=2,
upperRho=12,gridRho=4,alpha = 0.05,
featureVars = NULL)
plotCytoK(data_CytoK_HD,
group_factor = rep(c(0, 1), c(4, 4)),topK=10,
featureVars = NULL)
```

---

# vectorORNull-class *S4 Class union*

---

## Description

Class union allowing CytoKFeatureVars slot to be a vector or NULL

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