Package 'ADaM'

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Type Package

Title Adaptive Daisy Model

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Description The ADaM package implements a semi-supervised algorithm for computing a fuzzy-intersection of non-fuzzy sets by adaptively determining the minimal number of sets to which an element should belong in order to be a member of the fuzzy-intersection (the membership threshold). This threshold maximises the deviance from expectation of the cardinality of the resulting fuzzy-intersection, as well as the coverage of predefined elements. This method can be used to identify the minimal number of cell lines from a given tissue in which the inactivation of a gene (for example via CRISPR-Cas9 targeting) should exert a reduction of viabilty (or fitness effect) in order for that gene to be considered a core-fitness essential gene for the tissue under consideration. This method is used to discriminate between core-fitness and context-specific essential genes in a study describing a large scale genome-wide CRISPR-Cas9 pooled drop-out screening (Behan FM & Iorio F & Picco G et al., Prioritisation of cancer therapeutic targets using CRISPR-Cas9 screens. Nature, In press).

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LazyData true

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`ADAM.generateNullModel`

Generate null profile of number of fitness genes across fixed numbers of cell lines and cumulative sums.

Description

This function randomly perturbs the binary dependency matrix to generate a null distribution of profiles of fitness genes across fixed number of cell lines, and corresponding null distribution of cumulative sums.

Usage

```
ADAM.generateNullModle(depMat,ntrials=100,display=TRUE)
```

Arguments

depMat	Binary dependency matrix, rows are genes and columns are samples. 1 in position \emp[i,j] indicates that inactivation of the \empith gene exerts a significant loss of fitness in the \empjth sample, 0 otherwise.
ntrials	Integer, default =100. How many times to randomly perturb dependency matrix to generate the null distributions.
display	Boolean, default is TRUE. Should bar plots of the null profiles be plotted

Details

For a number of trials specified in (ntrials) the inputted binary dependency matrix is randomised, keeping its column marginal sums. The profiles of fitness genes across fixed number of cell lines, and corresponding cumulative sums, are returned for each random perturbation.

Value

A list with the following two matrices

nullProf	Matrix of number of fitness genes for fixed number of cell lines from. Each rows of matrix corresponds to a random trial.
nullCumSum	Matrix of profile of cumulative number of fitness genes in fixed number of cell lines. Each row of matrix is one random trial.

Author(s)

C. Pacini & F. Iorio

Examples

```
data(exampleDepMat)
pprofile <- ADAM.generateNullModel(depMat = exampleDepMat,ntrials=100)
```

`ADAM.panessprofile` *Calculate profile of number of fitness genes across fixed numbers of cell lines and cumulative sums.*

Description

This function calculates the numbers (and cumulative numbers) of genes whose inactivation exerts a fitness effect in *n* cell lines, varying *n* from 1 to the number of cell lines in the dataset in input.

Usage

```
ADAM.panessprofile(depMat,
                   display=TRUE,
                   main_suffix='fitness genes in at least 1 cell line',
                   xlab='n. dependent cell lines')
```

Arguments

`depMat`	Binary dependency matrix, rows are genes and columns are samples. 1 in position \emp[i,j] indicates that inactivation of the \empith gene exerts a significant loss of fitness in the \empjth sample, 0 otherwise.
`display`	Boolean, default is TRUE. Should bar plots of the dependency profiles be plotted
`main_suffix`	If display=TRUE, title suffix to give to plot of number of genes depleted in a give number of cell lines, default is 'genes depleted in at least 1 cell line'
`xlab`	If display=TRUE, label to give to x-axis of the plots, default is 'n. cell lines'

Value

A list with the following two named vectors:

`panessprof`	Number of genes that are depleted for a number of cell lines
`CUMsums`	Cumulative number of genes depleted in at least x cell lines

Author(s)

C. Pacini & F. Iorio

Examples

```
data(exampleDepMat)
pprofile <- ADAM.panessprofile(depMat = exampleDepMat)
```

ADAM.randomisedepMat *Binary matrix randomisation preserving column totals*

Description

This function takes in input a matrix and shuffles its entries column wisely. If the matrix is binary then then matrix resulting from this shuffling will have the same column marginal totals of the inpputted one.

Usage

```
ADAM.randomisedepMat(depMat)
```

Arguments

depMat	A numerical matrix.

Value

The matrix given in input with entries shuffled column wisely.

Author(s)

C. Pacini & F. Iorio

Examples

```
data(exampleDepMat)
rnd_exampleDepMat<-ADAM.randomisedepMat(exampleDepMat)
```

curated_BAGEL_essential *Referecence set of core-fitness essential genes*

Description

Reference set of predefined core-fitness essential genes used in [1], derived from [2] and further curated as follows. In order to avoid their status (essential/non-essential) being defined a priori, a set of high-confidence cancer driver genes from [3] were filtered out.

Usage

```
data(curated_BAGEL_essential)
```

Format

A vector of string with a gene symbol in each entry

References

[1] Behan FM & Iorio F & Picco G et al., Prioritisation of cancer therapeutic targets using CRISPR-Cas9 screens. Nature, In press.

[2] Hart T, Chandrashekhar M, Aregger M, Steinhart Z, Brown KR, MacLeod G, et al. High-Resolution CRISPR Screens Reveal Fitness Genes and Genotype-Specific Cancer Liabilities. Cell. 2015;163:1515–26.

[3] Iorio F, Knijnenburg TA, Vis DJ, Bignell GR, Menden MP, Schubert M, et al. A Landscape of Pharmacogenomic Interactions in Cancer. Cell. 2016;166:740–54.

Examples

```
data(curated_BAGEL_essential)
head(curated_BAGEL_essential)
```

`exampleDepMat` *Example dependency matrix data object*

Description

A binary matrix summarising the fitness effect status (1 = cellular fitness reduced upon gene inactivation via CRISPR-Cas9 targeting) of all the genes (at a genome scale) across 32 human colorectal cancer cell lines, derived from [1].

Usage

```
data("exampleDepMat")
```

Format

The format is: num [1:17995, 1:32] 0 0 0 0 0 0 0 0 0 0 ... - attr(*, "dimnames")=List of 2 ..$: chr [1:17995] "A1BG" "A1CF" "A2M" "A2ML1" ... ..$: chr [1:32] "Cell_line_1" "Cell_line_2" "Cell_line_3" "Cell_line_4" ...

References

[1] Behan FM & Iorio F & Picco G et al., *Prioritisation of cancer therapeutic targets using CRISPR-Cas9 screens*. **Nature**, In press.

Examples

```
data(exampleDepMat)
head(exampleDepMat)
```

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