

Package ‘SAIGEgds’

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Type Package

Title Scalable Implementation of Generalized mixed models using GDS files in Phenome-Wide Association Studies

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Description Scalable implementation of generalized mixed models with highly optimized C++ implementation and integration with Genomic Data Structure (GDS) files. It is designed for single variant tests and set-based aggregate tests in large-scale Phenome-wide Association Studies (PheWAS) with millions of variants and samples, controlling for sample structure and case-control imbalance. The implementation is based on the SAIGE R package (v0.45, Zhou et al. 2018 and Zhou et al. 2020), and it is extended to include the state-of-the-art ACAT-O set-based tests. Benchmarks show that SAIGEgds is significantly faster than the SAIGE R package.

License GPL-3

SystemRequirements GNU make

VignetteBuilder knitr

ByteCompile TRUE

URL <https://github.com/AbbVie-ComputationalGenomics/SAIGEgds>

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SAIGEgds-package	<i>Scalable Implementation of Generalized mixed models in Phenome-Wide Association Studies using GDS files</i>
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Description

Scalable and accurate implementation of generalized mixed mode with the support of Genomic Data Structure (GDS) files and highly optimized C++ implementation. It is designed for single variant tests in large-scale phenome-wide association studies (PheWAS) with millions of variants and hundreds of thousands of samples, e.g., UK Biobank genotype data, controlling for case-control imbalance and sample structure in single variant association studies.

The implementation of SAIGEgds is based on the original SAIGE R package (v0.29.4.4) [Zhou et al. 2018] <https://github.com/weizhouUMICH/SAIGE/releases/tag/v0.29.4.4>. All of the calculation with single-precision floating-point numbers in SAIGE are replaced by the double-precision calculation in SAIGEgds. SAIGEgds also implements some of the SPAtest functions in C to speed up the calculation of Saddlepoint Approximation.

Details

Package: SAIGEgds
 Type: Package
 License: GPL version 3

Author(s)

Xiuwen Zheng <xiuwen.zheng@abbvie.com>, Wei Zhou (the original author of the SAIGE R package, <https://github.com/weizhouUMICH/SAIGE>)

References

Zheng X, Davis J, Wade. SAIGEgds – an efficient statistical tool for large-scale PheWAS with mixed models. **Bioinformatics** (2020). DOI: 10.1093/bioinformatics/btaa731.

Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, LeFaive J, VandeHaar P, Gagliano SA, Gifford A, Bastarache LA, Wei WQ, Denny JC, Lin M, Hveem K, Kang HM, Abecasis GR, Willer CJ, Lee S. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. **Nat Genet** (2018). Sep;50(9):1335-1341.

Zhou W, Zhao Z, Nielsen JB, Fritsche LG, LeFaive J, Taliun SAG, Bi W, Gabrielsen ME, Daly MJ, Neale BM, Hveem K, Abecasis GR, Willer CJ, et al. Scalable generalized linear mixed model for region-based association tests in large biobanks and cohorts. *Nat Genet.* 2020; 52: 634-9.

Zheng X, Gogarten S, Lawrence M, Stilp A, Conomos M, Weir BS, Laurie C, Levine D. SeqArray – A storage-efficient high-performance data format for WGS variant calls. **Bioinformatics** (2017). DOI: 10.1093/bioinformatics/btx145.

Examples

```
# open the GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

# load phenotype
phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, trait.type="binary",
  geno.sparse=FALSE)

# p-value calculation
assoc <- seqAssocGLMM_SPA(gdsfile, glmm, mac=10)

head(assoc)

# close the GDS file
seqClose(gdsfile)
```

glmmHeritability

Heritability estimation

Description

Get the heritability estimate from the SAIGE model.

Usage

```
glmmHeritability(modobj, adjust=TRUE)
```

Arguments

modobj	an R object for SAIGE model parameters
adjust	if TRUE and binary outcomes, uses adjusted tau estimate for the heritability estimation

Details

In SAIGE, penalized quasi-likelihood (PQL) is used to estimate the variance component parameter tau. It is known to produce biased estimate of the variance component tau using PQL. If adjust=TRUE for binary outcomes, tau is adjusted based prevalence and observed tau using the data in Supplementary Table 7 (Zhou et al. 2018) to reduce the bias of PQL estimate of variance component.

Value

Return a liability scale heritability.

Author(s)

Xiuwen Zheng

See Also

[seqFitNullGLMM_SPA](#)

Examples

```
# open a GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

# load phenotype
phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, trait.type="binary")

glmmHeritability(glmm)

seqClose(gdsfile)
```

pACAT

Cauchy Combination Test

Description

P-value calculation from Cauchy combination test.

Usage

```
pACAT(p, w=NULL)
pACAT2(p, maf, wbeta=c(1,25))
```

Arguments

p	a numeric vector for p-values
w	weight for each p-value
maf	minor allele frequency for each p-value
wbeta	weights for per-variant effect, using beta distribution dbeta() according to variant's MAF

Value

Return a single number for the combined p-value.

References

Liu Y., Cheng S., Li Z., Morrison A.C., Boerwinkle E., Lin X.; ACAT: A Fast and Powerful p Value Combination Method for Rare-Variant Analysis in Sequencing Studies. *Am J Hum Genetics* 104, 410-421 (2019).

See Also

[seqFitNullGLMM_SPA](#), [seqAssocGLMM_SPA](#)

Examples

```
p1 <- 10^-4
p2 <- 10^-5
p3 <- 10^-(3:20)
sapply(p3, function(p) pACAT(c(p1, p2, p)))

pACAT2(c(10^-4, 10^-6), c(0.01, 0.005))
```

seqAssocGLMM_ACAT_O *ACAT-V tests*

Description

Set-based ACAT-O tests using mixed models.

Usage

```
seqAssocGLMM_ACAT_O(gdsfile, modobj, units, maxMAF=0.01, wbeta=AggrParamBeta,
  missing=0.05, collapse.mac=10, collapse.method=c("max", "sum"),
  ccimb.adj=TRUE, ER.mac=4.5, dsnode="", res.savefn="", res.compress="ZIP",
  parallel=FALSE, verbose=TRUE, verbose.maf=FALSE)
```

Arguments

<code>gdsfile</code>	a SeqArray GDS filename, or a GDS object
<code>modobj</code>	an R object for SAIGE model parameters
<code>units</code>	a list of units of selected variants, with S3 class "SeqUnitListClass" defined in the SeqArray package
<code>maxMAF</code>	a numeric vector for MAF thresholds, e.g., <code>c(0.01, 0.001)</code> for rare variants
<code>wbeta</code>	weights for per-variant effect, using beta distribution <code>dbeta()</code> according to variant's MAF; a length-two vector, or a matrix with two rows for multiple beta parameters; by default, using <code>beta(1,1)</code> and <code>beta(1,25)</code> both
<code>missing</code>	missing threshold for variants (checking <code><= missing</code>), <code>NaN</code> for no filter
<code>collapse.mac</code>	a threshold of minor allele count for collapsing ultra rare variants used in ACAT-V and SKAT tests if <code>mac <= collapse.mac</code> , 10 by default
<code>collapse.method</code>	"max" (by default), "sum"
<code>ccimb.adj</code>	whether adjusting for case-control imbalance
<code>ER.mac</code>	the maximum sum of MAC for the variants with efficient resampling p-values
<code>dsnode</code>	"" for automatically searching the GDS nodes "genotype" and "annotation/format/DS", or use a user-defined GDS node in the file
<code>res.savefn</code>	an RData or GDS file name, "" for no saving
<code>res.compress</code>	the compression method for the output file, it should be one of LZMA, LZMA_RA, ZIP, ZIP_RA and none
<code>parallel</code>	FALSE (serial processing), TRUE (multicore processing), a numeric value for the number of cores, or other value; <code>parallel</code> is passed to the argument <code>cl</code> in seqParallel , see seqParallel for more details
<code>verbose</code>	if TRUE, show information
<code>verbose.maf</code>	if TRUE, show summary of MAFs in units

Details

`seqUnitFilterCond()` in the SeqArray package can be used to restrict the variant sets units to a range of MAC and/or MAF. ACAT-O combines the p-values from ACAT-V, burden and SKAT together to calculate the final p-value via Cauchy distribution.

For more details of the ACAT-O method, please refer to the ACAT paper [Liu et al. 2019] (see the reference section).

Value

Return a `data.frame` with the following components if not saving to a file:

<code>chr</code>	chromosome;
<code>start</code>	the starting position;
<code>end</code>	the ending position;
<code>maxMAF</code>	maximum of MAFs;
<code>numvar</code>	the number of variants in the window; if <code>weight="Cauchy"</code> , it is the number of individual p-values in the Cauchy test
<code>macmin</code>	the minimum of MAC in the window;

macmed	the median of MAC in the window;
macmax	the maximum of MAC in the window;
summac	the sum of minor allele counts;
weight	the weighting strategy with the beta distribution parameters
pval	ACAT-O p-value;
n_collapse	the number of ultra rare variants for collapsing burden tests ($\leq$ collapse.mac);
p.burden	burden tests;
p.skot	SKAT tests;
p.acatv	ACAT-V tests;
burden.beta	beta coefficient of burden test;
burden.se	SE of burden beta coefficient;

Author(s)

Xiuwen Zheng

References

Liu Y., Chen S., Li Z., Morrison A.C., Boerwinkle E., Lin X. ACAT: A Fast and Powerful p Value Combination Method for Rare-Variant Analysis in Sequencing Studies. *Am J Hum Genetics* 104, 410-421 (2019).

See Also

[seqAssocGLMM_ACAT_V](#), [seqAssocGLMM_Burden](#), [seqAssocGLMM_SKAT](#), [seqUnitFilterCond](#)

Examples

```
# open a GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

sp_grm_fn <- system.file("extdata", "grm1k_10k_sp_grm.rds", package="SAIGEgds")
sp_grm <- readRDS(sp_grm_fn)

# load phenotype
phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, sp_grm,
  trait.type="binary")

# get a list of variant units for burden tests
units <- seqUnitSlidingWindows(gdsfile, win.size=50, win.shift=250)

a <- seqAssocGLMM_ACAT_O(gdsfile, glmm, units, maxMAF=c(0.1,0.01))
head(a)

# close the GDS file
seqClose(gdsfile)
```

seqAssocGLMM_ACAT_V *ACAT-V tests*

Description

Set-based ACAT-V tests using mixed models.

Usage

```
seqAssocGLMM_ACAT_V(gdsfile, modobj, units, maxMAF=0.01, wbeta=AggrParamBeta,
  missing=0.05, ccimb.adj=TRUE, collapse.mac=10, ER.mac=4.5, dsnode="",
  res.savefn="", res.compress="ZIP", parallel=FALSE, verbose=TRUE,
  verbose.maf=FALSE)
```

Arguments

<code>gdsfile</code>	a SeqArray GDS filename, or a GDS object
<code>modobj</code>	an R object for SAIGE model parameters
<code>units</code>	a list of units of selected variants, with S3 class "SeqUnitListClass" defined in the SeqArray package
<code>maxMAF</code>	a numeric vector for MAF thresholds, e.g., <code>c(0.01, 0.001)</code> for rare variants
<code>wbeta</code>	weights for per-variant effect, using beta distribution <code>dbeta()</code> according to variant's MAF; a length-two vector, or a matrix with two rows for multiple beta parameters; by default, using <code>beta(1,1)</code> and <code>beta(1,25)</code> both
<code>missing</code>	missing threshold for variants (checking <code><= missing</code>), NaN for no filter
<code>ccimb.adj</code>	whether adjusting for case-control imbalance or not
<code>collapse.mac</code>	a threshold of minor allele count for collapsing ultra rare variants if <code>mac <= collapse.mac</code> , 10 by default
<code>ER.mac</code>	the maximum sum of MAC for the variants with efficient resampling p-values
<code>dsnode</code>	"" for automatically searching the GDS nodes "genotype" and "annotation/format/DS", or use a user-defined GDS node in the file
<code>res.savefn</code>	an RData or GDS file name, "" for no saving
<code>res.compress</code>	the compression method for the output file, it should be one of LZMA, LZMA_RA, ZIP, ZIP_RA and none
<code>parallel</code>	FALSE (serial processing), TRUE (multicore processing), a numeric value for the number of cores, or other value; <code>parallel</code> is passed to the argument <code>c1</code> in seqParallel , see seqParallel for more details
<code>verbose</code>	if TRUE, show information
<code>verbose.maf</code>	if TRUE, show summary of MAFs in units

Details

`seqUnitFilterCond()` in the SeqArray package can be used to restrict the variant sets `units` to a range of MAC and/or MAF.

For more details of the ACAT-V method, please refer to the ACAT paper [Liu et al. 2019] (see the reference section).

Value

Return a data.frame with the following components if not saving to a file:

chr	chromosome;
start	the starting position;
end	the ending position;
maxMAF	maximum of MAFs;
numvar	the number of variants in the window; if weight="Cauchy", it is the number of individual p-values in the Cauchy test
macmin	the minimum of MAC in the window;
macmed	the median of MAC in the window;
macmax	the maximum of MAC in the window;
summac	the sum of minor allele counts;
weight	the weighting strategy with the beta distribution parameters
n_single	the number of variants running for single variant tests;
n_collapse	the number of ultra rare variants for collapsing burden tests (<= collapse.mac);
pval	ACAT-V p-value;

Author(s)

Xiuwen Zheng

References

Liu Y., Chen S., Li Z., Morrison A.C., Boerwinkle E., Lin X. ACAT: A Fast and Powerful p Value Combination Method for Rare-Variant Analysis in Sequencing Studies. *Am J Hum Genetics* 104, 410-421 (2019).

See Also

[seqAssocGLMM_ACAT_0](#), [seqAssocGLMM_Burden](#), [seqAssocGLMM_SKAT](#), [seqUnitFilterCond](#)

Examples

```
# open a GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

# load phenotype
phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, trait.type="binary")

# get a list of variant units for burden tests
units <- seqUnitSlidingWindows(gdsfile, win.size=500, win.shift=250)

a <- seqAssocGLMM_ACAT_V(gdsfile, glmm, units, maxMAF=c(0.1,0.01))
head(a)
```

```
# close the GDS file
seqClose(gdsfile)
```

seqAssocGLMM_Burden *Burden tests*

Description

Set-based burden tests using mixed models.

Usage

```
seqAssocGLMM_Burden(gdsfile, modobj, units, maxMAF=0.01, wbeta=AggrParamBeta,
  missing=0.05, ccimb.adj=TRUE, ER.mac=4.5, dsnode="", res.savefn="",
  res.compress="ZIP", parallel=FALSE, verbose=TRUE, verbose.maf=FALSE)
```

Arguments

<code>gdsfile</code>	a SeqArray GDS filename, or a GDS object
<code>modobj</code>	an R object for SAIGE model parameters
<code>units</code>	a list of units of selected variants, with S3 class "SeqUnitListClass" defined in the SeqArray package
<code>maxMAF</code>	a numeric vector for MAF thresholds, e.g., <code>c(0.01, 0.001)</code> for rare variants
<code>wbeta</code>	weights for per-variant effect, using beta distribution <code>dbeta()</code> according to variant's MAF; a length-two vector, or a matrix with two rows for multiple beta parameters; by default, using <code>beta(1,1)</code> and <code>beta(1,25)</code> both
<code>missing</code>	missing threshold for variants (checking <code><= missing</code>), <code>NaN</code> for no filter
<code>ccimb.adj</code>	whether adjusting for case-control imbalance or not
<code>ER.mac</code>	the maximum sum of MAC for the variants with efficient resampling p-values
<code>dsnode</code>	"" for automatically searching the GDS nodes "genotype" and "annotation/format/DS", or use a user-defined GDS node in the file
<code>res.savefn</code>	an RData or GDS file name, "" for no saving
<code>res.compress</code>	the compression method for the output file, it should be one of LZMA, LZMA_RA, ZIP, ZIP_RA and none
<code>parallel</code>	FALSE (serial processing), TRUE (multicore processing), a numeric value for the number of cores, or other value; <code>parallel</code> is passed to the argument <code>c1</code> in seqParallel , see seqParallel for more details
<code>verbose</code>	if TRUE, show information
<code>verbose.maf</code>	if TRUE, show summary of MAFs in units

Details

`seqUnitFilterCond()` in the SeqArray package can be used to restrict the variant sets units to a range of MAC and/or MAF.

Value

Return a `data.frame` with the following components if not saving to a file:

<code>chr</code>	chromosome;
<code>start</code>	the starting position;
<code>end</code>	the ending position;
<code>maxMAF</code>	maximum of MAFs;
<code>numvar</code>	the number of variants in the window; if <code>weight="Cauchy"</code> , it is the number of individual p-values in the Cauchy test
<code>macmin</code>	the minimum of MAC in the window;
<code>macmed</code>	the median of MAC in the window;
<code>macmax</code>	the maximum of MAC in the window;
<code>summac</code>	the sum of minor allele counts;
<code>weight</code>	the weighting strategy with the beta distribution parameters
<code>beta</code>	beta coefficient, log odds ratio if binary outcomes (alternative allele vs. reference allele);
<code>SE</code>	standard error for beta coefficient;
<code>pval</code>	final p-value (if the Saddlepoint approximation or efficient resampling is applied);
<code>method</code>	"Normal": pval is calculated by assuming asymptotic normality; "SPA": using the Saddlepoint approximation method; "ER": using the efficient resampling
<code>p.norm</code>	p-values based on asymptotic normality (could be 0 if it is too small, e.g., <code>pnorm(-50) = 0</code> in R; used for checking only
<code>converged</code>	whether the SPA algorithm converges or not for p-values.

Author(s)

Xiuwen Zheng

See Also

[seqAssocGLMM_ACAT_V](#), [seqAssocGLMM_ACAT_O](#), [seqAssocGLMM_SKAT](#), [seqUnitFilterCond](#)

Examples

```
# open a GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

# load phenotype
phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, trait.type="binary")

# get a list of variant units for burden tests
units <- seqUnitSlidingWindows(gdsfile, win.size=500, win.shift=250)
```

```

a <- seqAssocGLMM_Burden(gdsfile, glmm, units, maxMAF=c(0.1,0.01))
head(a)

# close the GDS file
seqClose(gdsfile)

```

seqAssocGLMM_SKAT	<i>SKAT tests</i>
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Description

Set-based SKAT tests using mixed models.

Usage

```

seqAssocGLMM_SKAT(gdsfile, modobj, units, maxMAF=0.01, wbeta=AggrParamBeta,
  missing=0.05, collapse.mac=10, collapse.method=c("max", "sum"),
  ccimb.adj=TRUE, ER.mac=4.5, dsnode="", res.savefn="", res.compress="ZIP",
  parallel=FALSE, verbose=TRUE, verbose.maf=FALSE)

```

Arguments

<code>gdsfile</code>	a SeqArray GDS filename, or a GDS object
<code>modobj</code>	an R object for SAIGE model parameters
<code>units</code>	a list of units of selected variants, with S3 class "SeqUnitListClass" defined in the SeqArray package
<code>maxMAF</code>	a numeric vector for MAF thresholds, e.g., <code>c(0.01, 0.001)</code> for rare variants
<code>wbeta</code>	weights for per-variant effect, using beta distribution <code>dbeta()</code> according to variant's MAF; a length-two vector, or a matrix with two rows for multiple beta parameters; by default, using <code>beta(1,1)</code> and <code>beta(1,25)</code> both
<code>missing</code>	missing threshold for variants (checking <code><= missing</code>), <code>NaN</code> for no filter
<code>collapse.mac</code>	the mac threshold for collapsing ultra rare variants
<code>collapse.method</code>	maximum of dosages of rare variants ("max", by default), sum up rare genotypes ("sum")
<code>ccimb.adj</code>	whether adjusting for case-control imbalance
<code>ER.mac</code>	the maximum sum of MAC for the variants with efficient resampling p-values
<code>dsnode</code>	"" for automatically searching the GDS nodes "genotype" and "annotation/format/DS", or use a user-defined GDS node in the file
<code>res.savefn</code>	an RData or GDS file name, "" for no saving
<code>res.compress</code>	the compression method for the output file, it should be one of LZMA, LZMA_RA, ZIP, ZIP_RA and none
<code>parallel</code>	FALSE (serial processing), TRUE (multicore processing), a numeric value for the number of cores, or other value; <code>parallel</code> is passed to the argument <code>cl</code> in seqParallel , see seqParallel for more details
<code>verbose</code>	if TRUE, show information
<code>verbose.maf</code>	if TRUE, show summary of MAFs in units

Details

seqUnitFilterCond() in the SeqArray package can be used to restrict the variant sets units to a range of MAC and/or MAF.

For more details of the SAIGE-GENE method, please refer to the SAIGE paper [Zhou et al. 2020] (see the reference section).

Value

Return a data.frame with the following components if not saving to a file:

chr	chromosome;
start	the starting position;
end	the ending position;
maxMAF	maximum of MAFs;
numvar	the number of variants in the window; if weight="Cauchy", it is the number of individual p-values in the Cauchy test
macmin	the minimum of MAC in the window;
macmed	the median of MAC in the window;
macmax	the maximum of MAC in the window;
summac	the sum of minor allele counts;
weight	the weighting strategy with the beta distribution parameters
n_collapse	the number of variants running for single variant tests;
g_ncol	the number of ultra rare variants for collapsing burden tests (<= collapse.mac);
g_minMAC	x
pval	SKAT p-value;

Author(s)

Xiuwen Zheng

References

Zhou W, Zhao Z, Nielsen JB, Fritsche LG, LeFaive J, Taliun SAG, Bi W, Gabrielsen ME, Daly MJ, Neale BM, Hveem K, Abecasis GR, Willer CJ, et al. Scalable generalized linear mixed model for region-based association tests in large biobanks and cohorts. Nat Genet. 2020; 52: 634-9.

See Also

[seqAssocGLMM_ACAT_V](#), [seqAssocGLMM_ACAT_0](#), [seqAssocGLMM_Burden](#), [seqUnitFilterCond](#)

Examples

```
# open a GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

sp_grm_fn <- system.file("extdata", "grm1k_10k_sp_grm.rds", package="SAIGEgds")
sp_grm <- readRDS(sp_grm_fn)

# load phenotype
```

```

phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, sp_grm,
  trait.type="binary")

# get a list of variant units for burden tests
units <- seqUnitSlidingWindows(gdsfile, win.size=50, win.shift=250)

a <- seqAssocGLMM_SKAT(gdsfile, glmm, units, maxMAF=c(0.1,0.01))
head(a)

# close the GDS file
seqClose(gdsfile)

```

seqAssocGLMM_SPA	<i>P-value calculation</i>
------------------	----------------------------

Description

P-value calculations using variance approximation and an adjustment of Saddlepoint approximation in the mixed model framework.

Usage

```

seqAssocGLMM_SPA(gdsfile, modobj, maf=NaN, mac=10, missing=0.05, spa=TRUE,
  ER.mac=4.5, dsnode="", geno.ploidy=2L, res.savefn="", res.compress="ZIP",
  parallel=FALSE, load.balancing=TRUE,
  verbose.pval=c(0, 5e-10, 5e-8, 5e-6, 5e-4, 1), verbose=TRUE)

```

Arguments

<code>gdsfile</code>	a SeqArray GDS filename, or a GDS object
<code>modobj</code>	an R object for SAIGE model parameters
<code>maf</code>	minor allele frequency threshold (checking $\geq$ maf), NaN for no filter
<code>mac</code>	minor allele count threshold (checking $\geq$ mac), NaN for no filter
<code>missing</code>	missing threshold for variants (checking $\leq$ missing), NaN for no filter
<code>spa</code>	TRUE for using the Saddlepoint approximation method for adjusting case-control imbalance
<code>ER.mac</code>	the maximum MAC for the variants with efficient resampling p-values
<code>dsnode</code>	"" for automatically searching the GDS nodes "genotype" and "annotation/format/DS", or use a user-defined GDS node in the file
<code>geno.ploidy</code>	specify the ploidy (2 by default); 0 or NA used for non-genotype data (e.g., CNV and dsnode should be specified for CNVs meanwhile)
<code>res.savefn</code>	an RData or GDS file name, "" for no saving
<code>res.compress</code>	the compression method for the output file, it should be one of ZIP, ZIP_RA, LZMA, LZMA_RA and none; see compression.gdsn for more details

parallel	FALSE (serial processing), TRUE (multicore processing), a numeric value for the number of cores, or other value; parallel is passed to the argument c1 in seqParallel , see seqParallel for more details
load.balancing	load balancing for the calculation in parallel if TRUE
verbose.pval	NULL or a numeric vector for dividing p-values into the intervals and show the corresponding counts
verbose	if TRUE, show information

Details

For more details of SAIGE algorithm, please refer to the SAIGE paper [Zhou et al. 2018] (see the reference section).

Value

Return a data.frame with the following components if not saving to a file:

id	variant ID in the GDS file;
chr	chromosome;
pos	position;
rs.id	the RS IDs if it is available in the GDS file as a node "annotation/id";
ref	the reference allele;
alt	the alternative allele;
AF.alt	allele frequency for the alternative allele; the minor allele frequency is $\text{pmin}(\text{AF.alt}, 1 - \text{AF.alt})$;
mac	minor allele count; the allele count for the alternative allele is $\text{ifelse}(\text{AF.alt} \leq 0.5, \text{mac}, 2 * \text{num} - \text{mac})$;
num	the number of samples with non-missing genotypes;
beta	beta coefficient, log odds ratio if binary outcomes (alternative allele vs. reference allele);
SE	standard error for beta coefficient;
pval	final p-value (if the Saddlepoint approximation or efficient resampling is applied);
method	"Normal": pval is calculated by assuming asymptotic normality; "SPA": using the Saddlepoint approximation method; "ER": using the efficient resampling
p.norm	p-values based on asymptotic normality (could be 0 if it is too small, e.g., $\text{pnorm}(-50) = 0$ in R; used for checking only
converged	whether the SPA algorithm converges or not for p-values.

Author(s)

Xiuwen Zheng

References

Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolford BN, LeFaive J, VandeHaar P, Gagliano SA, Gifford A, Bastarache LA, Wei WQ, Denny JC, Lin M, Hveem K, Kang HM, Abecasis GR, Willer CJ, Lee S. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat Genet* (2018). Sep;50(9):1335-1341.

See Also

[seqAssocGLMM_SPA](#), [seqSAIGE_LoadPval](#)

Examples

```
# open a GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

# load phenotype
phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, trait.type="binary")

# p-value calculation
a <- seqAssocGLMM_SPA(gdsfile, glmm, mac=10)
head(a)

# close the GDS file
seqClose(gdsfile)
```

seqFitLDpruning

Linkage disequilibrium pruning

Description

Construct LD-pruned SNP sets for genetic relationship matrix (GRM).

Usage

```
seqFitLDpruning(gdsfile, sample.id=NULL, variant.id=NULL,
  ld.threshold=0.1, maf=0.01, missing.rate=0.005, autosome.only=TRUE,
  use.cateMAC=TRUE, num.marker=100L, num.total=100000L, save.gdsfn=NULL,
  seed=200L, parallel=FALSE, parallel.multi=NULL, verbose=TRUE)
```

Arguments

<code>gdsfile</code>	a SeqArray GDS file name, a GDS object for genotypes, or a character vector for a list of GDS file names when genotypes are split by chromosomes
<code>sample.id</code>	NULL for all samples, or sample IDs in GRM
<code>variant.id</code>	a list of variant IDs, used to construct GRM
<code>ld.threshold</code>	the LD threshold; see <code>snpGDS::LDpruning()</code>
<code>maf</code>	minor allele frequency threshold for genotypes in <code>gdsfile</code> (checking $\geq$ maf), if <code>variant.id=NULL</code> ; NaN for no filter
<code>missing.rate</code>	threshold of missing rate (checking $\leq$ missing.rate), if <code>variant.id=NULL</code> ; NaN for no filter
<code>autosome.only</code>	TRUE for using autosomes only

<code>use.cateMAC</code>	FALSE, to use a single global variance ratio; TRUE (equal to <code>use.cateMAC=c(1.5, 2.5, 3.5, 4.5, 5.5, 10.5, 20.5)</code>) for MAC categories (0, 1.5), [1.5, 2.5), ... [10.5, 20.5) and [20.5, Inf); or a numeric vector (strictly increasing) for unique cut points
<code>num.marker</code>	the number of SNPs used to calculate the variance ratio in each MAC category
<code>num.total</code>	the total number of LD-pruned variants excluding ultra rare variants; if the number of variants selected by the process of LD pruning is larger than <code>num.total</code> , the random set is used
<code>save.gdsfn</code>	if a file name is specified, construct a GDS genotype file to include all selected variants
<code>parallel</code>	FALSE (serial processing), TRUE (multicore processing), a numeric value for the number of cores, or other value; <code>parallel</code> is passed to the argument <code>cl</code> in seqParallel , see seqParallel for more details
<code>parallel.multi</code>	only applicable when there are multiple input files in <code>gdsfile</code> and <code>save.gdsfn</code> is used; multiple GDS files can be extracted to create a sub GDS file in parallel via <code>parallel.multi</code> ; if NULL, use <code>parallel</code> instead; <code>parallel.multi</code> could have less CPU cores than <code>parallel</code> to reduce memory usage
<code>seed</code>	an integer passed to <code>set.seed()</code> as a seed for random numbers, or NULL for no action
<code>verbose</code>	if TRUE, show information

Details

This function calls [snpgdsLDpruning](#) in the SNPRelate package to perform linkage disequilibrium (LD) pruning. When `use.cateMAC` is not FALSE, the ultra rare variants will be selected according to the MAC categories, which could be used in the null model fitting.

Value

Returns variant IDs or a list of variant IDs for multiple input GDS files.

Author(s)

Xiuwen Zheng

See Also

[seqFitNullGLMM_SPA](#), [seqAssocGLMM_SPA](#), [snpgdsLDpruning](#)

Examples

```
library(SeqArray)
library(SAIGEgds)

# open a GDS file
gds_fn <- seqExampleFileName("KG_Phase1")

seqFitLDpruning(gds_fn, save.gdsfn="grm.gds")

# delete the temporary file
unlink("grm.gds", force=TRUE)
```

seqFitNullGLMM_SPA *Fit the null model with GRM*

Description

Fit the null model in the mixed model framework with genetic relationship matrix (GRM).

Usage

```
seqFitNullGLMM_SPA(formula, data, gdsfile=NULL, grm.mat=NULL,
  trait.type=c("binary", "quantitative"), sample.col="sample.id", maf=0.01,
  missing.rate=0.01, max.num.snp=1000000L, variant.id=NULL,
  variant.id.varratio=NULL, nsnp.sub.random=2000L, rel.cutoff=0.125,
  inv.norm=c("residuals", "quant", "none"), use.cateMAC=FALSE,
  cateMAC.inc.maf=TRUE, cateMAC.simu=TRUE, use.offset=FALSE, X.transform=TRUE,
  tol=0.02, maxiter=20L, nrun=30L, tolPCG=1e-5, maxiterPCG=500L,
  num.marker=30L, tau.init=c(0,0), traceCVcutoff=0.0025, ratioCVcutoff=0.001,
  geno.sparse=TRUE, num.thread=1L, model.savefn="", seed=200L,
  fork.loading=FALSE, verbose=TRUE)
```

Arguments

formula	an object of class formula (or one that can be coerced to that class), e.g., $y \sim x_1 + x_2$, see lm
data	a data frame for the formulas
gdsfile	a SeqArray GDS filename or a GDS object for genotypes used in the GRM calculation; see details
grm.mat	NULL, a user-defined GRM or an object of 'snpgdsGRMClass' returned from <code>SNPRelate::snpgdsGRM()</code> : a dense numeric matrix or a sparse symmetric matrix 'sparseMatrix' defined in Matrix; colnames and rownames should be sample IDs; or TRUE, call <code>seqFitSparseGRM()</code> to get a sparse GRM; see details
trait.type	"binary" for binary outcomes, "quantitative" for continuous outcomes
sample.col	the column name of sample IDs corresponding to the GDS file
maf	minor allele frequency threshold for genotypes in gdsfile (checking $\geq$ maf), if <code>variant.id=NULL</code> ; NaN for no filter
missing.rate	threshold of missing rate (checking $\leq$ missing.rate), if <code>variant.id=NULL</code> ; NaN for no filter
max.num.snp	the maximum number of SNPs used, or -1 for no limit
variant.id	a list of variant IDs, considered to be used in GRM; or NULL, all variants in the GDS file to be the candidate variants
variant.id.varratio	a list of variant IDs, to be used in the variance ratio estimation; or NULL to use the candidate variants according to <code>variant.id</code>
nsnp.sub.random	used in <code>seqFitSparseGRM()</code> when <code>grm.mat=TRUE</code> : the number of SNP markers randomly selected from the candidate variants for the initial scan of relatedness
rel.cutoff	relatedness threshold for treating two individuals as unrelated (check $\geq$ rel.cutoff), NaN or $-\text{Inf}$ for no threshold; only applicable when <code>grm.mat=TRUE</code>

use.cateMAC	FALSE, to use a single global variance ratio; TRUE (equal to use.cateMAC=c(1.5, 2.5, 3.5, 4.5, 5.5, 10.5, 20.5)) for MAC categories (0, 1.5), [1.5, 2.5), ... [10.5, 20.5) and [20.5, Inf); or a numeric vector (strictly increasing) for unique cut points
cateMAC.inc.maf	TRUE to include a MAC cut point according to MAF=maf, or a numeric vector for MAF; only applicable if use.cateMAC is not FALSE
cateMAC.simu	TRUE for using simulated independent genotypes under Hardy-Weinberg equilibrium if there are no enough SNP markers in the MAC category; only applicable if use.cateMAC is not FALSE
inv.norm	"residuals" (by default), perform the inverse normal transformation on the residuals after fitting the fixed effects; "quant", perform the inverse normal transformation on the outcome variable directly (the same behavior as the SAIGE package); "none", no transformation. If inv.norm=TRUE, perform inv.norm="residuals"; if inv.norm=FALSE, it is as the same as inv.norm="none"; See the reference for more discussion [Sofer et al., 2019]
use.offset	if TRUE, use the estimated residual offset to avoid calculating each fixed effect coefficient
X.transform	if TRUE, perform QR decomposition on the design matrix
tol	overall tolerance for model fitting
maxiter	the maximum number of iterations for model fitting; maxiter=0 for using a fixed tau parameter in tau.init
nrun	the number of random vectors in the trace estimation
tolPCG	tolerance of PCG iterations
maxiterPCG	the maximum number of PCG iterations
num.marker	the number of SNPs used to calculate the variance ratio
tau.init	a 2-length numeric vector, the initial values for variance components, tau; for binary traits, the first element is always be set to 1. if tau.init is not specified, the second element will be 0.5 for binary traits
traceCVcutoff	the threshold for coefficient of variation (CV) for the trace estimator, and the number of runs for trace estimation will be increased until the CV is below the threshold
ratioCVcutoff	the threshold for coefficient of variation (CV) for estimating the variance ratio, and the number of randomly selected markers will be increased until the CV is below the threshold
geno.sparse	if TRUE (by default), store the sparse structure for genotypes; otherwise, save genotypes in a 2-bit dense matrix; see details
num.thread	the number of threads, 1 by default
model.savefn	the filename of model output, R data file '.rda', '.RData', or '.rds'
seed	an integer passed to set.seed() as a seed for random numbers, or NULL for no action
fork.loading	load genotypes via parallel or not; multiple processes can reduce loading time of genotypes, but may double the memory usage
verbose	if TRUE, show information

Details

Utilizing the sparse structure of genotypes could significantly improve the computational efficiency of model fitting, but it also increases the memory usage. For more details of SAIGE algorithm, please refer to the SAIGE paper [Zhou et al., 2018] (see the reference section).

Value

Returns a list with the following components:

<code>coefficients</code>	the beta coefficients for fixed effects;
<code>tau</code>	a numeric vector of variance components 'Sigma_E' and 'Sigma_G';
<code>linear.predictors</code>	the linear fit on link scale;
<code>fitted.values</code>	fitted values from objects returned by modeling functions using <code>glm.fit</code> ;
<code>residuals</code>	residuals;
<code>cov</code>	covariance matrix of beta coefficients;
<code>converged</code>	whether the model is fitted or not;
<code>obj.noK</code>	internal use, returned object from the SPAtest package;
<code>var.ratio</code>	a data.frame with columns 'id' (variant.id), 'maf' (minor allele frequency), 'mac' (minor allele count), 'var1' (the variance of score statistic), 'var2' (a variance estimate without accounting for estimated random effects) and 'ratio' (var1/var2, estimated variance ratio for variance approximation);
<code>trait.type</code>	either "binary" or "quantitative";
<code>sample.id</code>	the sample IDs used in the model fitting;
<code>variant.id</code>	the variant IDs used in the model fitting.

Author(s)

Xiuwen Zheng

References

Zhou W, Nielsen JB, Fritsche LG, Dey R, Gabrielsen ME, Wolkord BN, LeFaive J, VandeHaar P, Gagliano SA, Gifford A, Bastarache LA, Wei WQ, Denny JC, Lin M, Hveem K, Kang HM, Abecasis GR, Willer CJ, Lee S. Efficiently controlling for case-control imbalance and sample relatedness in large-scale genetic association studies. *Nat Genet* (2018). Sep;50(9):1335-1341.

Zhou W, Zhao Z, Nielsen JB, Fritsche LG, LeFaive J, Taliun SAG, Bi W, Gabrielsen ME, Daly MJ, Neale BM, Hveem K, Abecasis GR, Willer CJ, et al. Scalable generalized linear mixed model for region-based association tests in large biobanks and cohorts. *Nat Genet*. 2020; 52: 634-9.

See Also

[seqAssocGLMM_SPA](#)

Examples

```
# open a GDS file
fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(fn)

# load phenotype
phenofn <- system.file("extdata", "pheno.txt.gz", package="SAIGEgds")
pheno <- read.table(phenofn, header=TRUE, as.is=TRUE)
head(pheno)

# fit the null model
glmm <- seqFitNullGLMM_SPA(y ~ x1 + x2, pheno, gdsfile, trait.type="binary")
glmm

# close the GDS file
seqClose(gdsfile)
```

seqFitSparseGRM

*Sparse & dense genetic relationship matrix***Description**

Construct sparse and dense genetic relationship matrix (GRM).

Usage

```
seqFitSparseGRM(gdsfile, sample.id=NULL, variant.id=NULL, nsnp.sub.random=2000L,
  rel.cutoff=0.125, maf=0.01, missing.rate=0.005, num.thread=1L,
  return.ID=FALSE, seed=200L, verbose=TRUE)
seqFitDenseGRM(gdsfile, sample.id=NULL, variant.id=NULL, maf=0.01,
  missing.rate=0.005, num.thread=1L, use.double=TRUE, return.ID=FALSE,
  verbose=TRUE)
```

Arguments

<code>gdsfile</code>	a SeqArray GDS file name or a GDS object for genotypes used in the GRM calculation; see details
<code>sample.id</code>	NULL for all samples, or sample IDs in GRM
<code>variant.id</code>	candidate variant IDs used for constructing GRM; or NULL for using all available candidate variants
<code>nsnp.sub.random</code>	the number of SNP markers randomly selected from the candidate variants for the initial scan of relatedness; if <code>nsnp.sub.random=0</code> , use all candidate SNPs
<code>rel.cutoff</code>	relatedness threshold for treating two individuals as unrelated (check $\geq$ <code>rel.cutoff</code>); NaN or $-\infty$ for no threshold
<code>maf</code>	minor allele frequency threshold for genotypes in <code>gdsfile</code> (checking $\geq$ <code>maf</code>), if <code>variant.id=NULL</code> ; NaN for no filter
<code>missing.rate</code>	threshold of missing rate (checking $\leq$ <code>missing.rate</code>), if <code>variant.id=NULL</code> ; NaN for no filter
<code>num.thread</code>	the number of threads, 1 by default

<code>use.double</code>	TRUE for using 64-bit double precision to calculate GRM; otherwise, to use 32-bit single precision
<code>return.ID</code>	if TRUE, return the IDs for samples, the full variant set and the subset of variants
<code>seed</code>	an integer passed to <code>set.seed()</code> as a seed for random numbers, or NULL for no action
<code>verbose</code>	if TRUE, show information

Details

The genetic relationship matrix (GRM) is defined as $\$grm_{ij} = \text{avg}_l [(g_{il} - 2*p_l)*(g_{jl} - 2*p_l) / 2*p_l*(1 - p_l)]$ for individuals i, j and locus l , where $\$g_{il}$ is 0, 1 or 2, and $\$p_l$ is the allele frequency at locus l . The missing genotypes are dropped from the calculation.

Value

If `return.ID=TRUE`, returns a list with `sample.id` for sample IDs, `variant.id` for the full set of variants, `variant.sub.id` for the subset of variants, and the GRM matrix. Otherwise, it returns a sparse or dense symmetric matrix for GRM, with sample IDs in `colnames()` and `rownames()`.

Author(s)

Xiuwen Zheng

See Also

[seqFitNullGLMM_SPA](#), [seqFitLDpruning](#)

Examples

```
library(Matrix)

# open a GDS file
gds_fn <- system.file("extdata", "grm1k_10k_snp.gds", package="SAIGEgds")
gdsfile <- seqOpen(gds_fn)

seqSetFilter(gdsfile, variant.sel=1:100)
m <- seqFitSparseGRM(gdsfile, rel.cutoff=0.125)
is(m)
nnzero(m)                # num of non-zero
nnzero(m) / prod(dim(m)) # percentage of non-zero

m <- seqFitDenseGRM(gdsfile)
str(m)

# close the GDS file
seqClose(gdsfile)
```

seqSAIGE_LoadPval	<i>Load the association results</i>
-------------------	-------------------------------------

Description

Load the association results from an RData, RDS or GDS file.

Usage

```
seqSAIGE_LoadPval(fn, varnm=NULL, index=NULL, verbose=TRUE)
```

Arguments

fn	RData, RDS or GDS file names, merging datasets if multiple files
varnm	NULL, or a character vector to include the column names; e.g., <code>c("chr", "position", "rs.id", "ref", "alt", "pval")</code>
index	NULL, or a logical/numeric vector for a set of rows
verbose	if TRUE, show information

Value

Return a `data.frame` including p-values.

Author(s)

Xiuwen Zheng

See Also

[seqFitNullGLMM_SPA](#), [seqAssocGLMM_SPA](#)

Examples

```
(fn <- system.file("unitTests", "saige_pval.rds", package="SAIGEgds"))
pval <- seqSAIGE_LoadPval(fn)

names(pval)
# [1] "id"      "chr"      "pos"      "rs.id"    "ref"
# [6] "alt"     "AF.alt"   "AC.alt"   "num"      "beta"
# [11] "SE"      "pval"     "pval.noadj" "converged"

head(pval)
```

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