Package 'hierGWAS'

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Title Asessing statistical significance in predictive GWA studies

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Description Testing individual SNPs, as well as arbitrarily large groups of SNPs in GWA studies, using a joint model of all SNPs. The method controls the FWER, and provides an automatic, data-driven refinement of the SNP clusters to smaller groups or single markers.

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License GPL-3

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Imports fastcluster,glmnet, fmsb

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Contents

`cluster.snp` *Hierarchical Clustering of SNP Data*

Description

Clusters SNPs hierachically.

Usage

```
cluster.snp(x = NULL, d = NULL, method = "average", SNP_index = NULL)
```

Arguments

`x`	The SNP data matrix of size `nobs` x `nvar`. Default value is `NULL`
`d`	`NULL` or a dissimilarity matrix. See the 'Details' section.
`method`	The agglomeration method to be used. This should be (an unambiguous abbreviation of) one of `"ward.D"`, `"ward.D2"`, `"single"`, `"complete"`, `"average"` (= UPGMA), `"mcquitty"` (= WPGMA), `"median"` (= WPGMC) or `"centroid"` (= UPGMC). See `hclust` for details.
`SNP_index`	`NULL` or the index vector of SNPs to be clustered. See the 'Details' section.

Details

The SNPs are clustered using `hclust`, which performs a hierarchical cluster analysis using a set of dissimilarities for the `nvar` objects being clustered. There are 3 possible scenarios.

If `d = NULL`, `x` is used to compute the dissimilarity matrix. The dissimilarity measure between two SNPs is `1 - LD` (Linkage Disequilibrium), where `LD` is defined as the square of the Pearson correlation coefficient. If `SNP_index = NULL`, all `nvar` SNPs will be clustered; otherwise only the SNPs with indices specified by `SNP_index` will be considered.

If the user wishes to use a different dissimilarity measure, `d` needs to be provided. `d` must be either a square matrix of size `nvar` x `nvar`, or an object of class `dist`. If `d` is provided, `x` and `SNP_index` will be ignored.

Value

An object of class `dendrogram` which describes the tree produced by the clustering algorithm `hclust`.

Examples

```
library(MASS)
x <- mvrnorm(60,mu = rep(0,60), Sigma = diag(60))
clust.1 <- cluster.snp(x = x, method = "average")
SNP_index <- seq(1,10)
clust.2 <- cluster.snp(x = x, method = "average", SNP_index = SNP_index)
d <- dist(x)
clust.3 <- cluster.snp(d = d, method = "single")
```

compute.r2 *R2 computation*

Description

Calculates the R2 of a cluster of SNPs.

Usage

```
compute.r2(x, y, res.multisplit, covar = NULL, SNP_index = NULL)
```

Arguments

x	The input matrix, of dimension nobs x nvar. Each row represents a subject, each column a SNP.
y	The response vector. It can be continuous or discrete.
res.multisplit	The output of multisplit.
covar	NULL or the matrix of covariates one wishes to control for, of size nobs x ncovar.
SNP_index	NULL or the index vector of the cluster of SNPs whose R2 will be computed. See the 'Details' section.

Details

The R2 of a cluster of SNPs is computed on the second half-samples. The cluster members, are intersected with the SNPs selected by the lasso, and the R2 of this model is calculated. Thus, we obtain B R2 values. Finally, the mean of these values is taken. If the value of SNP_index is NULL, the R2 of the full model with all the SNPs will be computed.

Value

The R2 value of the SNP cluster

References

Buzdugan, L. et al. (2015), Assessing statistical significance in predictive genome-wide association studies. (unpublished)

Examples

```
library(MASS)
x <- mvrnorm(60,mu = rep(0,60), Sigma = diag(60))
beta <- rep(0,60)
beta[c(5,9,3)] <- 1
y <- x %*% beta + rnorm(60)
SNP_index <- c(5,9,3)
res.multisplit <- multisplit(x, y)
r2 <- compute.r2(x, y, res.multisplit, SNP_index = SNP_index)
```

hierGWAS *Asessing statistical significance in predictive GWA studies*

Description

Testing individual SNPs, as well as arbitrarily large groups of SNPs in GWA studies, using a joint model of all SNPs. The method controls the FWER, and provides an automatic, data-driven refinement of the SNP clusters to smaller groups or single markers.

Details

hierGWAS is a package designed to assess statistical significance in GWA studies, using a hierarchical approach.

There are 4 functions provided: `cluster.snp`, `multisplit`, `test.hierarchy` and `compute.r2`. `cluster.snp` performs the hierarchical clustering of the SNPs, while `multisplit` runs multiple penalized regressions on repeated random subsamples. These 2 functions need to be executed before `test.hierarchy`, which does the hierarchical testing, though the order in which the 2 functions are executed does not matter. `test.hierarchy` provides the final output of the method: a list of SNP groups or individual SNPs, along with their corresponding p-values. Finally, `compute.r2` computes the explained variance of an arbitrary group of SNPs, of any size. This group can encompass all SNPs, SNPs belonging to a certain chromosome, or an individual SNP.

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References

Buzdugan, L. et al. (2015), Assessing statistical significance in predictive genome-wide association studies (unpublished)

multisplit *Variable Selection on Random Sample Splits.*

Description

Performs repeated variable selection via the lasso on random sample splits.

Usage

```
multisplit(x, y, covar = NULL, B = 50)
```

Arguments

x	The SNP data matrix, of size nobs x nvar. Each row represents a subject, each column a SNP.
y	The response vector. It can be continuous or discrete.
covar	NULL or the matrix of covariates one wishes to control for, of size nobs x ncovar.
B	The number of random splits. Default value is 50.

Details

The samples are divided into two random splits of approximately equal size. The first subsample is used for variable selection, which is implemented using **glmnet**. The first [nobs/6] variables which enter the lasso path are selected. The procedure is repeated B times.

If one or more covariates are specified, these will be added unpenalized to the regression.

Value

A data frame with 2 components. A matrix of size B x [nobs/2] containing the second subsample of each split, and a matrix of size B x [nobs/6] containing the selected variables in each split.

References

Meinshausen, N., Meier, L. and Buhlmann, P. (2009), P-values for high-dimensional regression, Journal of the American Statistical Association 104, 1671-1681.

Examples

```
library(MASS)
x <- mvrnorm(60,mu = rep(0,200), Sigma = diag(200))
beta <- rep(1,200)
beta[c(5,9,3)] <- 3
y <- x %*% beta + rnorm(60)
res.multisplit <- multisplit(x, y)
```

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simGWAS *Simulated GWAS data*

Description

This data set was simulated using PLINK. Please refer to the vignette for more details.

Usage

```
simGWAS
```

Format

The dataset contains the following components:

`SNP.1` The first SNP, of dimension `500` x `1`. Each row represents a subject.

...

`SNP.1000` The last SNP, of dimension `500` x `1`. Each row represents a subject.

`y` The response vector. It can be continuous or discrete.

`sex` The first covariate, represeting the sex of the subjects: 0 for men and 1 for women.

`age` The second covariate, represeting the age of the subjects.

Value

data.frame

Examples

```
data(simGWAS)
```

---

test.hierarchy *Hierarchical Testing of SNPs*

Description

Performs hierarchical testing of SNPs.

Usage

```
test.hierarchy(x, y, dendr, res.multisplit, covar = NULL, SNP_index = NULL,
  alpha = 0.05, global.test = TRUE, verbose = TRUE)
```

Arguments

`x`	The input matrix, of dimension `nobs` x `nvar`. Each row represents a subject, each column a SNP.
`y`	The response vector. It can be continuous or discrete.
`dendr`	The cluster tree obtained by hierchically clustering the SNPs using `cluster.snp`.
`res.multisplit`	The output of `multisplit`.
`covar`	`NULL` or the matrix of covariates one wishes to control for, of size `nobs` x `ncovar`.
`SNP_index`	`NULL` or the index vector of SNP to be tested. See the 'Details' section.
`alpha`	The significance level at which the FWER is controlled. Default value is 0.05.
`global.test`	Specifies wether the global null hypothesis should be tested. Default value is `TRUE`. See the 'Details' section.
`verbose`	Report information on progress. Default value is `TRUE`

Details

The testing is performed on the cluster tree given by `dendr`. If the SNP data matrix was divided (e.g. by chromosome), and clustered separately, the user must provide the argument `SNP_index`, to specify which part of the data is being tested.

Testing starts at the highest level, which includes all variables specified by `SNP_index`, and moves down the cluster tree. It stops when a cluster's null hypothesis cannot be rejected anymore. The smallest, still significant clusters will be returned.

By default the parameter `global.test = TRUE`, which means that first the global null hypothesis is tested. If the data is divided (e.g. by chromosome), and clustered separately, this parameter can be set to `FALSE` once the global null has been rejected. This helps save time.

Value

A list of significant SNP groups with the following components:

`SNP_index`	The indeces of the SNPs in the group
`pval`	The p-value of the SNP group

References

Buzdugan, L. et al. (2015), Assessing statistical significance in predictive genome-wide association studies

Examples

```
library(MASS)
x <- mvrnorm(60,mu = rep(0,60), Sigma = diag(60))
beta <- rep(0,60)
beta[c(5,9,3)] <- 1
y <- x %*% beta + rnorm(60)
dendr <- cluster.snp(x = x, method = "average")
res.multisplit <- multisplit(x, y)
sign.clusters <- test.hierarchy(x, y, dendr, res.multisplit)
```

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