Package 'LGEWIS'

October 14, 2015

Type Package

Title Tests for Genetic Association/Gene-Environment Interaction in Longitudinal Gene-Environment-Wide Interaction Studies

Version 0.2

Date 2015-10-07

Author Zihuai He, Seunggeun Lee, Bhramar Mukherjee, Min Zhang

Maintainer Zihuai He <zihuai@umich.edu>

Description

Functions for testing the genetic association/gene-environment interaction in longitudinal gene-environment-wide interaction studies. Generalized score type tests are used for set based analyses. Then GEE based score tests are applied to all single variants within the defined set.

License GPL-3

Depends CompQuadForm, SKAT, geeM, pls, splines

NeedsCompilation no

Repository CRAN

Date/Publication 2015-10-14 09:48:39

R topics documented:

GA.prelim *The preliminary data management for GA (tests for genetic association)*

Description

Before testing a specific region using a generalized score type test, this function does the preliminary data management, such as fitting the model under the null hypothesis.

Usage

```
GA.prelim(Y,time,X=NULL,corstr="exchangeable")
```

Arguments

Y	The outcome variable, an n*1 matrix where n is the total number of observations
time	An n*2 matrix describing how the observations are measured. The first column is the subject id. The second column is the measured exam (1,2,3,etc.).
X	An n*p covariates matrix where p is the total number of covariates.
corstr	The working correlation as specified in 'geeglm'. The following are permitted: "independence", "exchangeable", "ar1".

Value

It returns a list used for function GA.test().

Examples

```
library(LGEWIS)

# Load data example
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# time: describe longitudinal structure, n by 2 matrix
# G: genotype matrix, m by q matrix where m is the total number of subjects

data(LGEWIS.example)
Y<-LGEWIS.example$Y;time<-LGEWIS.example$time;X<-LGEWIS.example$X;G<-LGEWIS.example$G

# Preliminary data management
result.prelim<-GA.prelim(Y,time,X=X)
```

GA.SSD.All *Genetic association tests for multiple regions/genes using SSD format files*

Description

Test the association between an quantitative outcome and multiple region/genes using SSD format files.

Usage

```
GA.SSD.All(SSD.INFO, result.prelim, Gsub.id=NULL, MinP.adjust=NULL, ...)
```

Arguments

SSD.INFO	SSD format information file, output of function “Open_SSD". The sets are defined by this file.
result.prelim	Output of function "GA.prelim()".
Gsub.id	The subject id corresponding to the genotype matrix, an m dimensional vector. This is in order to match the phenotype and genotype matrix. The default is NULL, where the order is assumed to be matched with Y, X, E and time.
MinP.adjust	If the users would like to compare with the MinP test, this parameter specify the adjustment thereshold as in Gao, et al. (2008) "A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms". Values from 0 to 1 are permitted. The default is NULL, i.e., no comparison. The value suggested by Gao, et al. (2008) is 0.95.
...	Other options of the generalized score type test. Defined same as in function "GA.test()".

Value

results	Results of the set based analysis. First column contains the set ID; Second column (second and third columns when the MinP test is compared) contains the p-values; Last column contains the number of tested SNPs.
results.single	Results of the single variant analysis for all variants in the sets. First column contains the regions’ names; Second column is the variants’ names; Third column contains the minor allele frequencies; Last column contains the p.values.

Examples

```
# * Since the Plink data files used here are hard to be included in a R package,
# The usage is marked by "#" to pass the package check.

#  library(LGEWIS)
```

```
###############################################

# Plink data files: File.Bed, File.Bim, File.Fam
# Files defining the sets: File.SetID, File.SSD, File.Info
# For longitudinal data, outcome and covariates are saved in a separate file: Y, time, X, E.
# Preliminary work was done using function null.LGRF.

# Create the MW File
# File.Bed<-"./example.bed"
# File.Bim<-"./example.bim"
# File.Fam<-"./example.fam"
# File.SetID<-"./example.SetID"
# File.SSD<-"./example.SSD"
# File.Info<-"./example.SSD.info"

# Generate SSD file
# To use binary ped files, you have to generate SSD file first.
# If you already have a SSD file, you do not need to call this function.
# Generate_SSD_SetID(File.Bed, File.Bim, File.Fam, File.SetID, File.SSD, File.Info)

# SSD.INFO<-Open_SSD(File.SSD, File.Info)
# Number of samples
# SSD.INFO$nSample
# Number of Sets
# SSD.INFO$nSets

## Fit the null model
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# time: describe longitudinal structure, n by 2 matrix
# result.prelim<-GA.prelim(Y,time,X=X)

## Test all regions
# out_all<-GA.SSD.All(SSD.INFO, result.prelim, MinP.adjust=0.95)

# Example result
# out.all$results
#      SetID    P.value P.value_MinP N.Marker
# 1  GENE_01 0.91592151   1.00000000       94
# 2  GENE_02 0.31103681   0.06451609       84
# 3  GENE_03 0.05976685   0.49923701      108
# 4  GENE_04 0.09389408   1.00000000      101
# 5  GENE_05 0.10339403   0.67139314      103
# 6  GENE_06 0.94666614   1.00000000       94
# 7  GENE_07 0.47955756   1.00000000      104
# 8  GENE_08 0.99415148   1.00000000       96
# 9  GENE_09 0.29271727   0.78406742      100
# 10 GENE_10 0.29061419   0.67045802      100

# out.all$results.single
#     Region.name SNP.name               MAF              p.value
# 1       GENE_01  SNP0056             0.097    0.343641626676761
# 2       GENE_01  SNP0083              0.11     0.75884859949668
```

```
# 3       GENE_01  SNP0035              0.097    0.796572155483814
# ...
```

GA.SSD.OneSet_SetIndex

Genetic association tests for a single region/gene using SSD format files

---

Description

Test the genetic association between an quantitative outcome and one region/gene using SSD format files.

Usage

```
GA.SSD.OneSet_SetIndex(SSD.INFO, SetIndex, result.prelim, Gsub.id=NULL,
MinP.adjust=NULL, ...)
```

Arguments

SSD.INFO	SSD format information file, output of function “Open_SSD". The sets are defined by this file.
SetIndex	Set index. From 1 to the total number of sets.
result.prelim	Output of function "GA.prelim()".
Gsub.id	The subject id corresponding to the genotype matrix, an m dimensional vector. This is in order to match the phenotype and genotype matrix. The default is NULL, where the order is assumed to be matched with Y, X, E and time.
MinP.adjust	If the users would like to compare with the MinP test, this parameter specify the adjustment thereshold as in Gao, et al. (2008) "A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms". Values from 0 to 1 are permitted. The default is NULL, i.e., no comparison. The value suggested by Gao, et al. (2008) is 0.95.
...	Other options of the generalized score type test. Defined same as in function "GA.test()".

Value

p.value	P-value of the set based generalized score type test.
p.single	P-values of the incorporated single SNP analyses
p.MinP	P-value of the MinP test.
n.marker	number of tested SNPs in the SNP set.

Examples

```
# * Since the Plink data files used here are hard to be included in a R package,
# The usage is marked by "#" to pass the package check.

#  library(LGEWIS)

##############################################

# Plink data files: File.Bed, File.Bim, File.Fam
# Files defining the sets: File.SetID, File.SSD, File.Info
# For longitudinal data, outcome and covariates are saved in a separate file: Y, time, X.
# Preliminary work was done using function null.LGRF.

# Create the MW File
# File.Bed<-"./example.bed"
# File.Bim<-"./example.bim"
# File.Fam<-"./example.fam"
# File.SetID<-"./example.SetID"
# File.SSD<-"./example.SSD"
# File.Info<-"./example.SSD.info"

# Generate SSD file
# To use binary ped files, you have to generate SSD file first.
# If you already have a SSD file, you do not need to call this function.
# Generate_SSD_SetID(File.Bed, File.Bim, File.Fam, File.SetID, File.SSD, File.Info)

# SSD.INFO<-Open_SSD(File.SSD, File.Info)
# Number of samples
# SSD.INFO$nSample
# Number of Sets
# SSD.INFO$nSets

## Fit the null model
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# time: describe longitudinal structure, n by 2 matrix
# result.prelim<-GA.prelim(Y,time,X=X)

## Test a single region
# out_single<-GA.SSD.OneSet_SetIndex(SSD.INFO=SSD.INFO,
# SetIndex=3, result.prelim=result.prelim,MinP.adjust=0.95)

# Example result
# out_single
# $n.marker
# [1] 108

# $p.single
#           MAF     p.value
# SNP0254 0.098 0.094386616
# SNP0273 0.091 0.976357482
```

```
# SNP0199 0.118 0.629960577
# ...

# $p.MinP
# [1] 0.499237

# $p.value
# [1] 0.05976685
```

`GA.test` *Test the association between an quantitative outcome variable and a region/gene by a generalized score type test.*

Description

Once the preliminary work is done using "GA.prelim()", this function tests a specifc region/gene. Single SNP analyses are also incorporated.

Usage

```
GA.test(result.prelim,G,Gsub.id=NULL,bootstrap=NULL,
MinP.adjust=NULL,impute.method='fixed')
```

Arguments

`result.prelim`	The output of function "GEI.prelim()"
`G`	Genetic variants in the target region/gene, an m*q matrix where m is the subject ID and q is the total number of genetic variables. Note that the number of rows in Z should be same as the number of subjects.
`Gsub.id`	The subject id corresponding to the genotype matrix, an m dimensional vector. This is in order to match the phenotype and genotype matrix. The default is NULL, where the order is assumed to be matched with Y, X and time.
`bootstrap`	Whether to use bootstrap for small sample size adjustement. This is recommended when the number of subjects is small, or the set contains rare variants. The default is NULL, but a suggested number is 10000 when it is needed.
`MinP.adjust`	If the users would like to compare with the MinP test, this parameter specify the adjustment thereshold as in Gao, et al. (2008) "A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms". Values from 0 to 1 are permitted. The default is NULL, i.e., no comparison. The value suggested by Gao, et al. (2008) is 0.95.
`impute.method`	Choose the imputation method when there is missing genotype. Can be "random", "fixed" or "bestguess". Given the estimated allele frequency, "random" simulates the genotype from binomial distribution; "fixed" uses the genotype expectation; "Best guess" uses the genotype with highest probability.

Value

p.value	P-value of the set based generalized score type test.
p.single	P-values of the incorporated single SNP analyses
p.MinP	P-value of the MinP test.
n.marker	number of heterozygous SNPs in the SNP set.

Examples

```
## GA.prelim does the preliminary data management.
# Input: Y, time, X (covariates)
## GA.test tests a region.
# Input: G (genetic variants) and result of GEI.prelim

library(LGEWIS)

# Load data example
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# time: describe longitudinal structure, n by 2 matrix
# G: genotype matrix, m by q matrix where m is the total number of subjects

data(LGEWIS.example)
Y<-LGEWIS.example$Y;time<-LGEWIS.example$time;X<-LGEWIS.example$X;G<-LGEWIS.example$G

# Preliminary data management
result.prelim<-GA.prelim(Y,time,X=X)

# test without the MinP test
result<-GA.test(result.prelim,G,MinP.adjust=NULL)

# test with the MinP test
result<-GA.test(result.prelim,G,MinP.adjust=0.95)

# test with the MinP test and the small sample adjustment
result<-GA.test(result.prelim,G,MinP.adjust=0.95,bootstrap=1000)
```

GEI.prelim *The preliminary data management for GEI (tests for gene-environment interaction)*

Description

Before testing a specific region using a generalized score type test, this function does the preliminary data management, such as pareparing spline basis functions for E etc..

Usage

```
GEI.prelim(Y,time,E,X=NULL,E.method='ns',E.df=floor(sqrt(length(unique(time[,1])))),
corstr="exchangeable")
```

Arguments

Y	The outcome variable, an n*1 matrix where n is the total number of observations
time	An n*2 matrix describing how the observations are measured. The first column is the subject id. The second column is the measured exam (1,2,3,etc.).
E	An n*1 environmental exposure.
X	An n*p covariates matrix where p is the total number of covariates.
E.method	The method of sieves for the main effect of E. It can be "ns" for natural cubic spline sieves; "bs" for B-spline sieves; "ps" for polynomial sieves. The default is "ns".
E.df	Model complexity for the method of sieves, i.e., number of basis functions. The default is sqrt(m).
corstr	The working correlation as specified in 'geeglm'. The following are permitted: "independence", "exchangeable", "ar1".

Value

It returns a list used for function GEI.test().

Examples

```
library(LGEWIS)

# Load data example
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# E: environmental exposure, n by 1 matrix
# time: describe longitudinal structure, n by 2 matrix
# G: genotype matrix, m by q matrix where m is the total number of subjects

data(LGEWIS.example)
Y<-LGEWIS.example$Y;time<-LGEWIS.example$time;
E<-LGEWIS.example$E;X<-LGEWIS.example$X;G<-LGEWIS.example$G

# Preliminary data management
result.prelim<-GEI.prelim(Y,time,E,X=X)
```

GEI.SSD.All *Gene-environment interaction tests for multiple regions/genes using SSD format files*

Description

Test the interaction between an environmental exposure and multiple region/genes on a quantitative outcome using SSD format files.

Usage

```
GEI.SSD.All(SSD.INFO, result.prelim, Gsub.id=NULL, MinP.adjust=NULL, ...)
```

Arguments

SSD.INFO	SSD format information file, output of function “Open_SSD". The sets are defined by this file.
result.prelim	Output of function "GEI.prelim()".
Gsub.id	The subject id corresponding to the genotype matrix, an m dimensional vector. This is in order to match the phenotype and genotype matrix. The default is NULL, where the order is assumed to be matched with Y, X, E and time.
MinP.adjust	If the users would like to compare with the MinP test, this parameter specify the adjustment thereshold as in Gao, et al. (2008) "A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms". Values from 0 to 1 are permitted. The default is NULL, i.e., no comparison. The value suggested by Gao, et al. (2008) is 0.95.
...	Other options of the generalized score type test. Defined same as in function "GEI.test()".

Value

results	Results of the set based analysis. First column contains the set ID; Second column (second and third columns when the MinP test is compared) contains the p-values; Last column contains the number of tested SNPs.
results.single	Results of the single variant analysis for all variants in the sets. First column contains the regions’ names; Second column is the variants’ names; Third column contains the minor allele frequencies; Last column contains the p.values.

Examples

```
# * Since the Plink data files used here are hard to be included in a R package,
# The usage is marked by "#" to pass the package check.

# library(LGEWIS)
```

```
############################################

# Plink data files: File.Bed, File.Bim, File.Fam
# Files defining the sets: File.SetID, File.SSD, File.Info
# For longitudinal data, outcome and covariates are saved in a separate file: Y, time, X, E.
# Preliminary work was done using function null.LGRF.

# Create the MW File
# File.Bed<-"./example.bed"
# File.Bim<-"./example.bim"
# File.Fam<-"./example.fam"
# File.SetID<-"./example.SetID"
# File.SSD<-"./example.SSD"
# File.Info<-"./example.SSD.info"

# Generate SSD file
# To use binary ped files, you have to generate SSD file first.
# If you already have a SSD file, you do not need to call this function.
# Generate_SSD_SetID(File.Bed, File.Bim, File.Fam, File.SetID, File.SSD, File.Info)

# SSD.INFO<-Open_SSD(File.SSD, File.Info)
# Number of samples
# SSD.INFO$nSample
# Number of Sets
# SSD.INFO$nSets

## Fit the null model
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# E: covariates, n by 1 matrix
# time: describe longitudinal structure, n by 2 matrix
# result.prelim<-GEI.prelim(Y,time,E,X=X)

## Test all regions
# out_all<-GEI.SSD.All(SSD.INFO, result.prelim, MinP.adjust=0.95)

# Example result
# out.all$results
#      SetID   P.value P.value_MinP N.Marker
# 1  GENE_01 0.5617291  1.000000000       94
# 2  GENE_02 0.8079711  1.000000000       84
# 3  GENE_03 0.1046738  0.004664728      108
# 4  GENE_04 0.5976760  1.000000000      101
# 5  GENE_05 0.3240141  1.000000000      103
# 6  GENE_06 0.1277916  0.641227316       94
# 7  GENE_07 0.6957561  1.000000000      104
# 8  GENE_08 0.7630369  0.151874693       96
# 9  GENE_09 0.7164281  0.863155784      100
# 10 GENE_10 0.7292435  0.070854665      100

# out.all$results.single
#     Region.name SNP.name               MAF              p.value
# 1       GENE_01  SNP0056             0.097     0.72366448267218
```

```
# 2       GENE_01  SNP0083              0.11    0.814563709041184
# 3       GENE_01  SNP0035             0.097    0.999162315393064
# ...
```

`GEI.SSD.OneSet_SetIndex` *Gene-environment interaction tests for a single region/gene using SSD format files*

Description

Test the interaction between an environmental exposure and one region/gene on a quantitative outcome using SSD format files.

Usage

```
GEI.SSD.OneSet_SetIndex(SSD.INFO, SetIndex, result.prelim, Gsub.id=NULL,
MinP.adjust=NULL, ...)
```

Arguments

`SSD.INFO`	SSD format information file, output of function “Open_SSD". The sets are defined by this file.
`SetIndex`	Set index. From 1 to the total number of sets.
`result.prelim`	Output of function "GEI.prelim()".
`Gsub.id`	The subject id corresponding to the genotype matrix, an m dimensional vector. This is in order to match the phenotype and genotype matrix. The default is NULL, where the order is assumed to be matched with Y, X, E and time.
`MinP.adjust`	If the users would like to compare with the MinP test, this parameter specify the adjustment thereshold as in Gao, et al. (2008) "A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms". Values from 0 to 1 are permitted. The default is NULL, i.e., no comparison. The value suggested by Gao, et al. (2008) is 0.95.
`...`	Other options of the generalized score type test. Defined same as in function "GEI.test()".

Value

`p.value`	P-value of the set based generalized score type test.
`p.single`	P-values of the incorporated single SNP analyses
`p.MinP`	P-value of the MinP test.
`n.marker`	number of tested SNPs in the SNP set.
`E.df`	number of tested SNPs in the SNP set.
`G.df`	number of tested SNPs in the SNP set.

Examples

```
# * Since the Plink data files used here are hard to be included in a R package,
# The usage is marked by "#" to pass the package check.

# library(LGEWIS)

##############################################

# Plink data files: File.Bed, File.Bim, File.Fam
# Files defining the sets: File.SetID, File.SSD, File.Info
# For longitudinal data, outcome and covariates are saved in a separate file: Y, time, X, E.
# Preliminary work was done using function null.LGRF.

# Create the MW File
# File.Bed<-"./example.bed"
# File.Bim<-"./example.bim"
# File.Fam<-"./example.fam"
# File.SetID<-"./example.SetID"
# File.SSD<-"./example.SSD"
# File.Info<-"./example.SSD.info"

# Generate SSD file
# To use binary ped files, you have to generate SSD file first.
# If you already have a SSD file, you do not need to call this function.
# Generate_SSD_SetID(File.Bed, File.Bim, File.Fam, File.SetID, File.SSD, File.Info)

# SSD.INFO<-Open_SSD(File.SSD, File.Info)
# Number of samples
# SSD.INFO$nSample
# Number of Sets
# SSD.INFO$nSets

## Fit the null model
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# E: covariates, n by 1 matrix
# time: describe longitudinal structure, n by 2 matrix
# result.prelim<-GEI.prelim(Y,time,E,X=X)

## Test a single region
# out_single<-GEI.SSD.OneSet_SetIndex(SSD.INFO=SSD.INFO,
# SetIndex=3, result.prelim=result.prelim,MinP.adjust=0.95)

# Example result
# out_single
# $n.marker
# [1] 108

# $E.df
# [1] 22
```

```
# $G.df
# [1] 22

# $p.single
#           MAF      p.value
# SNP0254 0.098 5.920758e-01
# SNP0273 0.091 9.468959e-01
# SNP0199 0.118 4.131540e-01
# ...

# $p.MinP
# [1] 3.876731e-05

# $p.value
# [1] 0.1167991
```

`GEI.test` *Test the interaction between an environemental exposure and a region/gene by a generalized score type test.*

Description

Once the preliminary work is done using "GEI.prelim()", this function tests a specifc region/gene. Single SNP analyses are also incorporated.

Usage

```
GEI.test(result.prelim,G,Gsub.id=NULL,G.method='wPCA',G.df=floor(sqrt(nrow(G))),
bootstrap=NULL,MinP.adjust=NULL,impute.method='fixed')
```

Arguments

`result.prelim`	The output of function "GEI.prelim()"
`G`	Genetic variants in the target region/gene, an m*q matrix where m is the subject ID and q is the total number of genetic variables. Note that the number of rows in Z should be same as the number of subjects.
`Gsub.id`	The subject id corresponding to the genotype matrix, an m dimensional vector. This is in order to match the phenotype and genotype matrix. The default is NULL, where the order is assumed to be matched with Y, X and time.
`G.method`	The dimension reduction method for main effect adjustment of G. The following are permitted: "wPCA" for weighted principal component analysis; "PCA" for principal component analysis; "PLS" for partial least square regression; "R2" for ordering the principal components by their R-squares. The dimension reduction method is in order to analyze large regions, i.e., the number of variants is close to or larger than the number of subjects. The default is "wPCA".
`G.df`	Number of components selected by the dimension reduction method. The default is sqrt(m).

bootstrap	Whether to use bootstrap for small sample size adjustement. This is recommended when the number of subjects is small, or the set contains rare variants. The default is NULL, but a suggested number is 10000 when it is needed.
MinP.adjust	If the users would like to compare with the MinP test, this parameter specify the adjustment thereshold as in Gao, et al. (2008) "A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms". Values from 0 to 1 are permitted. The default is NULL, i.e., no comparison. The value suggested by Gao, et al. (2008) is 0.95.
impute.method	Choose the imputation method when there is missing genotype. Can be "random", "fixed" or "bestguess". Given the estimated allele frequency, "random" simulates the genotype from binomial distribution; "fixed" uses the genotype expectation; "Best guess" uses the genotype with highest probability.

Value

p.value	P-value of the set based generalized score type test.
p.single	P-values of the incorporated single SNP analyses
p.MinP	P-value of the MinP test.
n.marker	number of heterozygous SNPs in the SNP set.
E.df	number of tested SNPs in the SNP set.
G.df	number of tested SNPs in the SNP set.

Examples

```
## GEI.prelim does the preliminary data management.
# Input: Y, time, E, X (covariates)
## GEI.test tests a region.
# Input: G (genetic variants) and result of GEI.prelim

library(LGEWIS)

# Load data example
# Y: outcomes, n by 1 matrix where n is the total number of observations
# X: covariates, n by p matrix
# E: environmental exposure, n by 1 matrix
# time: describe longitudinal structure, n by 2 matrix
# G: genotype matrix, m by q matrix where m is the total number of subjects

data(LGEWIS.example)
Y<-LGEWIS.example$Y;time<-LGEWIS.example$time;
E<-LGEWIS.example$E;X<-LGEWIS.example$X;G<-LGEWIS.example$G

# Preliminary data management
result.prelim<-GEI.prelim(Y,time,E,X=X)

# test without the MinP test
result<-GEI.test(result.prelim,G,MinP.adjust=NULL)

# test with the MinP test
```

```
result<-GEI.test(result.prelim,G,MinP.adjust=0.95)

# test with the MinP test and the small sample adjustment
result<-GEI.test(result.prelim,G,MinP.adjust=0.95,bootstrap=1000)
```

LGEWIS.example *Data example for LGEWIS (tests for genetic association or gene-environment interaction)*

Description

The dataset contains outcome variable Y, covariate X, environmental exposure E, time, and genotype data Z. The first column in time is the subject ID and the second column is the measured exam. Y, X, E and time are all in long form. Z is a genotype matrix where each row corresponds to one subject.

Usage

```
data(LGEWIS.example)
```

Index