Package 'gwsem'

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Type Package

Title Genome-Wide Structural Equation Modeling

Version 0.1.17

Description Melds genome-wide association tests with structural equation modeling (SEM) using 'OpenMx'. This package contains low-level C/C++ code to rapidly read genetic data encoded in U.K. Biobank or 'plink' formats. Prebuilt modeling options include one and two factor models. Alternately, analyses may utilize arbitrary, user-provided SEMs. See Verhulst, Maes, & Neale (2017) <doi:10.1007/s10519-017-9842-6> for details. An updated manuscript is in preparation.

License GPL (>= 3)

URL https://github.com/jpritikin/gwsem

BugReports https://github.com/jpritikin/gwsem/issues

Depends R (>= 3.5),
OpenMx (>= 2.15.5)

Imports data.table,
methods,
qqman,
Rcpp,
lifecycle

Suggests testthat (>= 2.1.0),
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SystemRequirements GNU make

R topics documented:

`gwsem-package` *Genome-wide Structural Equation Modeling*

Description

Psychometricians have long known that little information can be gleened from a single item. Hence, there is a long-standing tradition in education, psychology, and many other fields to use more than one item to measure a latent trait. For example, a math test will always consist of more than one problem (or the single problem with consist of many parts).

Phenotypic data gathered at the same time as genetic data sometimes contains multiple items that measure different aspects of the same latent construct. However, due to the astronomic number of single nucleotide polymorphisms (SNPs) to test, fast analysis methods are generally preferred with much of the prior research employing regression. Regression is fast, but can only predict a single item at time. Hence, associations with rich phenotypic data cannot be properly investigated.

gwsem contains low-level C/C++ code to permit OpenMx to rapidly read genetic data encoded in U.K. Biobank or plink formats. The association between SNPs and a factor model can be explored.

`buildItem` *Build a model suitable for a single item genome-wide association study*

Description

Maturing

Usage

```
buildItem(
  phenoData,
  depVar,
  covariates = NULL,
  ...,
  fitfun = c("WLS", "ML"),
  minMAF = 0.01,
  gxe = NULL,
  exogenous = NA
)
```

Arguments

`phenoData`	A matrix or data.frame which provides all of the phenotype data to the model (both the items and the covariates). Data should be constructed so that variables are on the columns and individuals are on the rows.
`depVar`	the name of items to predict
`covariates`	A vector of data column names (from `phenoData`) to use as covariates (e.g. age, sex, and ancestry principle components).
`...`	Not used. Forces remaining arguments to be specified by name.
`fitfun`	A character string naming the fit function used to optimize the model. Must be either 'WLS' or 'ML'.
`minMAF`	A numerical value that specifies the minimum valid minor allele frequency for a SNP. SNPs with minimum minor allele frequencies that are smaller than the minMAF value will not be analyzed. Only used when `fitfun=WLS`
`gxe`	a vector of data column names. Creates additional data columns named paste0('snp_',columnName) that are the product of the SNP and the data in columnName. Add these new data columns to your list of covariates to use them as covariates.
`exogenous`	logical value. Whether the covariates should be treated as exogenous (TRUE) or endogenous (FALSE).

Details

This function is designed to be passed to the GWAS function. The model that is returned, however, is a valid OpenMx model and can be fitted using mxRun or mxTryHard. Models should be tested to ensure that they are identified and fit the data as expected to avoid unnecessary computation of an invalid model.

There is no limit on the number of items that can be included, but more items will exponentially increase computation time. To address this, we suggest that users use the 'WLS' fit function. The 'WLS' fit function is dramatically faster than the 'ML' fit function, especially for ordinal items.

Ordinal indicator thresholds are setup by setupThresholds. Exogenous covariates adjustments are setup by setupExogenousCovariates. You can plot the model using omxGraphviz.

Value

A MxModel

WLS Technical Note

When the `depVar` item is/are continuous, covariates are endogenous (the default), and the fit function is `WLS` then the `cumulants` method is used to create observed summary statistics (see mxFitFunctionWLS). In other cases, the `marginals` method is used. The `cumulants` method is more accurate than `marginals`. The difference in accuracy becomes vivid when comparing estimates against the `ML` fit function.

See Also

Other model builder: `buildOneFacRes()`, `buildOneFac()`, `buildTwoFac()`

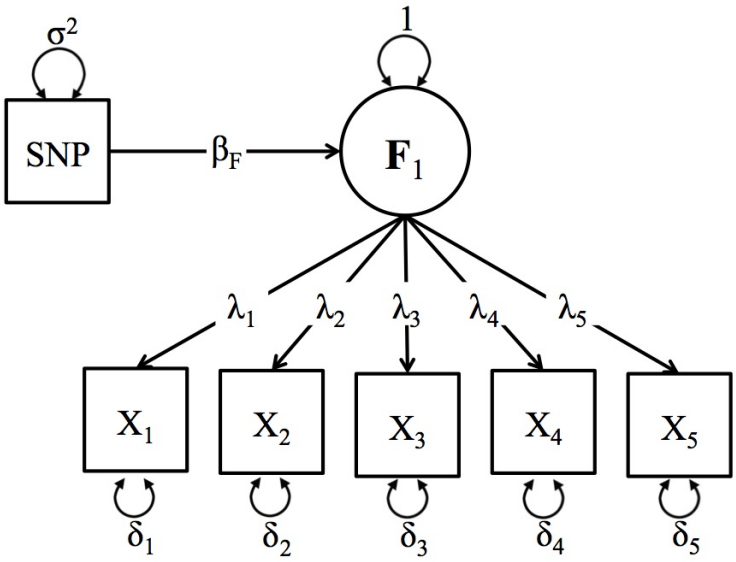
Examples

```
pheno <- data.frame(anxiety=cut(rnorm(500), c(-Inf, -.5, .5, Inf),
                    ordered_result = TRUE))
m1 <- buildItem(pheno, 'anxiety')
```

`buildOneFac` *Build a model suitable for a single factor genome-wide association study*

Description

Maturing The `buildOneFac` function is used to specify a single factor latent variable model where the latent variable is predicted by a genomic variant such as a single nucleotide polymorphism, as



well as range of covariates.

Usage

```
buildOneFac(
  phenoData,
  itemNames,
  covariates = NULL,
  ...,
  fitfun = c("WLS", "ML"),
  minMAF = 0.01,
  gxe = NULL,
  exogenous = NA
)
```

Arguments

`phenoData`	A matrix or data.frame which provides all of the phenotype data to the model (both the items and the covariates). Data should be constructed so that variables are on the columns and individuals are on the rows.
`itemNames`	A vector of phenotypic item names (from `phenoData`) that load on the latent factor.
`covariates`	A vector of data column names (from `phenoData`) to use as covariates (e.g. age, sex, and ancestry principle components).
`...`	Not used. Forces remaining arguments to be specified by name.
`fitfun`	A character string naming the fit function used to optimize the model. Must be either 'WLS' or 'ML'.
`minMAF`	A numerical value that specifies the minimum valid minor allele frequency for a SNP. SNPs with minimum minor allele frequencies that are smaller than the minMAF value will not be analyzed. Only used when `fitfun=WLS`

gxe	a vector of data column names. Creates additional data columns named paste0('snp_',columnName) that are the product of the SNP and the data in columnName. Add these new data columns to your list of covariates to use them as covariates.
exogenous	logical value. Whether the covariates should be treated as exogenous (TRUE) or endogenous (FALSE).

Details

This function is designed to be passed to the GWAS function. The model that is returned, however, is a valid OpenMx model and can be fitted using mxRun or mxTryHard. Models should be tested to ensure that they are identified and fit the data as expected to avoid unnecessary computation of an invalid model.

There is no limit on the number of items that can be included, but more items will exponentially increase computation time. To address this, we suggest that users use the 'WLS' fit function. The 'WLS' fit function is dramatically faster than the 'ML' fit function, especially for ordinal items.

Ordinal indicator thresholds are setup by setupThresholds. Exogenous covariates adjustments are setup by setupExogenousCovariates. You can plot the model using omxGraphviz.

Value

`buildOneFac` returns an MxModel object that can serve as input for the GWAS function.

See Also

Other model builder: `buildItem()`, `buildOneFacRes()`, `buildTwoFac()`

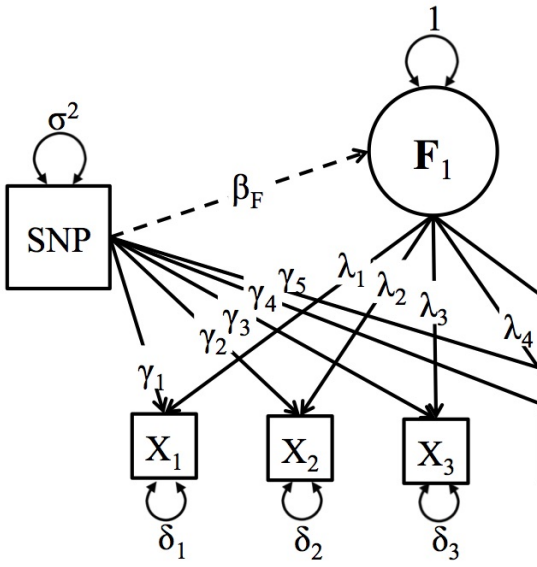
Examples

```
pheno <- list()
for (i in 1:5) pheno[[paste0('i',i)]] <- rnorm(500)
pheno <- as.data.frame(pheno)
buildOneFac(pheno, colnames(pheno))
```

`buildOneFacRes` *Build a model suitable for a single factor residual genome-wide association study*

Description

Maturing The `buildOneFacRes` function is used to specify a single factor latent variable model where a combination of items as well as the latent variable may be predicted by a genomic variant



such as a single nucleotide polymorphism, as well as range of covariates.

Usage

```
buildOneFacRes(
  phenoData,
  itemNames,
  factor = F,
  res = itemNames,
  covariates = NULL,
  ...,
  fitfun = c("WLS", "ML"),
  minMAF = 0.01,
  gxe = NULL,
  exogenous = NA
)
```

Arguments

phenoData	A matrix or data.frame which provides all of the phenotype data to the model (both the items and the covariates). Data should be constructed so that variables are on the columns and individuals are on the rows.
itemNames	A vector of phenotypic item names (from phenoData) that load on the latent factor.
factor	A logical expression (FALSE or TRUE) indicating whether to estimate a regression pathway from the SNP to the latent factor (default FALSE).
res	A character vector of phenotypic item names that indicate which specific items the user wishes to regress on the SNP. The default is to regress all of the items on the SNP.
covariates	A vector of data column names (from phenoData) to use as covariates (e.g. age, sex, and ancestry principle components).

...	Not used. Forces remaining arguments to be specified by name.
fitfun	A character string naming the fit function used to optimize the model. Must be either 'WLS' or 'ML'.
minMAF	A numerical value that specifies the minimum valid minor allele frequency for a SNP. SNPs with minimum minor allele frequencies that are smaller than the minMAF value will not be analyzed. Only used when fitfun=WLS
gxe	a vector of data column names. Creates additional data columns named paste0('snp_',columnName) that are the product of the SNP and the data in columnName. Add these new data columns to your list of covariates to use them as covariates.
exogenous	logical value. Whether the covariates should be treated as exogenous (TRUE) or endogenous (FALSE).

Details

Be aware that a latent variable model is not identified if all of the residuals as well as the latent variable are simultaneously predicted by the SNP. Specifically, if users wish to use the SNP to predict the latent variable, they much choose at least one (and preferably more that one) item to not be predicted by the SNP.

This function is designed to be passed to the GWAS function. The model that is returned, however, is a valid OpenMx model and can be fitted using mxRun or mxTryHard. Models should be tested to ensure that they are identified and fit the data as expected to avoid unnecessary computation of an invalid model.

There is no limit on the number of items that can be included, but more items will exponentially increase computation time. To address this, we suggest that users use the 'WLS' fit function. The 'WLS' fit function is dramatically faster than the 'ML' fit function, especially for ordinal items.

Ordinal indicator thresholds are setup by setupThresholds. Exogenous covariates adjustments are setup by setupExogenousCovariates. You can plot the model using omxGraphviz.

Value

buildOneFacRes returns an MxModel object that can serve as input for the GWAS function.

See Also

Other model builder: buildItem(), buildOneFac(), buildTwoFac()

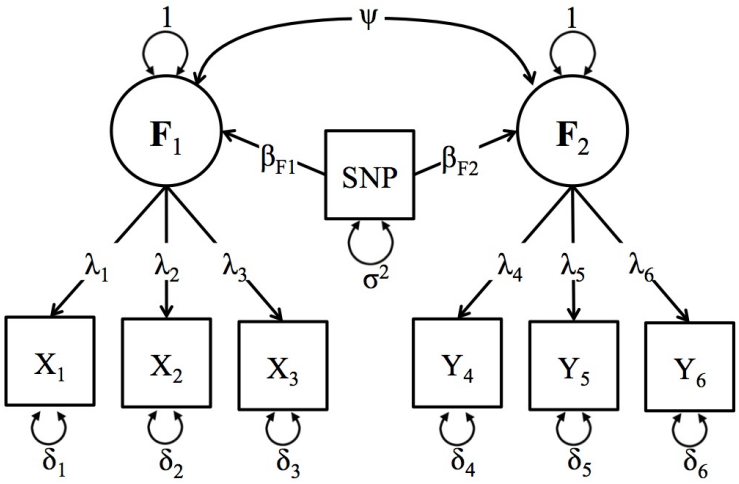
Examples

```
pheno <- list()
for (i in 1:5) pheno[[paste0('i',i)]] <- rnorm(500)
pheno <- as.data.frame(pheno)
buildOneFacRes(pheno, colnames(pheno))
```

buildTwoFac *Build a model suitable for a two factor genome-wide association study*

Description

Maturing The buildTwoFac function is used to specify a model with two latent variables where each latent variable is simultaneously predicted by a genomic variant such as a single nucleotide polymorphism, as well as range of covariates. The model allows the latent variables to correlate to accomodate comorbidity between latent traits.



Usage

```
buildTwoFac(
  phenoData,
  F1itemNames,
  F2itemNames,
  covariates = NULL,
  ...,
  fitfun = c("WLS", "ML"),
  minMAF = 0.01,
  gxe = NULL,
  exogenous = NA
)
```

Arguments

phenoData	A matrix or data.frame which provides all of the phenotype data to the model (both the items and the covariates). Data should be constructed so that variables are on the columns and individuals are on the rows.
F1itemNames	A vector of phenotypic item names (from phenoData) that load on the first latent factor.

F2itemNames	a vector of phenotypic item names (from phenoData) that load on the second latent factor.
covariates	A vector of data column names (from phenoData) to use as covariates (e.g. age, sex, and ancestry principle components).
...	Not used. Forces remaining arguments to be specified by name.
fitfun	A character string naming the fit function used to optimize the model. Must be either 'WLS' or 'ML'.
minMAF	A numerical value that specifies the minimum valid minor allele frequency for a SNP. SNPs with minimum minor allele frequencies that are smaller than the minMAF value will not be analyzed. Only used when fitfun=WLS
gxe	a vector of data column names. Creates additional data columns named paste0('snp_',columnName) that are the product of the SNP and the data in columnName. Add these new data columns to your list of covariates to use them as covariates.
exogenous	logical value. Whether the covariates should be treated as exogenous (TRUE) or endogenous (FALSE).

Details

This function is designed to be passed to the GWAS function. The model that is returned, however, is a valid OpenMx model and can be fitted using mxRun or mxTryHard. Models should be tested to ensure that they are identified and fit the data as expected to avoid unnecessary computation of an invalid model.

There is no limit on the number of items that can be included, but more items will exponentially increase computation time. To address this, we suggest that users use the 'WLS' fit function. The 'WLS' fit function is dramatically faster than the 'ML' fit function, especially for ordinal items.

Ordinal indicator thresholds are setup by setupThresholds. Exogenous covariates adjustments are setup by setupExogenousCovariates. You can plot the model using omxGraphviz.

Value

buildTwoFac returns an MxModel object that can serve as input for the GWAS function.

See Also

Other model builder: buildItem(), buildOneFacRes(), buildOneFac()

Examples

```
pheno <- list()
for (i in 1:10) pheno[[paste0('i',i)]] <- rnorm(500)
pheno <- as.data.frame(pheno)
buildTwoFac(pheno, paste0('i',1:6), paste0('i',5:10))
```

GWAS *Run a genome-wide association study (GWAS) using the provided model*

Description

Maturing The GWAS function is used to run a genome-wide association study based on the specified model. This function is design to take the output from buildOneFac, buildOneFacRes, and buildTwoFac as input, but can also take a similar user specified model. Users should be confident that the models they are running are statistically identified. It is advisable that the users empirically gauge time requirements by running a limited number of SNPs (e.g. 10) to ensure that all SNPs can be fit in a reasonable amount of time.

Usage

```
GWAS(model, snpData, out = "out.log", ..., SNP = NULL, startFrom = 1L)
```

Arguments

model	A fully specified MxModel object that can be fit to each SNP.
snpData	A character vector specifying the pathname of a file where the SNP data is stored.
out	A character vector containing the pathname where the results of fitted models shall be written.
...	Not used. Forces remaining arguments to be specified by name.
SNP	A vector of SNP indices to include in the analysis (e.g. 101:200 will run SNPs at offsets 101 to 200 counting from the beginning of the file); NULL is interpreted as all available SNPs.
startFrom	the index to start from when SNP=NULL

Details

Adds a compute plan returned by prepareComputePlan to the provided model and runs it. Once analyses are complete, load your aggregated results with loadResults.

Value

The results for each SNP are recorded in the specified log file (out). In addition, data and estimates for the last SNP run are returned as an MxModel object (similar to the return value of mxRun). In this way, the last SNP processed is available for close inspection.

Examples

```
dir <- system.file("extdata", package = "gwsem")
pheno <- data.frame(anxiety=rnorm(500))
m1 <- buildItem(pheno, 'anxiety')
GWAS(m1, file.path(dir,"example.pgen"),
     file.path(tempdir(),"out.log"))
```

`isSuspicious` *Determine which results are suspicious*

Description

Maturing The GWAS function writes all results, both valid and invalid, to a log file. This function uses heuristics to try to classify rows as suspicious or unsuspicious. The loadResults function returns unsuspicious rows while loadSuspicious returns suspicious rows.

Usage

```
isSuspicious(got, pars)
```

Arguments

`got`	output passed from loadResults
`pars`	names of the parameters available in `got`

Details

Is it not recommended to call `isSuspicious` directly because it is already called by loadResults and loadSuspicious.

OpenMx reports exceptions in the 'catch1' column. Any error message in the 'catch1' column is suspicious. Any optimizer status code besides 'OK' is suspicious. It is suspicious if the focal parameter or its standard error is `NA`. If 'signAdj' was requested and it is `NA` then suspicion is also aroused. A mean and standard deviation are computed for each available parameter. Any estimate with an absolute Z score larger than 10 is suspicious.

Value

a vector of logicals for each row of `got` indicating suspicion (if TRUE)

See Also

Other reporting: `loadResults()`, `loadSuspicious()`, `plot.gwsemResult()`

Examples

```
tdir <- tempdir()
dir <- system.file("extdata", package = "gwsem")
pheno <- data.frame(anxiety=rnorm(500))
m1 <- buildItem(pheno, 'anxiety')
GWAS(m1, file.path(dir,"example.pgen"),
    file.path(tdir,"out.log"))
loadResults(file.path(tdir,"out.log"), "snp2anxiety")  # called in here
```

`loadResults` *Load GWAS results into a single data.frame*

Description

Maturing The `signAdj` column is important and not optional for latent factor models. Loadings to factor indicators can take any sign. If your focus is the regression from the SNP to the factor then this regression estimate will need to be multiplied by the sign of one of the factor loadings. Pick a loading associated with a strong indicator of the factor.

Usage

```
loadResults(
  path,
  focus,
  ...,
  extraColumns = c(),
  .retainSE = FALSE,
  signAdj = NULL,
  moderatorLevel = NULL
)
```

Arguments

`path`	vector of paths to result files created by GWAS
`focus`	parameter name on which to calculate a Z score and p-value
`...`	Not used. Forces remaining arguments to be specified by name.
`extraColumns`	character vector of additional columns to load
`.retainSE`	logical. Keep a column for the SE of the focus parameter
`signAdj`	name of column. Value of focus parameter is multiplied by the sign of the named column
`moderatorLevel`	see details

Details

A1 is the reference allele and A2 is the alternate allele.

Two columns are added, `Z` and `P`. `Z` is the focal parameter divded by its standard error. `P` is the unadjusted two-sided normal CDF corresponding to the absolute `Z` score.

Suspicious rows are excluded.

See Also

Other reporting: `isSuspicious()`, `loadSuspicious()`, `plot.gwsemResult()`

Examples

```
tdir <- tempdir()
dir <- system.file("extdata", package = "gwsem")
pheno <- data.frame(anxiety=rnorm(500))
m1 <- buildItem(pheno, 'anxiety')
GWAS(m1, file.path(dir,"example.pgen"),
    file.path(tdir,"out.log"))
loadResults(file.path(tdir,"out.log"), "snp2anxiety")
```

`loadSuspicious` *Load suspicious GWAS results into a single data.frame*

Description

Maturing These rows are excluded by loadResults.

Usage

```
loadSuspicious(
  path,
  focus,
  ...,
  extraColumns = c(),
  signAdj = NULL,
  moderatorLevel = NULL
)
```

Arguments

`path`	vector of paths to result files created by GWAS
`focus`	parameter name on which to calculate a Z score and p-value
`...`	Not used. Forces remaining arguments to be specified by name.
`extraColumns`	character vector of additional columns to load
`signAdj`	name of column. Value of focus parameter is multiplied by the sign of the named column
`moderatorLevel`	see details

See Also

Other reporting: `isSuspicious()`, `loadResults()`, `plot.gwsemResult()`

Examples

```
tdir <- tempdir()
dir <- system.file("extdata", package = "gwsem")
pheno <- data.frame(anxiety=rnorm(500))
m1 <- buildItem(pheno, 'anxiety')
GWAS(m1, file.path(dir,"example.pgen"),
    file.path(tdir,"out.log"))
loadSuspicious(file.path(tdir,"out.log"), "snp2anxiety")
```

`plot.gwsemResult` *Creates a Manhattan plot*

Description

Uses the qqman package to create a Manhattan plot.

Usage

```
## S3 method for class 'gwsemResult'
plot(x, y, ...)
```

Arguments

`x`	the result of loadResults
`y`	an extra argument that should not be used
`...`	arguments forwarded to manhattan

Value

A Manhattan plot.

See Also

Other reporting: `isSuspicious()`, `loadResults()`, `loadSuspicious()`

Examples

```
tdir <- tempdir()
dir <- system.file("extdata", package = "gwsem")
pheno <- data.frame(anxiety=rnorm(500))
m1 <- buildItem(pheno, 'anxiety')
GWAS(m1, file.path(dir,"example.pgen"),
    file.path(tdir,"out.log"))
got <- loadResults(file.path(tdir,"out.log"), "snp_to_anxiety")
plot(got)
```

`prepareComputePlan` *Return a suitable compute plan for a genome-wide association study*

Description

Maturing Instead of using OpenMx's default model processing sequence (i.e., omxDefaultComputePlan), it is more efficient and convienient to assemble a compute plan tailored for a genome-wide association study. This function returns a compute plan that loads SNP data into model `modelName`, fits the model, outputs the results to `out`, and repeats this procedure for all SNPs.

Usage

```
prepareComputePlan(
  model,
  snpData,
  out = "out.log",
  ...,
  SNP = NULL,
  startFrom = 1L
)
```

Arguments

`model`	A fully specified MxModel object that can be fit to each SNP.
`snpData`	A character vector specifying the pathname of a file where the SNP data is stored.
`out`	A character vector containing the pathname where the results of fitted models shall be written.
`...`	Not used. Forces remaining arguments to be specified by name.
`SNP`	A vector of SNP indices to include in the analysis (e.g. 101:200 will run SNPs at offsets 101 to 200 counting from the beginning of the file); NULL is interpreted as all available SNPs.
`startFrom`	the index to start from when `SNP=NULL`

Details

You can request a specific list of SNPs using the `SNP` argument. The numbers provided in `SNP` refer to offsets in the `snpData` file. For example, `SNP=c(100,200)` will process the 100th and 200th SNP. The first SNP in the `snpData` file is at offset 1. When `SNP` is omitted then all available SNPs are processed.

The suffix of `snpData` filename is interpreted to signal the format of how the SNP data is stored on disk. Suffixes 'pgen', 'bed', and 'bgen' are supported. Per-SNP descriptions are found in different places depending on the suffix. For 'bgen', both the SNP data and description are built into the same file. In the case of 'pgen', an associated file with suffix 'pvar' is expected to exist (see the spec for details). In the case of 'bed', an associated 'bim' file is expected to exist (see the spec for details). The chromosome, base-pair coordinate, and variant ID are added to each line of `out`.

The code to implement method='pgen' is based on plink 2.0 alpha. plink's 'bed' file format is supported in addition to 'pgen'. Data are coerced appropriately depending on the type of the destination column. For a numeric column, data are recorded as the values NA, 0, 1, or 2. An ordinal column must have exactly 3 levels.

For `method='bgen'`, the file `path+".bgi"` must also exist. If not available, generate this index file with the bgenix tool.

For 'bgen' and 'pgen' formats, the numeric column can be populated with a dosage (sum of probabilities multiplied by genotypes) if these data are available.

A compute plan does not do anything by itself. You'll need to combine the compute plan with a model (such as returned by buildOneFac) to perform a GWAS.

Value

The given model with an appropriate compute plan.

See Also

GWAS

Examples

```
m1 <- mxModel("test", mxFitFunctionWLS())
dir <- system.file("extdata", package = "gwsem")
m1 <- prepareComputePlan(m1, file.path(dir,"example.pgen"))
m1$compute
```

`setupExogenousCovariates`

Set up exogenous model covariates

Description

Experimental In GWAS, including a number of the first principle components as covariates helps reduce false positives caused by population stratification. This function adds paths from covariates to manifest indicators (`itemNames`). Covariates are always treated as continuous variables (not ordinal).

Usage

```
setupExogenousCovariates(model, covariates, itemNames)
```

Arguments

`model`	A fully specified MxModel object that can be fit to each SNP.
`covariates`	a character vector naming covariates available in the model data
`itemNames`	a character vector of item names

Details

This is not the only way to adjust a model for covariates. For example, in a single factor model (e.g., buildOneFac), it would be more appropriate to adjust the latent factor instead of the manifest indicators. This is how endogenous covariates work. However, exogenous covariate adjustments to latent variables are only possible with a maximum likelihood fit function (mxFitFunctionML). For mxFitFunctionWLS, only manifest indicators can be adjusted for exogenous covariates. This function always adjusts manifest indicators regardless of the fit function.

You generally do not need to call this function directly because it is already called by buildOneFac and similar. This function is provided for advanced users who wish to write their own model building functions.

Value

The given MxModel with paths added from covariates to manifest indicators.

Examples

```
m1 <- mxModel("test", type="RAM",
              latentVars = "sex", manifestVars = "anxiety",
              mxData(data.frame(sex=rbinom(10,1,.5)), 'raw'))
m1 <- setupExogenousCovariates(m1, 'sex', 'anxiety')
```

---

setupThresholds *Set up thresholds for ordinal indicators*

Description

Experimental Ordinal indicator thresholds are freely estimated with fixed means and variance. This function adds thresholds to the given `model`. If no indicators are ordinal, the given `model` is returned without changes.

Usage

```
setupThresholds(model)
```

Arguments

`model`	A fully specified MxModel object that can be fit to each SNP.

Details

Thresholds are added using mxThreshold. Starting values for thresholds use the defaults provided by this function which assumes a mean of zero and variance of the square root of two. This variance is appropriate for buildOneFac where the implied model variance of ordinal indicators is one plus the square of the factor loading, and the loading's starting value is 1.0.

You generally do not need to call this function directly because it is already called by buildOneFac and similar. This function is provided for advanced users who wish to write their own model building functions.

Value

The given MxModel with appropriate thresholds added.

Examples

```
pheno <- data.frame(anxiety=cut(rnorm(500), c(-Inf, -.5, .5, Inf),
                    ordered_result = TRUE))
m1 <- buildItem(pheno, 'anxiety')
m1 <- setupThresholds(m1)
m1$Thresholds
```

Index