

Package ‘SEAGLE’

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Type Package

Title Scalable Exact Algorithm for Large-Scale Set-Based
Gene-Environment Interaction Tests

Version 1.0.1

Description The explosion of biobank data offers immediate opportunities for gene-environment (GxE) interaction studies of complex diseases because of the large sample sizes and rich collection in genetic and non-genetic information. However, the extremely large sample size also introduces new computational challenges in GxE assessment, especially for set-based GxE variance component (VC) tests, a widely used strategy to boost overall GxE signals and to evaluate the joint GxE effect of multiple variants from a biologically meaningful unit (e.g., gene).

We present 'SEAGLE', a Scalable Exact Algorithm for Large-scale Set-based GxE tests, to permit GxE VC test scalable to biobank data. 'SEAGLE' employs modern matrix computations to achieve the same “exact” results as the original GxE VC tests, and does not impose additional assumptions nor relies on approximations. 'SEAGLE' can easily accommodate sample sizes in the order of 10^5 , is implementable on standard laptops, and does not require specialized equipment.

The accompanying manuscript for this package can be found at Chi, Ipsen, Hsiao, Lin, Wang, Lee, Lu, and Tzeng. (2021+) <[arXiv:2105.03228](https://arxiv.org/abs/2105.03228)>.

URL <https://github.com/jocelynchi/SEAGLE>

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Depends R (>= 3.5.0), Matrix, CompQuadForm

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Suggests rmarkdown, knitr

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applyAt	<i>Function for applying $t(A)$ on the left for REML EM</i>
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Description

Function for applying $t(A)$ on the left for REML EM

Usage

```
applyAt(qrXtilde, RHS)
```

Arguments

qrXtilde	Object from QR decomposition of Xtilde
RHS	Object on right hand side of null of Xtilde ^T

Value

Matrix or vector resulting from left multiplication of A with matrix or vector input RHS

`cosihap`*Synthetic haplotype data generated from COSI software*

Description

A dataset containing 10,000 haplotypes of SNP sequences mimicking the European population generated from the COSI software

Usage

```
data(cosihap)
```

Format

An object of class `dgCMatrix` with 10000 rows and 604 columns.

Source

<https://genome.cshlp.org/content/15/11/1576.abstract>

`estimate.vc`*REML EM Algorithm*

Description

REML EM algorithm for estimating variance components

Usage

```
estimate.vc(  
  y,  
  Xtilde,  
  qrXtilde,  
  beta,  
  G,  
  init.sigma = 0.5,  
  init.tau = 0.5,  
  tol = 0.001,  
  maxiters = 1000  
)
```

Arguments

y	Vector of observed phenotypes
Xtilde	Matrix of covariates (first column contains the intercept, last column contains the E factor for studying the GxE effect)
qrXtilde	Object containing QR decomposition of Xtilde
beta	Coefficient vector for covariate matrix Xtilde
G	Matrix of genotype markers
init.sigma	Initial sigma input (Default is 0.5)
init.tau	Initial tau input (Default is 0.5)
tol	Tolerance for convergence (Default is 1e-3)
maxiters	Maximum number of iterations (Default is 1000)

Value

Estimates for tau and sigma

makeSimData	<i>Generate synthetic data according to a fixed effects model</i>
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Description

This function generates synthetic from the fixed effects model described in the experimental studies portion of the paper.

Usage

```
makeSimData(  
  H,  
  n,  
  L = 100,  
  maf = 0.01,  
  gamma0 = 1,  
  gammaX = 1,  
  gammaE = 1,  
  gammaG,  
  gammaGE,  
  causal = 40,  
  seed = 12345  
)
```

Arguments

H	Matrix of haplotype data (e.g. cosihap)
n	Number of individuals
L	Number of SNPs in the G matrix (Default is 100), should be a value between 1 and 604
maf	Minor allele frequency (Default is 0.01)
gamma0	gamma0 Fixed effect coefficient for intercept (Default is 1)
gammaX	gammaX Fixed effect coefficient for confounding covariates (Default is 1)
gammaE	gammaE Fixed effect coefficient for E effect (Default is 1)
gammaG	gammaG Fixed effect coefficient for G main effect
gammaGE	gammaGE Fixed effect coefficient for GxE interaction effect
causal	Number of causal SNPs (default is 40)
seed	Seed (Default is 12345)

Value

Synthetic dataset containing y, X, E, G, epsilon, and number of causal SNPs

Examples

```
dat <- makeSimData(H=cosihap, n=500, L=10, gammaG=1, gammaGE=0, causal=4, seed=1)
```

```
prep.SEAGLE
```

Prepare data for input into SEAGLE function

Description

This function checks and formats data for input into SEAGLE function

Usage

```
prep.SEAGLE(y, X, intercept, E, G)
```

Arguments

y	Vector of observed phenotypes
X	Matrix of covariates without genetic marker interactions
intercept	1 if the first column of X is the all ones vector, 0 otherwise
E	E Vector of environmental covariates
G	G Matrix of genotype data

Value

List object containing prepared data for input into SEAGLE function

Examples

```
dat <- makeSimData(H=cosihap, n=500, L=10, gammaG=1, gammaGE=0, causal=4, seed=1)
objSEAGLE <- prep.SEAGLE(y=dat$y, X=dat$X, intercept=1, E=dat$E, G=dat$G)
```

Rinv.AtG

Function for applying R inverse to AtG in REML EM algorithm

Description

Function for applying R inverse to AtG in REML EM algorithm

Usage

```
Rinv.AtG(G, AtG, GtAAtG, tau, sigma)
```

Arguments

G	Matrix of genotype markers (size n x L)
AtG	AtG from pre-computation
GtAAtG	GtAAtG from pre-computation
tau	Variance component from G main effect
sigma	Variance component from model noise epsilon

Value

Matrix resulting from left multiplication of Rinv with input matrix AtG

Rinv.u

Function for applying R inverse to u in REML EM algorithm

Description

Function for applying R inverse to u in REML EM algorithm

Usage

```
Rinv.u(G, AtG, GtAAtG, GtAu, u, tau, sigma)
```

Arguments

G	Matrix of genotype markers (size n x L)
AtG	AtG from precomputation
GtAAAtG	GtAAAtG from precomputation
GtAu	GtAu from precomputation
u	u=Aty from REML EM
tau	Variance component from G main effect
sigma	Variance component from model noise epsilon

Value

Vector resulting from left multiplication of Rinv with input vector u

SEAGLE	<i>Compute score-like test statistic and p-value for GxE test with SEAGLE algorithm</i>
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Description

This function computes the score test statistic and corresponding p-value for the GxE test with the SEAGLE algorithm with input data that have been prepared with the prep.SEAGLE function

Usage

```
SEAGLE(obj.SEAGLE, init.tau = 0.5, init.sigma = 0.5, pv = "liu")
```

Arguments

obj.SEAGLE	Input data prepared with prep.SEAGLE function
init.tau	Initial estimate for tau (Default is 0.5)
init.sigma	Initial estimate for sigma (Default is 0.5)
pv	Method of obtaining p-value (Either "liu" or "davies", Default is liu)

Value

Score-like test statistic T for the GxE effect and corresponding p-value

Examples

```
dat <- makeSimData(H=cosihap, n=500, L=10, gammaG=1, gammaGE=0, causal=4, seed=1)
objSEAGLE <- prep.SEAGLE(y=dat$y, X=dat$X, intercept=1, E=dat$E, G=dat$G)
res <- SEAGLE(objSEAGLE, init.tau=0.5, init.sigma=0.5)
```

`Vinv`*Function for applying V inverse in Algorithm 1*

Description

This function applies V inverse via the Woodbury matrix identity

Usage

```
Vinv(G, qrM, tau_over_sigma, sigma, RHS)
```

Arguments

<code>G</code>	Matrix of genotype markers (size $n \times L$)
<code>qrM</code>	Pre-computation for $L \times L$ linear system solve
<code>tau_over_sigma</code>	Tau over sigma from precomputation
<code>sigma</code>	Variance component from model noise epsilon
<code>RHS</code>	Matrix or vector on right-hand side of V inverse

Value

Matrix or vector resulting from left multiplication of Vinv with input RHS

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