Package 'SlaPMEG'

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Type Package

Title Pathway Testing for Longitudinal Omics

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Author Mitra Ebrahimpoor

Maintainer Mitra Ebrahimpoor <mitra.ebrahimpoor@gmail.com>

Description A self-contained hypothesis is tested for a given pathway of longitudinal omics. 'SlaPMEG' is a two-step procedure. First, a shared latent process mixed model is fitted over the longitudinal measures of omics in a pathway. This shared model allows deviation from the shared process at subject level (a random intercept, slope, or both per subject) and also at omic level (a random effect per omic). These random effects summarize the longitudinal trend of the observations which can be used to test for group differences using 'Globaltest' in the second step. If the pathway is large or the shared effect is small, the package fits a series of pairwise models and estimates the shared random effects based on them.

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`multslapmeg` *Testing multiple pathways using SLaPMEG (shared latent process mixed effects model and Globaltest) for longitudinal Omics data*

Description

Run slapmeg simultaneously for several pathways. For each pathway a p-value is calculated based on SLaPMEG prodcedure as in `multslapmeg`. Then the p-values are adjusted for multiple comparisons based on the selected procedure.

Usage

```
multslapmeg(pathlist, fixed, random, grouping, subject, method = "BH", data)
```

Arguments

`pathlist`	A list of pathways to be tested.
`fixed`	A one-sided linear formula object for specifying the fixed-effects in the linear mixed model at the latent process level that starts with the ~ sign.
`random`	A one-sided formula for the random-effects in the latent process mixed model and starts with the ~ sign. At least one random effect should be included. Covariates with a random-effect are separated by +.
`grouping`	name of the covariate representing the grouping structure.
`subject`	name of the covariate representing the repeated measures structure such as subject IDs.
`method`	Correction method for p-values, the default is "BH". For more methods see `?p.adjust`.
`data`	data frame containing the variables named in list of `pathlist`, `fixed`, `random`, `grouping` and `subject`.

Value

A datafram including the name of pathways and corresponding adjusted p-values.

Author(s)

Mitra Ebrahimpoor

<m.ebrahimpoor@lumc.nl>

References

Ebrahimpoor, Mitra, Pietro Spitali, Jelle J. Goeman, and Roula Tsonaka. "Pathway testing for longitudinal metabolomics." Statistics in Medicine (2021).

See Also

slapmeg, pairslapmeg, plotslapmeg

Examples

```
# simulate data with 20 omics
testdata<-simslapmeg(nY=20, ntime=5, nsubj = 30, seed=123)
head(testdata)

# creat a list of 3 random pathways of different sizes
pathlist<-list(path1=sample(colnames(testdata)[-c(1:3)],5),
               path2=sample(colnames(testdata)[-c(1:3)],11),
               path3=sample(colnames(testdata)[-c(1:3)],9) )


#use mult slampmeg to get test for the differential expression of all pathways
#and get adjusted p-values
mfit<- multslapmeg(pathlist, ~time, ~1+time, grouping="group", subject="ID", data=testdata)
summary(mfit)
```

---

pairsetinval *Estimating initial values for paired slapmeg based on seperate lme models*

Description

A seperate lme model is fited per omic in the pathway and the estimates are combined based on the indexes of pairs to create initial values for the pairslapmeg function.

Usage

```
pairsetinval(index, fixed, random, subject, data)
```

Arguments

index	Indexes of pairs used for replacing the parameters in the jopint model
fixed	A two-sided linear formula object for specifying the fixed-effects in the linear mixed model at the latent process level. Names of omics in the pathway are separated by + on the left of ~ and the covariates are separated by + on the right of the ~. For identifiability purposes, the intercept should always be present in the model.

random	A one-sided formula for the random-effects in the latent process mixed model and starts with the ~ sign. At least one random effect should be included. Covariates with a random-effect are separated by +.
subject	name of the covariate representing the repeated measures structure such as subject IDs.
data	data frame containing the variables named in fixed, random, grouping and subject.

Value

A list of vectors, each including vector of initial values corresponding to pairs based on the index file. These vectors will be used as input for multlcmm function of each paired model.

Author(s)

Mitra Ebrahimpoor <m.ebrahimpoor@lumc.nl>

`pairslapmeg` *Testing pathways using SLaPMEG (shared latent process mixed effects model and Globaltest) for longitudinal Omics data based on pairwise estimation approach (a computational solution for latrge pathways)*

Description

This function performs pathway testing for longitudinal omics within a two-step framework just as in `slapmeg` but instead of using a joint shared latent model in the first step, it uses a pairwise approach and runs much faste for larger pathways. After estimating the random effects of the joint model using pairwise fitting, the random effects are used within globaltest to compare the two groups at a pathway level.

Usage

```
pairslapmeg(fixed, random, grouping, subject, data)
```

Arguments

fixed	A two-sided linear formula object for specifying the fixed-effects in the linear mixed model at the latent process level. Names of omics in the pathway are separated by + on the left of ~ and the covariates are separated by + on the right of the ~. For identifiability purposes, the intercept should always be present in the model.
random	A one-sided formula for the random-effects in the latent process mixed model and starts with the ~ sign. At least one random effect should be included. Covariates with a random-effect are separated by +.
grouping	name of the covariate representing grouping by the phenotype

subject	name of the covariate representing the repeated measures structure such as subject IDs.
data	data frame containing the variables named in fixed, random, grouping and subject.

Value

A list is returned including:

call	the matched call
nfix	Number of fixed effect terms in the model, excluding the mandatory intercept
nrand	Number of random effect terms in the model
nsubj	Number of subjects in the sataset
nrep	Table of repeated measures, and number of subjects with the specified number of repeated measures
tgroup	Table of grouping, and number of subjects in each group
Ynames	Name of the Omics in the pathway
slapconv	Status of convergence: For joint method(=1 if the convergence criteria were satisfied, =2 if the maximum number of iterations was reached, =4 or 5 if a problem occured during optimisation); for the pairwise method, proportion of successfully converged pairs is reported
fixedform	Names of Fixed effect terms
randform	Names of random effect terms
slapmethod	The method which is "joint" if the original slapmeg approach is adopted and pairwise for the pairwise method
SLaP.par	Fitted values for the parameters in the joint class mixed model in the first step
Globaltest	The output from Globaltest at the second step
EB_pred	Empirical bayes estimates for the random effects from the joint model

Author(s)

Mitra Ebrahimpoor

<m.ebrahimpoor@lumc.nl>

References

Ebrahimpoor, Mitra, Pietro Spitali, Jelle J. Goeman, and Roula Tsonaka. "Pathway testing for longitudinal metabolomics." Statistics in Medicine (2021).

See Also

slapmeg, multslapmeg, plotslapmeg

Examples

```
# simulate data with 15 omics
testdata<-simslapmeg(nY=25, ntime=3, nsubj = 30, seed=123)
head(testdata)

#fit slapmeg to test for the differential expression of a pathway of size 15
slapmegfit<- pairslapmeg(Y1+Y2+Y6+Y7+Y8~time, ~1, grouping="group", subject="ID", data=testdata)
slapmegfit
summary(slapmegfit)
```

`plotslapmeg` *Plot the estimated random effects from SLaPMEG seperated for the study groups*

Description

This plot can provide a graphical insight into the source of effect (i.e. diffrential expression) in relevent pathway.

Usage

```
plotslapmeg(obj, ...)
```

Arguments

`obj`	An slapmeg object which is the output from `slapmeg` or `pairslapmeg`. Note that the `fullreturn=TRUE`) must have been used.
`...`	optional graphical parameters can be added with an + based on `ggplot2` structure.

Value

returns NULL

Author(s)

Mitra Ebrahimpoor

<m.ebrahimpoor@lumc.nl>

References

Ebrahimpoor, Mitra, Pietro Spitali, Jelle J. Goeman, and Roula Tsonaka. "Pathway testing for longitudinal metabolomics." Statistics in Medicine (2021).

See Also

slapmeg, multslapmeg, pairslapmeg

Examples

```
# simulate data with 8 omics
testdata<-simslapmeg(nY=8, ntime=5, nsubj = 30, seed=123)
head(testdata)

#fit slapmeg to test for the differential expression of a pathway of size 5
fit<- slapmeg(Y1+Y2+Y6+Y7+Y8~time, ~1, grouping="group", subject="ID", data=testdata)

#Density plots for the estimated random effects
plotslapmeg(fit)
```

---

print.mslapmeg *Print objects from* multslapmeg

Description

Provides an overview of mSLaPMEG results for each pathway through multslapmeg object.

Usage

```
## S3 method for class 'mslapmeg'
print(x, ...)
```

Arguments

x	an object inheriting from class multslapmeg
...	further arguments to be passed to or from other methods, which will be ignored in this function.

Value

Returns result summary of mSLAPMEG approach

Author(s)

Mitra Ebrahimpoor

See Also

multslapmeg,slapmeg, pairslapmeg

print.slapmeg *Print objects from* slapmeg

Description

Provides an overview of SLaPMEG approach through slapmeg and pairslapmeg objects.

Usage

```
## S3 method for class 'slapmeg'
print(x, ...)
```

Arguments

x	an object inheriting from class slapmeg
...	further arguments to be passed to or from other methods, which will be ignored in this function.

Value

Returns result summaries of SLAPMEG approach

Author(s)

Mitra Ebrahimpoor

See Also

slapmeg, pairslapmeg

setinval *Estimating initial values for slapmeg based on seperate lme models*

Description

A seperate lme model is fited per omic in the pathway and the estimates are combined to create initial values for the slapmeg function.

Usage

```
setinval(fixed, random, subject, data)
```

Arguments

fixed	A two-sided linear formula object for specifying the fixed-effects in the linear mixed model at the latent process level. Names of omics in the pathway are separated by + on the left of ~ and the covariates are separated by + on the right of the ~. For identifiability purposes, the intercept should always be present in the model.
random	A one-sided formula for the random-effects in the latent process mixed model and starts with the ~ sign. At least one random effect should be included. Covariates with a random-effect are separated by +.
subject	name of the covariate representing the repeated measures structure such as subject IDs.
data	data frame containing the variables named in fixed, random, grouping and subject.

Value

A vector of initial values to be used as input for multlcmm function

Author(s)

Mitra Ebrahimpoor

<m.ebrahimpoor@lumc.nl>

---

simslapmeg *Simulate longitudinal data based on a shared latent process mixed effects model (SlaPMEG)*

Description

This is a simple function to simulate longitudinal data from a shared latent process mixed effects model the data provides a good example for application of slapmeg and pairslapmeg and pairslapmeg objects.

Usage

```
simslapmeg(
  nY,
  ntime,
  nsubj,
  pDif = 1/3,
  fixed = ~1 + time,
  random = ~1 + time,
  fixedbeta = c(0, 2),
  randbeta = c(0, 2),
  group,
  groupbeta = 2,
```

```
  sigma.b,
  sigma.u,
  seed = as.integer(runif(1, 0, .Machine$integer.max)),
  returnpar = FALSE
)
```

Arguments

nY	number of omics in the data
ntime	number of repeated measures
nsubj	number of subjects
pDif	proportion of differentially expressed omics in the data (the default is 1/3)
fixed	A one-sided formula for the fixed-effects excluding the group variable, the default includes an intercept and time
random	A one-sided formula for the random-effects, the default includes an intercept and time
fixedbeta	effect size of fixed terms in formula, the length should match the fixed formula, the default is 0 (intercept) and 2 (time)
randbeta	effect size of random terms in formula, the length should match the random formula, the default is 0 (intercept) and 2 (time)
group	Vector indicating group membership, the length should match the number of subjects, The default is random allocation of half of subjects to each group. If use with slapmeg is intended, the group variable should have only two groups
groupbeta	effect size of group variable, the default is 2
sigma.b	variance of the omic- / subject- specific random effects, the length should math nY. If not specified, nY values from normal distribution will be randomly assigned.
sigma.u	Variance of the subject-specific random effects, the length should math the random effects defined in random formula. If not specified, 2 values from normal distribution will be randomly assigned.
seed	Value of seed, if not specified a random integer will be assigned
returnpar	logical if TRUE, all simulation parameters will be returned along with the simulated data.

Value

Returns a dataframe where the rows represent the observations and the columns represent the subject Id, time and group variable followed by the omics in pathway; if returnpar is TRUE, a list with both data and parametrs is returned

Author(s)

Mitra Ebrahimpoor

See Also

slapmeg, pairslapmeg

slapGT *Run step II via globaltest package*

Description

Globaltest is used to test the association between phenotype variable and estimated random effects from step I.

Usage

```
slapGT(EBS, data_inf, rand_nam, Ynames, grouping, Emethod)
```

Arguments

EBS	Estimated random effects by either joint or pairwise approach
data_inf	Dataframe with variables required for the test
rand_nam	Names of random effects defined in model
Ynames	Name of omics in pathway
grouping	Name of the covariate representing the grouping by the phenotype
Emethod	Estimation method for the random effects which is either joint or pairwise

Value

A GT object containing globaltest results

Author(s)

Mitra Ebrahimpoor

<m.ebrahimpoor@lumc.nl>

slapmeg *Testing pathways using SLaPMEG (shared latent process mixed effects model and Globaltest) for longitudinal Omics data*

Description

A two-step procedure is adopted, first a joint latent process mixed effects model is fitted and on the longitudinal data to summarize the temporal trend in terms of several random effects. For computational efficacy, if the size of pathway is larger than 10 a paired approah is used to estimate the random effects with the pairslapmeg function. The random effects are the input for globaltest which is used to compare the two groups at a pathway level.

Usage

```
slapmeg(fixed, random, grouping, subject, data, nlimit = 10)
```

Arguments

fixed	A two-sided linear formula object for specifying the fixed-effects in the linear mixed model at the latent process level. Names of omics in the pathway are separated by + on the left of ~ and the covariates are separated by + on the right of the ~. For identifiability purposes, the intercept should always be present in the model.
random	A one-sided formula for the random-effects in the latent process mixed model and starts with the ~ sign. At least one random effect should be included. Covariates with a random-effect are separated by +.
grouping	name of the covariate representing grouping by the phenotype
subject	name of the covariate representing the repeated measures structure such as subject IDs.
data	data frame containing the variables named in fixed, random, grouping and subject.
nlimit	A controling arguments telling slapmeg to use pairwise approach for pathways larger than this value, default is 10. Note: fitting the joint model may take long for pathways larger than 20 omics.

Value

A list is returned including:

call	the matched call
nfix	Number of fixed effect terms in the model, excluding the mandatory intercept
nrand	Number of random effect terms in the model
nsubj	Number of subjects in the sataset
nrep	Table of repeated measures, and number of subjects with the specified number of repeated measures
tgroup	Table of grouping, and number of subjects in each group
Ynames	Name of the Omics in the pathway
slapconv	Status of convergence: For joint method(=1 if the convergence criteria were satisfied, =2 if the maximum number of iterations was reached, =4 or 5 if a problem occured during optimisation); for the pairwise method, proportion of successfully converged pairs is reported
fixedform	Names of Fixed effect terms
randform	Names of random effect terms
slapmethod	The method which is "joint" if the original slapmeg approach is adopted and pairwise for the pairwise method
SLaP.par	Fitted values for the parameters in the joint class mixed model in the first step
Globaltest	The output from Globaltest at the second step
EB_pred	Empirical bayes estimates for the random effects from the joint model

Author(s)

Mitra Ebrahimpoor

<m.ebrahimpoor@lumc.nl>

References

Ebrahimpoor, Mitra, Pietro Spitali, Jelle J. Goeman, and Roula Tsonaka. "Pathway testing for longitudinal metabolomics." Statistics in Medicine (2021).

See Also

multslapmeg, pairslapmeg, plotslapmeg

Examples

```
# simulate data with 8 omics
testdata<-simslapmeg(nY=8, ntime=5, nsubj = 30, seed=123)
head(testdata)

#fit slapmeg to test for the differential expression of a pathway of size 5
fit<- slapmeg(Y1+Y2+Y6+Y7+Y8~time, ~1, grouping="group", subject="ID", data=testdata)
fit
summary(fit)
```

---

summary.mslapmeg *Summary of* slapmeg *objects*

Description

Provides a table of sorted p-values for the output of multSLaPMEG approach within multslapmeg objects.

Usage

```
## S3 method for class 'mslapmeg'
summary(object, n = 5, ...)
```

Arguments

object	an object inheriting from classes multslapmeg
n	an integer indicating number of pathways to be printed the default is 5
...	further arguments to be passed to or from other methods, which will be ignored in this function.

Value

'Returns the fixed effect estimates and random effects variances from the model in step 1 and the details of Globaltest along with p-value from step 2.

Author(s)

Mitra Ebrahimpoor

See Also

multslapmeg, pairslapmeg,

---

summary.slapmeg *Summary of* slapmeg *objects*

Description

Provides a summary of values estimated with SLaPMEG approach within slapmeg and pairslapmeg objects.

Usage

```
## S3 method for class 'slapmeg'
summary(object, ...)
```

Arguments

object	an object inheriting from classes slapmeg
...	further arguments to be passed to or from other methods, which will be ignored in this function.

Value

'Returns the fixed effect estimates and random effects variances from the model in step 1 and the details of Globaltest along with p-value from step 2.

Author(s)

Mitra Ebrahimpoor

See Also

slapmeg, pairslapmeg,

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