Package ‘coxmeg’

May 5, 2020

Type Package
Title Cox Mixed-Effects Models for Genome-Wide Association Studies
Version 1.0.11
Date 2020-05-04
Author Liang He
Maintainer Liang He <liang.he@duke.edu>
Description Fast algorithms for fitting a Cox mixed-effects model for e.g., genome-wide association studies. See Liang He and Alexander Kulminski (2019) <doi:10.1101/729285>.
License GPL
Imports nloptr, MASS, matrixcalc, SNPRelate, rARPACK, stats, Matrix, methods, utils, coxme, microbenchmark
LinkingTo Rcpp, RcppEigen
Depends R (>= 3.4), Rcpp (>= 0.12.18)
RoxygenNote 6.1.1
Suggests knitr, rmarkdown
VignetteBuilder knitr
Repository CRAN
Repository/R-Forge/Project coxmeg
Repository/R-Forge/Revision 17
Repository/R-Forge/DateTimeStamp 2020-05-05 15:55:01
Date/Publication 2020-05-05 20:40:03 UTC
NeedsCompilation yes

R topics documented:

coxmeg-package ................................................................. 2
coxmeg ................................................................. 3
coxmeg_m ................................................................. 5
coxmeg_plink ............................................................... 8
fit_ppl ................................................................. 11
Description

Fast algorithms for fitting a Cox mixed-effects model for e.g., genome-wide association studies. See Liang He and Alexander Kulminski (2019) <doi:10.1101/729285>.

Details

coxmeg is an R package for efficiently conducting GWAS of age-at-onset traits using a Cox mixed-effects model. coxmeg introduces a fast estimation algorithm for general sparse relatedness matrices including but not limited to block-diagonal pedigree-based matrices. coxmeg also introduces a fast and powerful score test for fully dense relatedness matrices, accounting for both population stratification and family structure. In addition, coxmeg can handle positive semidefinite relatedness matrices. Compared to coxme, coxmeg substantially improves the computational efficiency for estimating or testing genetic effects by using a variance component estimated once from a null model, and introducing fast algorithms, including inexact newton methods, preconditioned conjugate gradient methods and stochastic Lanczos quadrature.

Author(s)

Liang He
Maintainer: Liang He <liang.he@duke.edu>

References

He, L, Kulminski, A.M., Genome-wide association analysis of age-at-onset traits using Cox mixed-effects models. 2019

Examples

library(Matrix)
library(MASS)
library(coxme)

## simulate a block-diagonal relatedness matrix
tau_var <- 0.2
n_f <- 100
mat_list <- list()
size <- rep(10,n_f)
offd <- 0.5
for(i in 1:n_f)
{
  mat_list[[i]] <- matrix(offd,size[i],size[i])
  diag(mat_list[[i]]) <- 1
}
# simulate random effects and outcomes
x <- mvrnorm(1, rep(0, n), tau_var*sigma)
myrates <- exp(x-1)
y <- rexp(n, rate = myrates)
cen <- rexp(n, rate = 0.02)
ycen <- pmin(y, cen)
outcome <- cbind(ycen, as.numeric(y <= cen))

## fit the Cox mixed-effects model
re = coxmeg(outcome, sigma, type='bd', order=1, detap='diagonal')
re

---

**Description**

`coxmeg` returns estimates of the variance component, the HRs and p-values for the predictors.

**Usage**

```r
coxmeg(outcome, corr, type, X = NULL, FID = NULL, eps = 1e-06,
       min_tau = 1e-04, max_tau = 5, order = 1, detap = NULL,
       opt = "bobyqa", solver = NULL, spd = TRUE, verbose = TRUE,
       mc = 100)
```

**Arguments**

- **outcome**: A matrix contains time (first column) and status (second column). The status is a binary variable (1 for events / 0 for censored).
- **corr**: A relatedness matrix. Can be a matrix or a 'dgCMatrix' class in the Matrix package. Must be symmetric positive definite or symmetric positive semidefinite.
- **type**: A string indicating the sparsity structure of the relatedness matrix. Should be 'bd' (block diagonal), 'sparse', or 'dense'. See details.
- **X**: An optional matrix of the predictors with fixed effects. Can be quantitative or binary values. Categorical variables need to be converted to dummy variables. Each row is a sample, and the predictors are columns.
- **FID**: An optional string vector of family ID. If provided, the data will be reordered according to the family ID.
- **eps**: An optional positive scalar indicating the tolerance in the optimization algorithm. Default is 1e-6.
- **min_tau**: An optional positive scalar indicating the lower bound in the optimization algorithm for the variance component tau. Default is 1e-4.
max_tau: An optional positive scalar indicating the upper bound in the optimization algorithm for the variance component $\tau$. Default is 5.

order: An optional integer starting from 0. Only valid when dense=FALSE. It specifies the order of approximation used in the inexact Newton method. Default is 1.

detap: An optional string indicating whether to use approximation for log-determinant. Can be 'exact', 'diagonal' or 'slq'. Default is NULL, which lets the function select a method based on 'type' and other information. See details.

opt: An optional logical scalar for the Optimization algorithm for $\tau$. Can have the following values: 'bobyqa', 'Brent' or 'NM'. Default is 'bobyqa'.

solver: An optional binary value that can be either 1 (Cholesky Decomposition using ReplEigen), 2 (PCG) or 3 (Cholesky Decomposition using Matrix). Default is NULL, which lets the function select a solver. See details.

spd: An optional logical value indicating whether the relatedness matrix is symmetric positive definite. Default is TRUE. See details.

verbose: An optional logical scalar indicating whether to print additional messages. Default is TRUE.

mc: An optional integer scalar specifying the number of Monte Carlo samples used for approximating the log-determinant. Only valid when dense=TRUE and detap='slq'. Default is 100.

Value

beta: The estimated coefficient for each predictor in X.

HR: The estimated HR for each predictor in X.

sd_beta: The estimated standard error of beta.

p: The p-value.

iter: The number of iterations until convergence.

tau: The estimated variance component.

int_ll: The marginal likelihood (-2*log(lik)) of $\tau$ evaluated at the estimate of $\tau$.

rank: The rank of the relatedness matrix.

nsam: Actual sample size.

About type

'bd' is used for a block-diagonal relatedness matrix, or a sparse matrix the inverse of which is also sparse. 'sparse' is used for a general sparse relatedness matrix the inverse of which is not sparse.

About spd

When spd=TRUE, the relatedness matrix is treated as SPD. If the matrix is SPSD or not sure, use spd=FALSE.
About solver

When solver=1,3/solver=2, Cholesky decompositon/PCG is used to solve the linear system. When solver=3, the solve function in the Matrix package is used, and when solver=1, it uses RcppEigen:LDLT to solve linear systems. When type='dense', it is recommended to set solver=2 to have better computational performance.

About detap

When detap='exact', the exact log-determinant is computed for estimating the variance component. Specifying detap='diagonal' uses diagonal approximation, and is only effective for a sparse relatedness matrix. Specifying detap='slq' uses stochastic lanczos quadrature approximation.

Examples

library(Matrix)
library(MASS)
library(coxmeg)

## simulate a block-diagonal relatedness matrix
tau_var <- 0.2
n_f <- 100
mat_list <- list()
size <- rep(10,n_f)
offd <- 0.5
for(i in 1:n_f)
{
  mat_list[[i]] <- matrix(offd,size[i],size[i])
  diag(mat_list[[i]]) <- 1
}
sigma <- as.matrix(bdiag(mat_list))
n <- nrow(sigma)

## simulate random effects and outcomes
x <- mvrnorm(1, rep(0,n), tau_var*sigma)
myrates <- exp(x-1)
y <- rexp(n, rate = myrates)
cen <- rexp(n, rate = 0.02)
ycen <- pmin(y, cen)
outcome <- cbind(ycen,as.numeric(y <= cen))

## fit a Cox mixed-effects model
re = coxmeg(outcome,sigma,type='bd',detap='diagonal',order=1)
re
Description

`coxmeg_m` first estimates the variance component under a null model with only `cov`, and then analyzing each predictor in `X` one by one.

Usage

```r
coxmeg_m(X, outcome, corr, type, FID = NULL, cov = NULL, tau = NULL,
min_tau = 1e-04, max_tau = 5, eps = 1e-06, order = NULL,
detap = NULL, opt = "bobyqa", score = FALSE, threshold = 0,
solver = NULL, spd = TRUE, verbose = TRUE, mc = 100)
```

Arguments

- **X**: A matrix of the predictors. Can be quantitative or binary values. Categorical variables need to be converted to dummy variables. Each row is a sample, and the predictors are columns.
- **outcome**: A matrix contains time (first column) and status (second column). The status is a binary variable (1 for failure / 0 for censored).
- **corr**: A relatedness matrix. Can be a matrix or a 'dgCMatrix' class in the Matrix package. Must be symmetric positive definite or symmetric positive semidefinite.
- **type**: A string indicating the sparsity structure of the relatedness matrix. Should be 'bd' (block diagonal), 'sparse', or 'dense'. See details.
- **FID**: An optional string vector of family ID. If provided, the data will be reordered according to the family ID.
- **cov**: An optional matrix of the covariates included in the null model for estimating the variance component. Can be quantitative or binary values. Categorical variables need to be converted to dummy variables. Each row is a sample, and the covariates are columns.
- **tau**: An optional positive value for the variance component. If `tau` is given, the function will skip estimating the variance component, and use the given `tau` to analyze the predictors.
- **min_tau**: An optional positive value indicating the lower bound in the optimization algorithm for the variance component `tau`. Default is 1e-4.
- **max_tau**: An optional positive value indicating the upper bound in the optimization algorithm for the variance component `tau`. Default is 5.
- **eps**: An optional positive value indicating the tolerance in the optimization algorithm. Default is 1e-6.
- **order**: An optional integer value starting from 0. Only valid when `dense=FALSE`. It specifies the order of approximation used in the inexact newton method. Default is NULL, which lets coxmeg choose an optimal order.
- **detap**: An optional string indicating whether to use approximation for log-determinant. Can be 'exact', 'diagonal' or 'slq'. Default is NULL, which lets the function select a method based on 'type' and other information. See details.
- **opt**: An optional logical value for the Optimization algorithm for `tau`. Can have the following values: 'bobyqa', 'Brent' or 'NM'. Default is 'bobyqa'. 
score: An optional logical value indicating whether to perform a score test. Default is FALSE.

threshold: An optional non-negative value. If threshold>0, coxmeg_m will reestimate HRs for those SNPs with a p-value<threshold by first estimating a variant-specific variance component. Default is 0.

solver: An optional binary value that can be either 1 (Cholesky Decomposition using RcppEigen), 2 (PCG) or 3 (Cholesky Decomposition using Matrix). Default is NULL, which lets the function select a solver. See details.

spd: An optional logical value indicating whether the relatedness matrix is symmetric positive definite. Default is TRUE. See details.

verbose: An optional logical value indicating whether to print additional messages. Default is TRUE.

mc: An optional integer value specifying the number of Monte Carlo samples used for approximating the log-determinant. Only valid when dense=TRUE and detap='slq'. Default is 100.

Value

beta: The estimated coefficient for each predictor in X.
HR: The estimated HR for each predictor in X.
sd_beta: The estimated standard error of beta.
p: The p-value of each SNP.
tau: The estimated variance component.
iter: The number of iterations until convergence.

About type

'bd' is used for a block-diagonal relatedness matrix, or a sparse matrix the inverse of which is also sparse. ‘sparse’ is used for a general sparse relatedness matrix the inverse of which is not sparse.

About spd

When spd=TRUE, the relatedness matrix is treated as SPD. If the matrix is SPSD or not sure, use spd=FALSE.

About solver

When solver=1,3/solver=2, Cholesky decompositon/PCG is used to solve the linear system. When solver=3, the solve function in the Matrix package is used, and when solver=1, it uses RcppEigen:LDLT to solve linear systems. When type='dense', it is recommended to set solver=2 to have better computational performance.

About detap

When detap='exact', the exact log-determinant is computed for estimating the variance component. Specifying detap='diagonal' uses diagonal approximation, and is only effective for a sparse relatedness matrix. Specifying detap='slq' uses stochastic lanczos quadrature approximation.
Examples

```r
library(Matrix)
library(MASS)
library(coxmeg)

## simulate a block-diagonal relatedness matrix
tau_var <- 0.2
n_f <- 100
mat_list <- list()
size <- rep(10,n_f)
offd <- 0.5
for(i in 1:n_f)
{
  mat_list[[i]] <- matrix(offd, size[i], size[i])
  diag(mat_list[[i]]) <- 1
}
sigma <- as.matrix(bdiag(mat_list))
n <- nrow(sigma)

## simulate random effects and outcomes
x <- mvrnorm(1, rep(0,n), tau_var*sigma)
myrates <- exp(x-1)
y <- rexp(n, rate = myrates)
cen <- rexp(n, rate = 0.02)
ycen <- pmin(y, cen)
outcome <- cbind(ycen, as.numeric(y <= cen))

## simulate genotypes
g = matrix(rbinom(n*5,2,0.5), n, 5)

## The following command will first estimate the variance component without g,
## and then use it to estimate the HR for each preditor in g.
re = coxmeg_m(g, outcome, sigma, type="bd", tau=0.5, detap='diagonal', order=1)
re
```

coxmeg_plink

Perform GWAS using a Cox mixed-effects model with plink files as input

description

coxmeg_plink first estimates the variance component under a null model with only cov if tau is not given, and then analyzing each SNP in the plink files.

Usage

```r
coxmeg_plink(pheno, corr, type, bed = NULL, tmp_dir = NULL, cov_file = NULL, tau = NULL, maf = 0.05, min_tau = 1e-04, max_tau = 5, eps = 1e-06, order = NULL, detap = NULL,
```
coxmeg_plink

```
opt = "bobyqa", score = FALSE, threshold = 0, solver = NULL,
spd = TRUE, mc = 100, verbose = TRUE)
```

### Arguments

- **pheno**: A string value indicating the file name or the full path of a pheno file. The file must be in the working directory if the full path is not given. The file is in plink pheno format, containing the following four columns, family ID, individual ID, time and status. The status is a binary variable (1 for events/0 for censored).

- **corr**: A relatedness matrix. Can be a matrix or a 'dgCMatrix' class in the Matrix package. Must be symmetric positive definite or symmetric positive semidefinite.

- **type**: A string indicating the sparsity structure of the relatedness matrix. Should be 'bd' (block diagonal), 'sparse', or 'dense'. See details.

- **bed**: A optional string value indicating the file name or the full path of a plink bed file (without .bed). The files must be in the working directory if the full path is not given. If not provided, only the variance component will be returned.

- **tmp_dir**: A optional directory to store temporary .gds files. The directory needs to be specified when bed is provided.

- **cov_file**: An optional string value indicating the file name or the full path of a covariate file. The files must be in the working directory if the full path is not given. Same as the cov file in plink, the first two columns are family ID and individual ID. The covariates are included in the null model for estimating the variance component. The covariates can be quantitative or binary values. Categorical variables need to be converted to dummy variables.

- **tau**: An optional positive value for the variance component. If tau is given, the function will skip estimating the variance component, and use the given tau to analyze the SNPs.

- **maf**: An optional positive value. All SNPs with MAF<maf in the bed file will not be analyzed. Default is 0.05.

- **min_tau**: An optional positive value indicating the lower bound in the optimization algorithm for the variance component tau. Default is 1e-4.

- **max_tau**: An optional positive value indicating the upper bound in the optimization algorithm for the variance component tau. Default is 5.

- **eps**: An optional positive value indicating the tolerance in the optimization algorithm. Default is 1e-6.

- **order**: An optional integer value starting from 0. Only effective when dense=FALSE. It specifies the order of approximation used in the inexact newton method. Default is NULL, which lets coxme choose an optimal order.

- **detap**: An optional string indicating whether to use approximation for log-determinant. Can be 'exact', 'diagonal' or 'slq'. Default is NULL, which lets the function select a method based on 'type' and other information. See details.

- **opt**: An optional string value for the Optimization algorithm for tau. Can have the following values: 'bobyqa', 'Brent' or 'NM'. Default is 'bobyqa'.

- **score**: An optional logical value indicating whether to perform a score test. Default is FALSE.
threshold  An optional non-negative value. If threshold>0, coxmeg_m will reestimate HRs for those SNPs with a p-value<threshold by first estimating a variant-specific variance component. Default is 0.

solver   An optional binary value taking either 1 or 2. Default is 1. See details.

spd     An optional logical value indicating whether the relatedness matrix is symmetric positive definite. Default is TRUE. See details.

mc      An optional integer value specifying the number of Monte Carlo samples used for approximating the log-determinant. Only valid when dense=TRUE and detap='slq'. Default is 100.

verbose An optional logical value indicating whether to print additional messages. Default is TRUE.

Value

beta: The estimated coefficient for each predictor in X.
HR: The estimated HR for each predictor in X.
sd_beta: The estimated standard error of beta.
p: The p-value of each SNP.
tau: The estimated variance component.
rank: The rank of the relatedness matrix.
nsam: Actual sample size.

About type

'bd' is used for a block-diagonal relatedness matrix, or a sparse matrix the inverse of which is also sparse. 'sparse' is used for a general sparse relatedness matrix the inverse of which is not sparse.

About corr

The subjects in corr must be in the same order as in the plink fam file.

About missing values

pheno -9 for missing values, cov_file NA for missing values.

About temporary files

The function will create a temporary gds file with approximately the same size as the bed file. The temporary file will be removed when the analysis is done.

About spd

When spd=TRUE, the relatedness matrix is treated as SPD. If the matrix is SPSD or not sure, set spd=FALSE.
About `solver`

When `solver=1`, `solver=2`, Cholesky decomposition/PCG is used to solve the linear system. When `solver=3`, the solve function in the Matrix package is used, and when `solver=1`, it uses RcppEigen:LDLT to solve linear systems. When `type='dense'`, it is recommended to set `solver=2` to have better computational performance.

About `detap`

When `detap='exact'`, the exact log-determinant is computed for estimating the variance component. Specifying `detap='diagonal'` uses diagonal approximation, and is only effective for a sparse relatedness matrix. Specifying `detap='slq'` uses stochastic lanczos quadrature approximation.

Examples

```r
library(Matrix)
library(MASS)
library(coxmeg)

## build a block-diagonal relatedness matrix
n_f <- 600
mat_list <- list()
size <- rep(5,n_f)
offd <- 0.5
for(i in 1:n_f)
{
  mat_list[[i]] <- matrix(offd,size[i],size[i])
  diag(mat_list[[i]]) <- 1
}
sigma <- as.matrix(bdiag(mat_list))

## Estimate variance component under a null model
pheno = system.file("extdata", "ex_pheno.txt", package = "coxmeg")
cov = system.file("extdata", "ex_cov.txt", package = "coxmeg")
bed = system.file("extdata", "example_null.bed", package = "coxmeg")
bed = substr(bed,1,nchar(bed)-4)
re = coxmeg_plink(pheno,sigma,type="bd",bed=bed,tmp_dir=tempdir(),cov_file=cov,
detap='diagonal',order=1)
re
```

---

**fit_ppl**

Estimate HRs using PPL given a known variance component (tau)

Description

`fit_ppl` returns estimates of HRs and their p-values given a known variance component (tau).

Usage

`fit_ppl(X, outcome, corr, type, tau = 0.5, FID = NULL, eps = 1e-06,
          order = 1, solver = NULL, spd = TRUE, verbose = TRUE)`
Arguments

X: A matrix of the predictors. Can be quantitative or binary values. Categorical variables need to be converted to dummy variables. Each row is a sample, and the predictors are columns.

outcome: A matrix contains time (first column) and status (second column). The status is a binary variable (1 for failure / 0 for censored).

corr: A relatedness matrix. Can be a matrix or a `dgCMatrix` class in the Matrix package. Must be symmetric positive definite or symmetric positive semidefinite.

type: A string indicating the sparsity structure of the relatedness matrix. Should be 'bd' (block diagonal), 'sparse', or 'dense'. See details.

tau: A positive scalar. A variance component given by the user. Default is 0.5.

FID: An optional string vector of family ID. If provided, the data will be reordered according to the family ID.

eps: An optional positive value indicating the tolerance in the optimization algorithm. Default is 1e-6.

order: An optional integer value starting from 0. Only valid when dense=FALSE. It specifies the order of approximation used in the inexact newton method. Default is 1.

solver: An optional binary value that can be either 1 (Cholesky Decomposition using RcppEigen), 2 (PCG) or 3 (Cholesky Decomposition using Matrix). Default is NULL, which lets the function select a solver. See details.

spd: An optional logical value indicating whether the relatedness matrix is symmetric positive definite. Default is TRUE.

verbose: An optional logical value indicating whether to print additional messages. Default is TRUE.

Value

beta: The estimated coefficient for each predictor in X.

HR: The estimated HR for each predictor in X.

sd_beta: The estimated standard error of beta.

p: The p-value.

iter: The number of iterations until convergence.

ppl: The PPL when the convergence is reached.

About type

'bd' is used for a block-diagonal relatedness matrix, or a sparse matrix the inverse of which is also sparse. 'sparse' is used for a general sparse relatedness matrix the inverse of which is not sparse.

About solver

When solver=1,3/solver=2, Cholesky decompositon/PCG is used to solve the linear system. When solver=3, the solve function in the Matrix package is used, and when solver=1, it uses RcppEigen:LDLT to solve linear systems.
library(Matrix)
library(MASS)
library(coxmeg)

## simulate a block-diagonal relatedness matrix
tau_var <- 0.2
n_f <- 100
mat_list <- list()
size <- rep(10,n_f)
offd <- 0.5
for(i in 1:n_f)
{
  mat_list[[i]] <- matrix(offd,size[i],size[i])
  diag(mat_list[[i]]) <- 1
}
sigma <- as.matrix(bdiag(mat_list))
n <- nrow(sigma)

## simulate random effects and outcomes
x <- mvrnorm(1, rep(0,n), tau_var*sigma)
myrates <- exp(x-1)
y <- rexp(n, rate = myrates)
cen <- rexp(n, rate = 0.02 )
ycen <- pmin(y, cen)
outcome <- cbind(yacen,as.numeric(y <= cen))

## fit the ppl
re = fit_ppl(x,outcome,sigma,type='bd',tau=0.5,order=1)
re
Index

*Topic **Cox**
  - coxmeg, 3
  - coxmeg_m, 5
  - coxmeg_plink, 8
  - fit_ppl, 11
*Topic **mixed-effects**
  - coxmeg, 3
  - coxmeg_m, 5
  - coxmeg_plink, 8
  - fit_ppl, 11
*Topic **model**
  - coxmeg, 3
  - coxmeg_m, 5
  - coxmeg_plink, 8
  - fit_ppl, 11
*Topic **package**
  - coxmeg-package, 2

coxmeg, 3
coxmeg-package, 2
coxmeg_m, 5
coxmeg_plink, 8
fit_ppl, 11