Package 'MAGEE'

June 3, 2022

Type Package

Version 1.2.0

Date 2022-06-02

Title Mixed Model Association Test for GEne-Environment Interaction

Description Use a 'glmmkin' class object (GMMAT package) from the null model to perform generalized linear mixed model-based single-variant and variant set main effect tests, gene-environment interaction tests, and joint tests for association, as proposed in Wang et al. (2020) <DOI:10.1002/gepi.22351>.

License GPL-3

Copyright See COPYRIGHTS for details.

Imports Rcpp, Matrix, parallel, MASS, SeqArray, SeqVarTools, foreach, GMMAT, CompQuadForm

Suggests doMC, testthat

LinkingTo Rcpp, RcppArmadillo

Encoding UTF-8

LazyData true

Depends R (>= 3.2.0)

NeedsCompilation yes

Author Xinyu Wang [aut],

Han Chen [aut, cre],

Duy Pham [aut],

Kenneth Westerman [aut],

Cong Pan [aut]

Maintainer Han Chen <han.chen.2@uth.tmc.edu>

Repository CRAN

Date/Publication 2022-06-03 07:40:02 UTC

2 MAGEE-package

R topics documented:

MAGE!	E-package		M	ixed	l N	100	lel	' A	SS	oci	iat	tioi	n I	Tes	st f	or	G	Ei	ne	-E	'nv	ir	on	m	en	t I	nt	ero	acı	tio	n		
Index																																	14
	MAGEE.meta .										•				•	•					•						٠	•				٠	11
	MAGEE																																
	glmm.gei.meta																																
	glmm.gei																																3
	example																																
	MAGEE-package	· .																															2

Description

An R package for performing generalized linear mixed model-based single-variant and variant set main effect tests, gene-environment interaction tests, and joint tests for association, as proposed in Wang et al. (2020) <DOI:10.1002/gepi.22351>.

Details

Package: MAGEE
Type: Package
Version: 1.0.2
Date: 2022-01-27
License: GPL-3

Author(s)

Xinyu Wang, Han Chen, Duy T. Pham

Maintainer: Han Chen < Han. Chen. 2@uth.tmc.edu>

References

Wang, X., Lim, E., Liu, C, Sung, Y.J., Rao, D.C., Morrison, A.C., Boerwinkle, E., Manning, A. K., and Chen, H. (2020) Efficient gene-environment interaction tests for large biobank-scale sequencing studies. Genetic Epidemiology, 44(8): 908-923.

Chen, H., Huffman, J.E., Brody, J.A., Wang, C., Lee, S., Li, Z., Gogarten, S.M., Sofer, T., Bielak, L.F., Bis, J.C., et al. (2019) Efficient variant set mixed model association tests for continuous and binary traits in large-scale whole-genome sequencing studies. The American Journal of Human Genetics, 104 (2): 260-274.

example 3

Wang, X., Pham, D.T., Westerman, K.E., Pan, C., Manning, A.K., Chen, H., (2022) Genomic summary statistics and meta-analysis for set-based gene-environment interaction tests in large-scale sequencing studies. medrxiv.

example

Example dataset

Description

Example dataset for MAGEE.

Format

Contains the following objects:

pheno a data frame of 400 observations from a cross-sectional study with 5 variables: id, disease, trait, age and sex.

pheno2 a data frame of 2,000 observations from a longitudinal study with 400 individuals and 5 variables: id, y.repeated, y.trend, time and sex.

GRM a genetic relationship matrix for 400 observations.

glmm.gei

GLMM based single variant tests for gene-environment interactions

Description

Use a glmmkin class object from the null GLMM to perform single variant main effect score test, gene-environment interaction test, or joint test for association with genotypes in a GDS file .gds.

Usage

```
glmm.gei(null.obj, interaction, geno.file, outfile, bgen.samplefile = NULL,
interaction.covariates = NULL, meta.output = F, center=T, MAF.range = c(1e-7, 0.5),
miss.cutoff = 1, missing.method = "impute2mean", nperbatch=100, ncores = 1,
verbose = FALSE)
```

Arguments

null.obj	a class glmmkin object, returned by fitting the null GLMM using glmmkin().
interaction	a numeric or a character vector indicating the environmental factors. If a numeric vector, it represents which indices in the order of covariates are the environmental factors; if a character vector, it represents the variable names of the environmental factors.
geno.file	the full name of a GDS file (including the suffix .gds).

4 glmm.gei

outfile the output file name.

bgen.samplefile

path to the BGEN .sample file. Required when the BGEN file does not contain sample identifiers.

interaction.covariates

a numeric or a character vector indicating the interaction covariates. If a numeric vector, it represents which indices in the order of covariates are the interaction covariates; if a character vector, it represents the variable names of the interac-

tion covariates.

boolean value to modiy the output file.If TRUE, the GxE effect estimate and meta.output

variance and covariance associated with the effect estimate are included in the

output file. (default = FALSE)

a logical switch for centering genotypes before tests. If TRUE, genotypes will center

be centered to have mean 0 before tests, otherwise raw values will be directly

used in tests (default = TRUE).

MAF.range a numeric vector of length 2 defining the minimum and maximum minor allele

frequencies of variants that should be included in the analysis (default = c(1e-7),

(0.5)).

miss.cutoff the maximum missing rate allowed for a variant to be included (default = 1,

including all variants).

method of handling missing genotypes. Either "impute2mean" or "omit" (default missing.method

= "impute2mean").

nperbatch an integer for how many SNPs should be tested in a batch (default = 100).

> The computational time can increase dramatically if this value is either small or large. The optimal value for best performance depends on the user's system.

a positive integer indicating the number of cores to be used in parallel computing ncores

(default = 1).

a logical switch for whether failed matrix inversions should be written to outfile.err verbose

for debugging (default = FALSE).

Value

NULL

Author(s)

Xinyu Wang, Han Chen, Duy Pham

References

Chen, H., Wang, C., Conomos, M.P., Stilp, A.M., Li, Z., Sofer, T., Szpiro, A.A., Chen, W., Brehm, J.M., Celedón, J.C., Redline, S., Papanicolaou, G.J., Thornton, T.A., Laurie, C.C., Rice, K. and Lin, X. (2016) Control forpopulation structure and relatedness for binary traits in genetic association studies via logistic mixed models. The American Journal of Human Genetics 98, 653-666.

glmm.gei.meta 5

Examples

glmm.gei.meta

GLMM based meta-analysis of single variant tests for geneenvironment interactions

Description

Use a glmmkin class object from the null GLMM to perform meta-analysis of single variant main effect score test, gene-environment interaction test, or joint test for association with genotypes in a GDS file .gds.

Usage

Arguments

files

tab or space delimited plain text files (or compressed files that can be recognized by the R function read.table) with at least the following columns: SNPID, CHR, POS, Non_Effect_Allele, Effect_Allele, N_Samples, AF, Beta_Marginal, SE_Beta_Marginal, P_Value_Marginal, Beta_G, Beta_G_sex, SE_Beta_G, SE_Beta_G_sex, Cov_Beta_G_G.sex, P_Value_Interaction, P_Value_Joint. Generally, if each study performs score tests using genotypes in PLINK binary PED format or GDS format, the score test output from glmm.score can be directly used as input files.

outfile

the output file name.

6 glmm.gei.meta

interaction a numeric or a character vector indicating the environmental factors. If a nu-

meric vector, it represents which indices in the order of covariates are the environmental factors; if a character vector, it represents the variable names of the

environmental factors.

SNPID a character vector of SNPID column names in each input file. The length

and order must match the length and order of files (default = rep("SNPID",

length(files))).

CHR a character vector of CHR column names in each input file. The length and order

must match the length and order of files (default = rep("CHR", length(files))).

POS a character vector of POS column names in each input file. The length and order

must match the length and order of files (default = rep("POS", length(files))).

Non_Effect_Allele

a character vector of Non_Effect_Allele column names in each input file. The

length and order must match the length and order of files (default = rep("Non Effect Allele",

length(files))).

Effect_Allele a character vector of Effect_Allele column names in each input file. The length

and order must match the length and order of files (default = rep("Effect_Allele",

length(files))).

Value

a data frame containing the following:

SNPID SNP name.

CHR chromosome.

POS physical position.

Non_Effect_Allele

non_effect allele frequency.

Effect_Allele effect allele frequency.

N_Samples number of samples.

AF allele frequency.

Beta_Marginal coefficient estimate for the marginal genetic effect.

SE_Beta_Marginal

standard error of the marginal genetic effect.

P_Value_Marginal

marginal effect score test p-value.

Beta_G coefficient estimate for the genetic main effect.

Beta_G-* coefficient estimate for the interaction terms.

SE_Beta_G model-based standard error associated with the genetic main effect.

SE_Beta_G-* mdel-based standard error associated with any GxE or interaction covariate terms.

Cov_Beta_G_G-* model-based covariance between the genetic main effect and any GxE or inter-

action covariate terms.

P_Value_Interaction

gene-environment interaction test p-value.

P_Value_Joint joint test p-value.

Author(s)

Xinyu Wang, Han Chen, Duy Pham

References

Chen, H., Wang, C., Conomos, M.P., Stilp, A.M., Li, Z., Sofer, T., Szpiro, A.A., Chen, W., Brehm, J.M., Celedón, J.C., Redline, S., Papanicolaou, G.J., Thornton, T.A., Laurie, C.C., Rice, K. and Lin, X. (2016) Control forpopulation structure and relatedness for binary traits in genetic association studies via logistic mixed models. The American Journal of Human Genetics 98, 653-666.

Examples

```
infile1 <- system.file("extdata", "meta1.txt", package = "MAGEE")
infile2 <- system.file("extdata", "meta2.txt", package = "MAGEE")
infile3 <- system.file("extdata", "meta3.txt", package = "MAGEE")
infile4 <- system.file("extdata", "meta4.txt", package = "MAGEE")
infile5 <- system.file("extdata", "meta5.txt", package = "MAGEE")
outfile <- "glmm.gei.meta.testoutfile.txt"
glmm.gei.meta(files = c(infile1, infile2, infile3, infile4, infile5),
outfile = outfile, interaction="sex")
unlink(outfile)</pre>
```

MAGEE

Mixed model Association tests for GEne-Environment interactions

Description

Use a glmmkin class object from the null GLMM to perform variant set-based main effect tests, gene-environment interaction tests, and joint tests for association with genotypes in a GDS file (.gds). 7 user-defined tests are included: Main effect variance component test (MV), Main effect hybrid test of burden and variance component test using Fisher's method (MF), Interaction variance component test (IV), Interaction hybrid test of burden and variance component test using Fisher's method (IF), Joint variance component test (JV), Joint hybrid test of burden and variance component test using Fisher's method (JF), and Joint hybrid test of burden and variance component test using double Fisher's procedures (JD).

Usage

```
MAGEE(null.obj, interaction, geno.file, group.file, group.file.sep = "\t",
   bgen.samplefile = NULL, interaction.covariates = NULL, meta.file.prefix = NULL,
   MAF.range = c(1e-7, 0.5), MAF.weights.beta = c(1, 25), miss.cutoff = 1,
   missing.method = "impute2mean", method = "davies", tests = "JF",
   use.minor.allele = FALSE, auto.flip = FALSE,
   Garbage.Collection = FALSE, is.dosage = FALSE, ncores = 1)
```

MAGEE.prep(null.obj, interaction, geno.file, group.file, interaction.covariates = NULL,

```
group.file.sep = "\t", auto.flip = FALSE)
```

MAGEE.lowmem(MAGEE.prep.obj, geno.file = NULL, meta.file.prefix = NULL, MAF.range = c(1e-7, 0.5), MAF.weights.beta = c(1, 25), miss.cutoff = 1, missing.method = "impute2mean", method = "davies", tests = "JF", use.minor.allele = FALSE, Garbage.Collection = FALSE, is.dosage = FALSE, ncores = 1)

Arguments

null.obj a class glmmkin object, returned by fitting the null GLMM using glmmkin().

a numeric or a character vector indicating the environmental factors. If a numinteraction

beric vector, it represents which indices in the order of covariates are the environmental factors; if a character vector, it represents the variable names of the

environmental factors.

a .gds file for the full genotypes. The sample.id in geno.file should overlap geno.file

> id_include in null.obj. It is recommended that sample.id in geno.file include the full samples (at least all samples as specified in id_include of null.obj). It is not necessary for the user to take a subset of geno.file before

running the analysis.

group.file a plain text file with 6 columns defining the test units. There should be no headers in the file, and the columns are group name, chromosome, position,

reference allele, alternative allele and weight, respectively.

group.file.sep the delimiter in group.file (default = "\t").

bgen.samplefile

path to the BGEN .sample file. Required when the BGEN file does not contain

sample identifiers.

interaction.covariates

a numeric or a character vector indicating the interaction covariates. If a numeric vector, it represents which indices in the order of covariates are the interaction covariates; if a character vector, it represents the variable names of the interaction covariates.

meta.file.prefix

the prefix for meta-analysis (default = "NULL").

MAF.range

a numeric vector of length 2 defining the minimum and maximum minor allele frequencies of variants that should be included in the analysis (default = c(1e-7),

0.5)).

MAF.weights.beta

a numeric vector of length 2 defining the beta probability density function parameters on the minor allele frequencies. This internal minor allele frequency weight is multiplied by the external weight given by the group.file. To turn off internal minor allele frequency weight and only use the external weight given by the group file, use c(1, 1) to assign flat weights (default = c(1, 25)).

the maximum missing rate allowed for a variant to be included (default = 1, miss.cutoff including all variants).

method of handling missing genotypes. Either "impute2mean" or "impute2zero" missing.method (default = "impute2mean").

method

a method to compute p-values for the test statistics (default = "davies"). "davies" represents an exact method that computes a p-value by inverting the characteristic function of the mixture chisq distribution, with an accuracy of 1e-6. When "davies" p-value is less than 1e-5, it defaults to method "kuonen". "kuonen" represents a saddlepoint approximation method that computes the tail probabilities of the mixture chisq distribution. When "kuonen" fails to compute a p-value, it defaults to method "liu". "liu" is a moment-matching approximation method for the mixture chisq distribution.

tests

a character vector indicating which MAGEE tests should be performed ("MV" for the main effect variance component test, "MF" for the main effect combined test of the burden and variance component tests using Fisher's method, "IV" for the interaction variance component test, "IF" for the interaction combined test of the burden and variance component tests using Fisher's method, "JV" for the joint variance component test for main effect and interaction, "JF" for the joint combined test of the burden and variance component tests for main effect and interaction using Fisher's method, or "JD" for the joint combined test of the burden and variance component tests for main effect and interaction using double Fisher's method.). The "MV" and "IV" test are automatically included when performing "JV", and the "MF" and "IF" test are automatically included when performing "JF" or "JD" (default = "JF").

use.minor.allele

a logical switch for whether to use the minor allele (instead of the alt allele) as the coding allele (default = FALSE). It does not change "MV", "IV", and "JV" results, but "MF", "IF", "JF", and "JD" results will be affected. Along with the MAF filter, this option is useful for combining rare mutations, assuming rare allele effects are in the same direction.

auto.flip

a logical switch for whether to enable automatic allele flipping if a variant with alleles ref/alt is not found at a position, but a variant at the same position with alleles alt/ref is found (default = FALSE). Use with caution for whole genome sequence data, as both ref/alt and alt/ref variants at the same position are not uncommon, and they are likely two different variants, rather than allele flipping.

Garbage.Collection

a logical switch for whether to enable garbage collection in each test (default = FALSE). Pay for memory efficiency with slower computation speed.

is.dosage a logical switch (default = FALSE).

ncores a positive integer indicating the number of cores to be used in parallel computing

(default = 1).

MAGEE.prep.obj a class MAGEE.prep object, returned by MAGEE.prep.

Value

a data frame with the following components:

group name of the test unit group.

n.variants number of variants in the test unit group that pass the missing rate and allele

frequency filters.

miss.min minimum missing rate for variants in the test unit group.

	miss.mean	mean missing rate for variants in the test unit group.						
	miss.max	maximum missing rate for variants in the test unit group.						
	freq.min	minimum coding allele frequency for variants in the test unit group.						
	freq.mean	mean coding allele frequency for variants in the test unit group.						
	freq.max	maximum coding allele frequency for variants in the test unit group.						
freq.strata.min								
		minimum coding allele frequency of each strata if the environmental factor is categorical.						
	freq.strata.max							
		maximum coding allele frequency of each strata if the environmental factor is categorical.						
	MV.pval	MV test p-value.						
	MF.pval	MF test p-value.						
	IV.pval	IV test p-value.						
	IF.pval	IF test p-value.						
	JV.pval	JV test p-value.						
	JF.pval	JF test p-value.						
	JD.pval	JD test p-value.						

Author(s)

Xinyu Wang, Han Chen, Duy Pham

References

Wang, X., Lim, E., Liu, C, Sung, Y.J., Rao, D.C., Morrison, A.C., Boerwinkle, E., Manning, A. K., and Chen, H. (2020) Efficient gene-environment interaction tests for large biobank-scale sequencing studies. Genetic Epidemiology, 44(8): 908-923. Chen, H., Huffman, J.E., Brody, J.A., Wang, C., Lee, S., Li, Z., Gogarten, S.M., Sofer, T., Bielak, L.F., Bis, J.C., et al. (2019) Efficient variant set mixed model association tests for continuous and binary traits in large-scale whole-genome sequencing studies. The American Journal of Human Genetics, 104 (2): 260-274.

Examples

MAGEE.meta 11

MAGEE.meta	Mixed model Association tests for GEne-Environment interactions
	meta-analysis

Description

Use a glmmkin class object from the null GLMM to perform meta-analysis of variant set-based main effect tests, gene-environment interaction tests, and joint tests for association with genotypes in a GDS file (.gds).

Usage

Arguments

meta.files.prefix

a character vector for prefix of intermediate files (.score.* and .var.*) required in a meta-analysis. Each element represents the prefix of .score.* and .var.* from one cohort. The length of vector should be equal to the number of cohorts.

n.files

an integer vector with the same length as meta.files.prefix, indicating how many sets of intermediate files (.score.* and .var.*) are expected from each cohort, usually as the result of multi-threading in creating the intermediate files (default = rep(1, length(meta.files.prefix))).

cohort.group.idx

a vector with the same length as meta.files.prefix, indicating which cohorts should be grouped together in the meta-analysis assuming homogeneous genetic effects. For example, c("a","b","a","a","b") means cohorts 1, 3, 4 are assumed to have homogeneous genetic effects, and cohorts 2, 5 are in another group with homogeneous genetic effects (but possibly heterogeneous with group "a"). If NULL, all cohorts are in the same group (default = NULL).

group.file

a plain text file with 6 columns defining the test units. There should be no headers in the file, and the columns are group name, chromosome, position, reference allele, alternative allele and weight, respectively.

group.file.sep the delimiter in group.file (default = "\t").

E.match environmental factors that match the interactions (default = "\t").

MAF.range

a numeric vector of length 2 defining the minimum and maximum minor allele frequencies of variants that should be included in the analysis (default = c(1e-7, 0.5)). Filter applied to the combined samples.

12 MAGEE.meta

MAF.weights.beta

a numeric vector of length 2 defining the beta probability density function parameters on the minor allele frequencies. This internal minor allele frequency weight is multiplied by the external weight given by the group file. To turn off internal minor allele frequency weight and only use the external weight given by the group file, use c(1, 1) to assign flat weights (default = c(1, 25)). Applied to the combined samples.

miss.cutoff

the maximum missing rate allowed for a variant to be included (default = 1, including all variants). Filter applied to the combined samples.

method

a method to compute p-values for SKAT-type test statistics (default = "davies"). "davies" represents an exact method that computes a p-value by inverting the characteristic function of the mixture chisq distribution, with an accuracy of 1e-6. When "davies" p-value is less than 1e-5, it defaults to method "kuonen". "kuonen" represents a saddlepoint approximation method that computes the tail probabilities of the mixture chisq distribution. When "kuonen" fails to compute a p-value, it defaults to method "liu". "liu" is a moment-matching approximation method for the mixture chisq distribution.

tests

a character vector indicating which MAGEE tests should be performed ("MV" for the main effect variance component test, "MF" for the main effect combined test of the burden and variance component tests using Fisher's method, "IV" for the interaction variance component tests using Fisher's method, "JV" for the joint variance component test susing Fisher's method, "JV" for the joint variance component test for main effect and interaction, "JF" for the joint combined test of the burden and variance component tests for main effect and interaction using Fisher's method, or "JD" for the joint combined test of the burden and variance component tests for main effect and interaction using double Fisher's method.). The "MV" and "IV" test are automatically included when performing "JV", and the "MF" and "IF" test are automatically included when performing "JF" or "JD" (default = "JF").

use.minor.allele

a logical switch for whether to use the minor allele (instead of the alt allele) as the coding allele (default = FALSE). It does not change "MV", "IV", and "JV" results, but "MF", "IF", and "JD" results will be affected. Along with the MAF filter, this option is useful for combining rare mutations, assuming rare allele effects are in the same direction.

Value

group name of the test unit group.

n.variants number of variants in the test unit group that pass the missing rate and allele

frequency filters.

MV. pval MV test p-value.

MF. pval MF test p-value.

IV. pval IV test p-value.

IF. pval IF test p-value.

JV. pval JV test p-value.

MAGEE.meta 13

```
JF.pval JF test p-value.

JD.pval JD test p-value.
```

Author(s)

Xinyu Wang, Han Chen, Duy Pham

References

Wang, X., Lim, E., Liu, C, Sung, Y.J., Rao, D.C., Morrison, A.C., Boerwinkle, E., Manning, A. K., and Chen, H. (2020) Efficient gene-environment interaction tests for large biobank-scale sequencing studies. Genetic Epidemiology, 44(8): 908-923. Chen, H., Huffman, J.E., Brody, J.A., Wang, C., Lee, S., Li, Z., Gogarten, S.M., Sofer, T., Bielak, L.F., Bis, J.C., et al. (2019) Efficient variant set mixed model association tests for continuous and binary traits in large-scale whole-genome sequencing studies. The American Journal of Human Genetics, 104 (2): 260-274. Wang, X., Pham, D.T., Westerman, K.E., Pan, C., Manning, A.K., Chen, H., (2022) Genomic summary statistics and meta-analysis for set-based gene-environment interaction tests in large-scale sequencing studies. medrxiv.

Examples

```
library(GMMAT)
  data(example)
  attach(example)
  model0 <- glmmkin(disease ~ age + sex, data = pheno, kins = GRM,
  id = "id", family = binomial(link = "logit"))
  geno.file <- system.file("extdata", "geno.gds", package = "MAGEE")
  group.file <- system.file("extdata", "SetID.withweights.txt", package = "MAGEE")
  out <- MAGEE(model0, interaction="sex",geno.file=geno.file,
      group.file=group.file, meta.file.prefix = "MAGEE.meta",
      MAF.range = c(0, 0.5), miss.cutoff = 1,
      method = "davies", tests = c("JV","JF","JD"))
  print(out)
  out1 <- MAGEE.meta("MAGEE.meta", group.file = group.file, tests = c("JV","JF","JD"))
  print(out1)
  unlink(paste0("MAGEE.meta.", c("score", "cov"), ".1"))</pre>
```

Index

```
\ast gene-environment interaction
    glmm.gei, 3
    glmm.gei.meta, 5
    MAGEE, 7
    MAGEE-package, 2
    MAGEE.meta, 11
* generalized linear mixed model
    glmm.gei, 3
    glmm.gei.meta, 5
    MAGEE, 7
    MAGEE-package, 2
    MAGEE.meta, 11
* joint test
    glmm.gei, 3
    glmm.gei.meta, 5
    MAGEE, 7
    MAGEE-package, 2
    {\tt MAGEE.meta}, \textcolor{red}{11}
* meta-analysis
    {\tt glmm.gei.meta,5}
    MAGEE.meta, 11
* package
    MAGEE-package, 2
* variant set-based test
    MAGEE, 7
    MAGEE.meta, 11
example, 3
glmm.gei, 3
glmm.gei.meta, 5
MAGEE, 7
MAGEE-package, 2
MAGEE.meta, 11
```