Package: statgenQTLxT (via r-universe)

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Type Package

Title Multi-Trait and Multi-Trial Genome Wide Association Studies

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Description Fast multi-trait and multi-trail Genome Wide Association Studies (GWAS) following the method described in Zhou and Stephens. (2014), <doi:10.1038/nmeth.2848>. One of a series of statistical genetic packages for streamlining the analysis of typical plant breeding experiments developed by Biometris.

License GPL-3

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`gDataDropsRestr` *Subset of DROPS data for use in examples*

Description

A `gData` object based on a subset of the DROPS data set used in the statgenGWAS package. The data is restricted to 3 traits and 10% (just over 4000) of the available markers. For a full description of the data set see `dropsData`.

Usage

```
gDataDropsRestr
```

Format

An object of class `gData` of length 5.

Source

doi:10.15454/IASSTN

References

Millet, E. J., Pommier, C., et al. (2019). A multi-site experiment in a network of European fields for assessing the maize yield response to environmental scenarios - Data set. doi:10.15454/IASSTN

Ganal MW, et al. (2011) A Large Maize (Zea mays L.) SNP Genotyping Array: Development and Germplasm Genotyping, and Genetic Mapping to Compare with the B73 Reference Genome. PLoS ONE 6(12): e28334. doi:10.1371/journal.pone.0028334

runMultiTraitGwas *Perform multi-trait GWAS*

Description

runMultiTraitGwas performs multi-trait or multi-environment Genome Wide Association mapping on phenotypic and genotypic data contained in a gData object.

Usage

```
runMultiTraitGwas(
  gData,
  trials = NULL,
  traits = NULL,
  covar = NULL,
  snpCov = NULL,
  kin = NULL,
  kinshipMethod = c("astle", "IBS", "vanRaden", "identity"),
  GLSMethod = c("single", "multi"),
  estCom = FALSE,
  useMAF = TRUE,
  MAF = 0.01,
  MAC = 10,
  genomicControl = FALSE,
  fitVarComp = TRUE,
  covModel = c("unst", "pw", "fa"),
  VeDiag = TRUE,
  maxIter = 2e+05,
  mG = 1,
  mE = 1,
  Vg = NULL,
  Ve = NULL,
  thrType = c("bonf", "fixed", "small", "fdr"),
  alpha = 0.05,
  LODThr = 4,
  nSnpLOD = 10,
  pThr = 0.05,
  rho = 0.4,
  sizeInclRegion = 0,
  minR2 = 0.5,
  parallel = FALSE,
  nCores = NULL
)
```

Arguments

gData	An object of class gData containing at least map, markers and pheno. The latter should not contain missing values. Multi-trait or multi-environment GWAS is

performed for all variables in pheno.

trials — A vector specifying the environment on which to run GWAS. This can be either a numeric index or a character name of a list item in pheno.

traits — A vector of traits on which to run GWAS. These can be either numeric indices or character names of columns in pheno. If NULL, GWAS is run on all traits.

covar — An optional vector of covariates taken into account when running GWAS. These can be either numeric indices or character names of columns in covar in gData. If NULL, no covariates are used. An intercept is included automatically (and should not be assigned as covariate). SNP-covariates should be assigned using the snpCov parameter.

snpCov — An optional character vector of SNP-names to be included as covariates. SNP-names should match those used in gData.

kin — An optional kinship matrix or list of kinship matrices. These matrices can be from the matrix class as defined in the base package or from the dsyMatrix class, the class of symmetric matrices in the Matrix package.
If GLSMethod = "single" then one matrix should be provided, if GLSMethod = "multi", a list of chromosome specific matrices of length equal to the number of chromosomes in map in gData.
If NULL then matrix kinship in gData is used.
If both kin is provided and gData contains a matrix kinship then kin is used.

kinshipMethod — An optional character indicating the method used for calculating the kinship matrix(ces). Currently "astle" (Astle and Balding, 2009), "IBS", "vanRaden" (VanRaden, 2008), and "identity" are supported. If a kinship matrix is supplied either in gData or in parameter kin, kinshipMethod is ignored.

GLSMethod — A character string indicating the method used to estimate the marker effects. Either single for using a single kinship matrix, or multi for using chromosome specific kinship matrices.

estCom — Should the common SNP-effect model be fitted? If TRUE not only the SNP-effects but also the common SNP-effect and QTL x E effect are estimated.

useMAF — Should the minor allele frequency be used for selecting SNPs for the analysis. If FALSE, the minor allele count is used instead.

MAF — The minor allele frequency (MAF) threshold used in GWAS. A numerical value between 0 and 1. SNPs with MAF below this value are not taken into account in the analysis, i.e. p-values and effect sizes are put to missing (NA). Ignored if useMAF is FALSE.

MAC — A numerical value. SNPs with minor allele count below this value are not taken into account for the analysis, i.e. p-values and effect sizes are set to missing (NA). Ignored if useMAF is TRUE.

genomicControl — Should genomic control correction as in Devlin and Roeder (1999) be applied?

fitVarComp — Should the variance components be fitted? If FALSE, they should be supplied in Vg and Ve.

covModel — A character string indicating the covariance model for the genetic background (Vg) and residual effects (Ve); see details. Either unst for unstructured for both Vg and Ve (as in Zhou and Stephens (2014)), pw for unstructered for both Vg

	and Ve (pairwise, as in Furlotte and Eskin (2013)) or `fa` for factor-analytic for both Vg and Ve. Ignored if `fitVarComp = FALSE`
`VeDiag`	Should there be environmental correlations if covModel = "unst" or "pw"? If traits are measured on the same individuals, put `TRUE`.
`maxIter`	An integer for the maximum number of iterations. Only used when `covModel = "fa"`.
`mG`	An integer. The order of the genetic part of the factor analytic model. Only used when `covModel = "fa"`.
`mE`	An integer. The order of the environmental part of the factor analytic model. Only used when `covModel = "fa"`.
`Vg`	An optional matrix with genotypic variance components. `Vg` should have row and column names corresponding to the column names of `gData$pheno`. It may contain additional rows and columns which will be ignored. Ignored if fitVarComp = `TRUE`.
`Ve`	An optional matrix with environmental variance components. `Ve` should have row names column names corresponding to the column names of `gData$pheno`. It may contain additional rows and columns which will be ignored. Ignored if fitVarComp = `TRUE`.
`thrType`	A character string indicating the type of threshold used for the selection of candidate loci. Either `bonf` for using the Bonferroni threshold, a LOD-threshold of $-log10(alpha/p)$, where p is the number of markers and alpha can be specified in `alpha`, `fixed` for a self-chosen fixed LOD-threshold, specified in `LODThr` or `small`, the LOD-threshold is chosen such as the SNPs with the `nSnpLOD` smallest p-values are selected. `nSnpLOD` can be specified.
`alpha`	A numerical value used for calculating the LOD-threshold for `thrType` = "bonf" and the significant p-Values for `thrType` = "fdr".
`LODThr`	A numerical value used as a LOD-threshold when `thrType` = "fixed".
`nSnpLOD`	A numerical value indicating the number of SNPs with the smallest p-values that are selected when `thrType` = "small".
`pThr`	A numerical value just as the cut off value for p-Values for `thrType` = "fdr".
`rho`	A numerical value used a the minimum value for SNPs to be considered correlated when using `thrType` = "fdr".
`sizeInclRegion`	An integer. Should the results for SNPs close to significant SNPs be included? If so, the size of the region in centimorgan or base pairs. Otherwise 0.
`minR2`	A numerical value between 0 and 1. Restricts the SNPs included in the region close to significant SNPs to only those SNPs that are in sufficient Linkage Disequilibrium (LD) with the significant snp, where LD is measured in terms of R^2. If for example `sizeInclRegion` = 200000 and `minR2` = 0.5, then for every significant SNP also those SNPs whose LD (R^2) with the significant SNP is at least 0.5 AND which are at most 200000 away from this significant snp are included. Ignored if `sizeInclRegion` = 0.
`parallel`	Should the computation of variance components be done in parallel? Only used if `covModel = "pw"`. A parallel computing environment has to be setup by the user.

`nCores` A numerical value indicating the number of cores to be used by the parallel part of the algorithm. If `NULL` the number of cores used will be equal to the number of cores available on the machine - 1.

Value

An object of class `GWAS`.

Details

runMultiTraitGwas estimates the effect of a SNP in different trials or on different traits, one SNP at a time. Genetic and residual covariances are fitted only once, for a model without SNPs. Following the diagonalization scheme of Zhou and Stephens (2014), the following model is fit

$$Y = \begin{pmatrix} Y_1 \\ \vdots \\ Y_p \end{pmatrix} = \begin{pmatrix} X_1\gamma_1 \\ \vdots \\ X_p\gamma_p \end{pmatrix} + \begin{pmatrix} x_1\beta_1 \\ \vdots \\ x_p\beta_p \end{pmatrix} + \begin{pmatrix} G_1 \\ \vdots \\ G_p \end{pmatrix} + \begin{pmatrix} E_1 \\ \vdots \\ E_p \end{pmatrix}$$

where Y is a $np \times 1$ vector of phenotypic values for n genotypes and p traits or trials. x is the $n \times 1$ vector of scores for the marker under consideration, and X the $n \times q$ design matrix for the other covariates. By default only a trait (environment) specific intercept is included. The vector of genetic background effects ($\begin{pmatrix} G_1 \\ \vdots \\ G_p \end{pmatrix}$) is Gaussian with zero mean and covariance $V_g \otimes K$, where V_g is a $p \times p$ matrix of genetic (co)variances, and K an $n \times n$ kinship matrix. Similarly, the residual errors ($\begin{pmatrix} E_1 \\ \vdots \\ E_p \end{pmatrix}$) have covariance $V_e \otimes I_n$, for a $p \times p$ matrix V_e of residual (co)variances.

Hypotheses for the SNP-effects

For each SNP, the null-hypothesis $\beta_1 = \cdots = \beta_p = 0$ is tested, using the likelihood ratio test (LRT) described in Zhou and Stephens (2014). If `estCom = TRUE`, additional tests for a common effect and for QTL x E are performed, using the parameterization $\beta_j = \alpha + \alpha_j (1 \leq j \leq p)$. As in Korte et al (2012), we use likelihood ratio tests, but not restricted to the bivariate case. For the common effect, we fit the reduced model $\beta_j = \alpha$, and test if $\alpha = 0$. For QTL-by-environment interaction, we test if $\alpha_1 = \cdots = \alpha_p = 0$.

Models for the genetic and residual covariance

V_g and V_e can be provided by the user (`fitVarComp = FALSE`); otherwise one of the following models is used, depending on covModel. If `covModel = "unst"`, an unstructured model is assumed, as in Zhou and Stephens (2014): V_g and V_e can be any positive-definite matrix, requiring a total of $p(p+1)/2$ parameters per matrix. If `covModel = "fa"`, a factor-analytic model is fitted using an EM-algorithm, as in Millet et al (2016). V_g and V_e are assumed to be of the form $WW^t + D$, where W is a $p \times m$ matrix of factor loadings and D a diagonal matrix with trait or environment specific values. m is the order of the model, and the parameters `mG` and `mE` specify the order used for respectively V_g and V_e. `maxIter` sets the maximum number of iterations used in the EM-algorithm. Finally, if `covModel = "pw"`, V_g and V_e are estimated 'pairwise', as in Furlotte and Eskin (2015).

Looping over pairs of traits or trials $1 \leq j < k \leq p$, $V_g[j,k] = V_g[k,j]$ and $V_e[j,k] = V_e[k,j]$ are estimated assuming a bivariate mixed model. The diagonals of V_g and V_e are fitted assuming univariate mixed models. If the resulting V_g or V_e is not positive-definite, they are replaced by the nearest positive-definite matrix. In case `covModel = "unst"` or `"pw"` it is possible to assume that V_e is diagonal (`VeDiag = TRUE`)

References

Dahl et al. (2013). Network inference in matrix-variate Gaussian models with non-independent noise. arXiv preprint arXiv:1312.1622.

Furlotte, N.A. and Eskin, E. (2015). Efficient multiple-trait association and estimation of genetic correlation using the matrix-variate linear mixed model. Genetics, May 2015, Vol.200-1, p. 59-68.

Korte et al. (2012). A mixed-model approach for genome-wide association studies of correlated traits in structured populations. Nature Genetics, 44(9), 1066–1071. doi:10.1038/ng.2376

Millet et al. (2016). Genome-wide analysis of yield in Europe: allelic effects as functions of drought and heat scenarios. Plant Physiology, pp.00621.2016. doi:10.1104/pp.16.00621

Thoen et al. (2016). Genetic architecture of plant stress resistance: multi-trait genome-wide association mapping. New Phytologist, 213(3), 1346–1362. doi:10.1111/nph.14220

Zhou, X. and Stephens, M. (2014). Efficient multivariate linear mixed model algorithms for genome-wide association studies. Nature Methods, February 2014, Vol. 11, p. 407–409.

Examples

```
## First create a gData object.
## See the vignette for a detailed description.
## Here we use the gData object included in the package

## Run multi-trait GWAS
## Use a factor analytic model to estimate variance components.

mtg0 <- runMultiTraitGwas(gDataDropsRestr,
                          trial = "Mur13W",
                          covModel = "fa")


## Plot the results.
## For details on the different plots see plot.GWAS

plot(mtg0, plotType = "qq")
plot(mtg0, plotType = "manhattan")
plot(mtg0, plotType = "qtl", yThr = 3.5)


## Run multi-trait GWAS
## Use a pairwise model to estimate variance components.
## Estimate common effects and set a fixed threshold for significant SNPs

mtg1 <- runMultiTraitGwas(gDataDropsRestr,
                          trial = "Mur13W",
                          covModel = "pw",
```

```
                          estCom = TRUE,
                          thrType = "fixed",
                          LODThr = 3)


## Run multi-trait GWAS
## Use an unstructured model to estimate variance components.
## Identify the 5 SNPs with smallest p-values as significant SNPs.
## Compute the kinship matrix using the vanRaden method.

mtg2 <- runMultiTraitGwas(gDataDropsRestr,
                          trial = "Mur13W",
                          kinshipMethod = "vanRaden",
                          covModel = "unst",
                          thrType = "small",
                          nSnpLOD = 5)
```

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