

# Package ‘PAC’

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**Type** Package

**Title** Partition-Assisted Clustering and Multiple Alignments of Networks

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**Author** Ye Henry Li, Dangna Li

**Maintainer** Ye Henry Li <hlow12@gmail.com>

**Description** Implements partition-assisted clustering and multiple alignments of networks. It 1) utilizes partition-assisted clustering to find robust and accurate clusters and 2) discovers coherent relationships of clusters across multiple samples. It is particularly useful for analyzing single-cell data set. Please see Li et al. (2017) <doi:10.1371/journal.pcbi.1005875> for detail method description.

**URL** <https://doi.org/10.1371/journal.pcbi.1005875>

**License** GPL-3

**Imports** Rcpp (>= 0.12.2),igraph,parmigene,infotheo,dplyr, Rtsne, ggplot2, ggrepel

**Suggests** knitr, rmarkdown

**VignetteBuilder** knitr

**LinkingTo** Rcpp

**RoxygenNote** 5.0.1

**NeedsCompilation** yes

**SystemRequirements** C++11

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aggregateData	<i>Aggregates results from the clustering and merging step.</i>
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## Description

Aggregates results from the clustering and merging step.

## Usage

```
aggregateData(dataInput, labelsInput)
```

## Arguments

dataInput	Data matrix, with first column being SampleID.
labelsInput	cluster labels from PAC.

## Value

The aggregated data of dataInput, with average signal levels for all clusters and sample combinations.

**Examples**

```
n = 5e3 # number of observations
p = 1 # number of dimensions
K = 3 # number of clusters
w = rep(1,K)/K # component weights
mu <- c(0,2,4) # component means
sd <- rep(1,K)/K # component standard deviations
g <- sample(1:K,prob=w,size=n,replace=TRUE) # ground truth for clustering
X <- as.matrix(rnorm(n=n,mean=mu[g],sd=sd[g]))
y <- PAC(X, K)
X2<-as.matrix(rnorm(n=n,mean=mu[g],sd=sd[g]))
y2<-PAC(X2,K)
X<-cbind("Sample1", as.data.frame(X)); colnames(X)<-c("SampleID", "Value")
X2<-cbind("Sample2", as.data.frame(X2)); colnames(X2)<-c("SampleID", "Value")
aggregateData(rbind(X,X2),c(y,y2))
```

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annotateClades	<i>Creates annotation matrix for the clades in aggregated format. The matrix contains average signals of each dimension for each clade in each sample</i>
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**Description**

Creates annotation matrix for the clades in aggregated format. The matrix contains average signals of each dimension for each clade in each sample

**Usage**

```
annotateClades(sampleIDs, topHubs)
```

**Arguments**

sampleIDs	sampleID vector
topHubs	number of top ranked genes to output for annotation; annotation is a concatenated list of top ranked genes.

**Value**

Annotated clade matrix

---

annotationMatrix\_withSubpopProp

*Adds subpopulation proportion for the annotation matrix for the clades*

---

### Description

Adds subpopulation proportion for the annotation matrix for the clades

### Usage

```
annotationMatrix_withSubpopProp(aggregateMatrix_withAnnotation)
```

### Arguments

aggregateMatrix\_withAnnotation  
the annotated clade matrix

### Value

Annotated clade matrix with subpopulation proportions

---

BSPLeaveCenter

*Finds N Leaf centers in the data*

---

### Description

Finds N Leaf centers in the data

### Usage

```
BSPLeaveCenter(data, N = 40, method = "dsp")
```

### Arguments

data	a n x p data matrix
N	number of leaves centers
method	partition method, either "dsp (discrepancy based partition)", or "ll (bayesian sequential partition limited-look ahead)"

### Value

leafctr N leaves centers

---

constellationPlot	<i>Makes constellation plot, in which the centroids are clusters are embedded in the t-SNE 2D plane and the cross-sample relationships are plotted as lines connecting related sample clusters (clades).</i>
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### Description

Makes constellation plot, in which the centroids are clusters are embedded in the t-SNE 2D plane and the cross-sample relationships are plotted as lines connecting related sample clusters (clades).

### Usage

```
constellationPlot(pacman_results, perplexity, max_iter, seed,
  plotTitle = "Constellations of Clades", nudge_x = 0.3, nudge_y = 0.3)
```

### Arguments

pacman_results	PAC-MAN analysis result matrix that contains network annotation, clade IDs and mean (centroid) clade expression levels.
perplexity	perplexity setting for running t-SNE
max_iter	max_iter setting for running t-SNE
seed	set seed to make t-SNE and constellation plot to be reproducible
plotTitle	max_iter setting for running t-SNE
nudge_x	nudge on x coordinate of centroid labels
nudge_y	nudge on y coordinate of centroid labels

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fmeasure	<i>F-measure Calculation</i>
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### Description

Compute the F measure between the ground truth and the estimated label

### Usage

```
fmeasure(g, t)
```

### Arguments

g	the ground truth
t	estimated labels

### Value

f the F measure

getAverageSpreadOf2SubpopClades

*Calculate the (global) average spread of subpopulations in clades with 2 subpopulations on the constellation plot.*

---

### Description

Calculate the (global) average spread of subpopulations in clades with 2 subpopulations on the constellation plot.

### Usage

```
getAverageSpreadOf2SubpopClades(tsneResults, pacman_results)
```

### Arguments

`tsneResults` t-SNE output of clade centroids' embedding.  
`pacman_results` PAC-MAN analysis result matrix that contains network annotation, clade IDs and mean (centroid) clade expression levels.

### Value

Returns global average of 2-subpopulation clade spread on the constellation plot.

---

getExtraneousCladeSubpopulations

*Calculates subpopulations in clades (with two or more subpopulations) that are too far away from other subpopulations (within the same clade) on the constellation plot; these far away subpopulations should be pruned away from the original clades.*

---

### Description

Calculates subpopulations in clades (with two or more subpopulations) that are too far away from other subpopulations (within the same clade) on the constellation plot; these far away subpopulations should be pruned away from the original clades.

### Usage

```
getExtraneousCladeSubpopulations(tsneResults, pacman_results,  
  threshold_multiplier, max_threshold)
```

**Arguments**

tsneResults	t-SNE output of clade centroids' embedding.
pacman_results	PAC-MAN analysis result matrix that contains network annotation, clade IDs and mean (centroid) clade expression levels.
threshold_multiplier	how many times the threshold ( (a) spread from center of clade for clades with three or more sample subpopulations and (b) distance from each subpopulation centroid for clades with exactly two subpopulations).
max_threshold	the maximum distance (on t-SNE plane) allowed for sample subpopulations to be categorized into the same clade.

**Value**

Returns clade subpopulations to be pruned.

---

getRepresentativeNetworks  
*Representative Networks*

---

**Description**

Outputs representative networks for clades/subpopulations larger than a size filter (very small subpopulations are not considered in downstream analyses)

**Usage**

```
getRepresentativeNetworks(sampleIDs, dim_subset, SubpopSizeFilter,
  num_networkEdge)
```

**Arguments**

sampleIDs	sampleID vector
dim_subset	a string vector of string names to subset the data columns for PAC; set to NULL to use all columns
SubpopSizeFilter	the cutoff for small subpopulations. Smaller subpopulations have unstable covariance structure, so no network structure is calculated
num_networkEdge	the number of edges to draw for each subpopulation mutual information network

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heatmapInput	<i>Creates the matrix that can be easily plotted with a heatmap function available in an R package</i>
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**Description**

Creates the matrix that can be easily plotted with a heatmap function available in an R package

**Usage**

```
heatmapInput(aggregateMatrix_withAnnotation)
```

**Arguments**

aggregateMatrix\_withAnnotation  
the annotated clade matrix

**Value**

the heatmap input matrix

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JaccardSM	<i>Calculates the Jaccard similarity matrix.</i>
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**Description**

Calculates the Jaccard similarity matrix.

**Usage**

```
JaccardSM(network1, network2)
```

**Arguments**

network1      first network matrix input  
network2      second network matrix input

**Value**

the alignment/co-occurrence score



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MAN	<i>Creates network alignments using network constructed from subpopulations after PAC</i>
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**Description**

Creates network alignments using network constructed from subpopulations after PAC

**Usage**

```
MAN(sampleIDs, num_PACSupop, smallSubpopCutoff, k_clades)
```

**Arguments**

sampleIDs	sampleID vector
num_PACSupop	number of subpopulations learned in PAC step for each sample
smallSubpopCutoff	Population size cutoff for subpopulations in clade calculation. The small subpopulations will be considered in the refinement step.
k_clades	number of clades to output before refinement

**Value**

clades\_network\_only the clades constructed without small subpopulations (by cutoff) using mutual information network alignments

---

MINetworkPlot_topEdges	<i>Plots mutual information network (mrnet algorithm) connection using the parmigene package. Mutual information calculated with infotheo package.</i>
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---

**Description**

Plots mutual information network (mrnet algorithm) connection using the parmigene package. Mutual information calculated with infotheo package.

**Usage**

```
MINetworkPlot_topEdges(dataMatrix, threshold)
```

**Arguments**

dataMatrix	data matrix
threshold	the maximum number of edges to draw for each subpopulation mutual information network

MINetwork\_matrix\_topEdges

*Mutual information network connection matrix generation (mrnet algorithm) using the parmigene package. Mutual information calculated with infotheo package.*

---

### **Description**

Mutual information network connection matrix generation (mrnet algorithm) using the parmigene package. Mutual information calculated with infotheo package.

### **Usage**

```
MINetwork_matrix_topEdges(dataMatrix, threshold)
```

### **Arguments**

dataMatrix	data matrix
threshold	the number of edges to draw for each subpopulation mutual information network

### **Value**

the mutual information network connection matrix with top edges

---

MINetwork\_simplified\_topEdges

*Outputs the vectorized summary of a network based on the number of edges connected to a node*

---

### **Description**

Outputs the vectorized summary of a network based on the number of edges connected to a node

### **Usage**

```
MINetwork_simplified_topEdges(dataMatrix, threshold)
```

### **Arguments**

dataMatrix	data matrix
threshold	the number of edges to draw for each subpopulation mutual information network

---

outputNetworks\_topEdges\_matrix

*Wrapper to output the mutual information networks for subpopulations with size larger than a desired threshold.*

---

### Description

Wrapper to output the mutual information networks for subpopulations with size larger than a desired threshold.

### Usage

```
outputNetworks_topEdges_matrix(dataMatrix, subpopulationLabels, threshold)
```

### Arguments

dataMatrix	data matrix with first column being the sample ID
subpopulationLabels	the subpopulation labels
threshold	the number of edges to draw for each subpopulation mutual information network

---

outputRepresentativeNetworks\_topEdges

*Outputs the representative/clade networks (plots and summary vectors) for subpopulations with size larger than a desired threshold. Saves the networks and the data matrices without the smaller subpopulations.*

---

### Description

Outputs the representative/clade networks (plots and summary vectors) for subpopulations with size larger than a desired threshold. Saves the networks and the data matrices without the smaller subpopulations.

### Usage

```
outputRepresentativeNetworks_topEdges(dataMatrix, subpopulationLabels,
    threshold)
```

### Arguments

dataMatrix	data matrix with first column being the sample ID
subpopulationLabels	the subpopulation labels
threshold	the number of edges to draw for each subpopulation mutual information network

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PAC	<i>Partition Assisted Clustering PAC 1) utilizes dsp or bsp-ll to recursively partition the data space and 2) applies a short round of kmeans style postprocessing to efficiently output clustered labels of data points.</i>
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---

### Description

Partition Assisted Clustering PAC 1) utilizes dsp or bsp-ll to recursively partition the data space and 2) applies a short round of kmeans style postprocessing to efficiently output clustered labels of data points.

### Usage

```
PAC(data, K, maxlevel = 40, method = "dsp", max.iter = 50)
```

### Arguments

data	a n x p data matrix
K	number of final clusters in the output
maxlevel	the maximum level of the partition
method	partition method, either "dsp(discrepancy based partition)", or "bsp(bayesian sequential partition)"
max.iter	maximum iteration for the kmeans step

### Value

y cluster labels for the input

### Examples

```
n = 5e3           # number of observations
p = 1             # number of dimensions
K = 3            # number of clusters
w = rep(1,K)/K   # component weights
mu <- c(0,2,4)   # component means
sd <- rep(1,K)/K # component standard deviations
g <- sample(1:K,prob=w,size=n,replace=TRUE) # ground truth for clustering
X <- as.matrix(rnorm(n=n,mean=mu[g],sd=sd[g]))
y <- PAC(X, K)
print(fmeasure(g,y))
```

---

`recordWithinClusterSpread`*Calculates the within cluster spread*

---

**Description**

Calculates the within cluster spread

**Usage**

```
recordWithinClusterSpread(sampleIDs, dim_subset = NULL, SubpopSizeFilter)
```

**Arguments**

`sampleIDs` A vector of sample names.

`dim_subset` a string vector of string names to subset the data columns for PAC; set to NULL to use all columns.

`SubpopSizeFilter` threshold to filter out very small clusters with too few points; these very small subpopulations may not be outliers and not biologically relevant.

**Value**

Returns the sample within cluster spread

---

`refineSubpopulationLabels`*Refines the subpopulation labels from PAC using network alignment and small subpopulation information. Outputs a new set of files containing the representative labels.*

---

**Description**

Refines the subpopulation labels from PAC using network alignment and small subpopulation information. Outputs a new set of files containing the representative labels.

**Usage**

```
refineSubpopulationLabels(sampleIDs, dim_subset, clades_network_only,  
expressionGroupClamp)
```

**Arguments**

sampleIDs	sampleID vector
dim_subset	a string vector of string names to subset the data columns for PAC; set to NULL to use all columns
clades_network_only	the alignment results from MAN; used to translate the original sample-specific labels into clade labels
expressionGroupClamp	clamps the subpopulations into desired number of expression groups for assigning small subpopulations into larger groups or their own groups.

---

renamePrunedSubpopulations

*Prune away specified subpopulations in clades that are far away.*

---

**Description**

Prune away specified subpopulations in clades that are far away.

**Usage**

```
renamePrunedSubpopulations(pacman_results, subpopulationsToPrune)
```

**Arguments**

pacman_results	PAC-MAN analysis result matrix that contains network annotation, clade IDs and mean (centroid) clade expression levels.
subpopulationsToPrune	A vector of clade IDs; these clades will be pruned.

**Value**

Returns PAC-MAN analysis result matrix with pruned clades. The pruning process creates new clades to replace the original clade ID of the specified subpopulations.

---

`runElbowPointAnalysis` *Runs elbow point analysis to find the practical optimal number of clades to output. Outputs the average within sample cluster spread for all samples and the elbow point analysis plot with loess line fitted through the results.*

---

### Description

Runs elbow point analysis to find the practical optimal number of clades to output. Outputs the average within sample cluster spread for all samples and the elbow point analysis plot with loess line fitted through the results.

### Usage

```
runElbowPointAnalysis(ks, sampleIDs, dim_subset, num_PACSupop,
  smallSubpopCutoff, expressionGroupClamp, SubpopSizeFilter)
```

### Arguments

<code>ks</code>	Vector that is a sequence of clade sizes.
<code>sampleIDs</code>	A vector of sample names.
<code>dim_subset</code>	a string vector of string names to subset the data columns for PAC; set to NULL to use all columns.
<code>num_PACSupop</code>	Number of PAC subpopulation explored in each sample.
<code>smallSubpopCutoff</code>	Cutoff of minor subpopulation not used in multiple alignments of networks
<code>expressionGroupClamp</code>	clamps the subpopulations into desired number of expression groups for assigning small subpopulations into larger groups or their own groups.
<code>SubpopSizeFilter</code>	threshold to filter out very small clusters with too few points in the calculation of cluster spreads; these very small subpopulations may be outliers and not biologically relevant.

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<code>samplePass</code>	<i>Run PAC for Specified Samples</i>
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---

### Description

A wrapper to run PAC and output subpopulation mutual information networks. Please use the PAC function itself for individual samples or if the MAN step is not needed.

**Usage**

```
samplePass(sampleIDs, dim_subset, hyperrectangles, num_PACSupop, max.iter,  
           num_networkEdge)
```

**Arguments**

<code>sampleIDs</code>	sampleID vector
<code>dim_subset</code>	a string vector of string names to subset the data columns for PAC; set to NULL to use all columns
<code>hyperrectangles</code>	number of hyperrectangles to learn for each sample
<code>num_PACSupop</code>	number of subpopulations to output for each sample using PAC
<code>max.iter</code>	postprocessing kmeans iterations
<code>num_networkEdge</code>	a threshold on the number of edges to output for each subpopulation mutual information network



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