Package ‘gap’

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Type Package

Title Genetic Analysis Package

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Description
As first reported [Zhao, J. H. 2007. ``gap: Genetic Analysis Package''. J Stat Soft 23(8):1-18. <doi:10.18637/jss.v023.i08>], it is designed as an integrated package for genetic data analysis of both population and family data. Currently, it contains functions for sample size calculations of both population-based and family-based designs, probability of familial disease aggregation, kinship calculation, statistics in linkage analysis, and association analysis involving genetic markers including haplotype analysis with or without environmental covariates. Over years, the package has been developed in-between many projects hence also in line with the name (gap).

License GPL (>= 2)

URL https://github.com/jinghuazhao/R

BugReports https://github.com/jinghuazhao/R/issues

Depends R (>= 2.10), gap.datasets (>= 0.0.6)

Imports dplyr, ggplot2, plotly, Rdpack

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LazyLoad Yes

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`a2g` *Allele-to-genotype conversion*

Description

Allele-to-genotype conversion

Usage

```
a2g(a1, a2)
```

Arguments

`a1`	first allele.
`a2`	second allele.

`ab` *Test/Power calculation for mediating effect*

Description

Test/Power calculation for mediating effect

Usage

```
ab(
  type = "power",
  n = 25000,
  a = 0.15,
  sa = 0.01,
  b = log(1.19),
  sb = 0.01,
  alpha = 0.05,
  fold = 1
)
```

Arguments

`type`	string option: "test", "power".
`n`	default sample size to be used for power calculation.
`a`	regression coefficient from indepdendent variable to mediator.
`sa`	SE(a).
`b`	regression coefficient from mediator variable to outcome.
`sb`	SE(b).
`alpha`	size of siginficance test for power calculation.
`fold`	fold change for power calculation, as appropriate for a range of sample sizes.

Details

This function tests for or obtains power of mediating effect based on estimates of two regression coefficients and their standard errors. Note that for binary outcome or mediator, one should use log-odds ratio and its standard error.

Value

The returned value are z-test and significance level for significant testing or sample size/power for a given fold change of the default sample size.

Author(s)

Jing Hua Zhao

References

Freathy RM, Timpson NJ, Lawlor DA, Pouta A, Ben-Shlomo Y, Ruokonen A, Ebrahim S, Shields B, Zeggini E, Weedon MN, Lindgren CM, Lango H, Melzer D, Ferrucci L, Paolisso G, Neville MJ, Karpe F, Palmer CN, Morris AD, Elliott P, Jarvelin MR, Smith GD, McCarthy MI, Hattersley AT, Frayling TM (2008). "Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI." *Diabetes*, **57**(5), 1419-26. doi:10.2337/db071466.

Kline RB. Principles and practice of structural equation modeling, Second Edition. The Guilford Press 2005.

MacKinnon DP. Introduction to Statistical Mediation Analysis. Taylor & Francis Group 2008.

Preacher KJ, Leonardelli GJ. Calculation for the Sobel Test-An interactive calculation tool for mediation tests https://quantpsy.org/sobel/sobel.htm

See Also

`ccsize`

Examples

```
## Not run:
ab()
n <- power <- vector()
for (j in 1:10)
{
   z <- ab(fold=j*0.01)
   n[j] <- z[1]
   power[j] <- z[2]
}
plot(n,power,xlab="Sample size",ylab="Power")
title("SNP-BMI-T2D association in EPIC-Norfolk study")

## End(Not run)
```

ACDE *Fit AE, ACE or ADE biometric mixed models to nuclear family data*

Description

Fits classical biometric variance–decomposition models using a linear mixed model formulation implemented with nlme::lme.

Usage

```
ACDE(model, data, type = c("AE", "ACE", "ADE"), method = "ML")
```

Arguments

`model`	Fixed-effects formula.
`data`	Data frame in long format (one row per individual).
`type`	Model type: `"AE"`, `"ACE"` or `"ADE"`.
`method`	Estimation method: `"ML"` (default) or `"REML"`.

Details

The function estimates additive genetic (A), shared environmental (C), dominance genetic (D), and unique environmental (E) variance components from **nuclear family data (parents and offspring)** in long format.

Supported family structures:

- Parent-child trios (one offspring)
- Nuclear families with **any number of siblings**

The function automatically detects the family structure and selects the correct additive-genetic parameterisation.

Only AE, ACE and ADE models are fitted.

Phenotypic variance is decomposed as

$$V_P = V_A + V_C + V_D + V_E$$

The model is fitted as a linear mixed model with family-level random effects and individual residual variance.

Automatic family detection:

The function detects whether families contain one or multiple offspring.

- **Trios:** collapsed additive parameterisation.
- **Siblings:** transmission decomposition parameterisation.

Trio parameterisation:
Additive effects represented as:

$$A = 0.5Mother + 0.5Father + 1Child$$

This reproduces the expected parent–offspring covariance:

$$Cov = 1/2V_A$$

Multi-sibling parameterisation:
Additive genetic variance is decomposed into:

- maternal transmission (A_m)
- paternal transmission (A_f)
- Mendelian sampling (M_s)

For offspring:

$$A = A_m + A_f + M_s$$

Total additive variance:

$$V_A = 2(\sigma^2_{Am} + \sigma^2_{Af}) + \sigma^2_{Ms}$$

This produces correct covariances:

- Parent–offspring: $1/2V_A$
- Sibling–sibling: $1/2V_A$

This formulation generalises to **any number of siblings**.

Identifiability of C and D:
Nuclear family data cannot fully separate shared environment (C) and dominance (D). ACE and ADE models should be interpreted jointly.

Value

Object of class `"ACDEfit"` containing:

- fit `nlme::lme` object
- var Variance components (A,C,D,E)
- h2 Narrow-sense heritability
- c2 Shared environment (ACE only)
- d2 Dominance (ADE only)
- H2 Broad-sense heritability (ADE only)

Required columns in `data`

- familyid Nuclear family identifier.
- var1 Maternal transmission coefficient.
- var2 Paternal transmission coefficient.

- var3 Offspring (Mendelian sampling) indicator.

These variables encode expected genetic transmission and **are not role indicators**.

Coding for a nuclear family:

```
role     var1  var2  var3
-------------------------
father     0     1     0
mother     1     0     0
child      1     1     1
```

For **multiple siblings**, each offspring receives identical coding:

```
role     var1  var2  var3
-------------------------
father     0     1     0
mother     1     0     0
sib1       1     1     1
sib2       1     1     1
sib3       1     1     1
```

Note

This complements `pbsize()` and `fbsize()`.

Author(s)

ChatGPT

Examples

```
library(nlme)
set.seed(1)

simulate_families <- function(n_fam = 200)
{
  VA <- 0.4; VC <- 0.2; VD <- 0.1; VE <- 0.3
  out <- list()

  for(f in 1:n_fam){
    Cfam <- rnorm(1,0,sqrt(VC))
    Af <- rnorm(1,0,sqrt(VA))
    Am <- rnorm(1,0,sqrt(VA))

    make_child <- function(){
      Mend <- rnorm(1,0,sqrt(0.5*VA))
      A  <- 0.5*(Af+Am)+Mend
      D  <- rnorm(1,0,sqrt(VD))
      E  <- rnorm(1,0,sqrt(VE))
      A + D + Cfam + E
    }
```

```
    out[[f]] <- data.frame(
      familyid=f,
      role=c("father","mother","sib1","sib2","sib3"),
      y=c(
        Af + Cfam + rnorm(1,0,sqrt(VE)),
        Am + Cfam + rnorm(1,0,sqrt(VE)),
        make_child(), make_child(), make_child()
      )
    )
  }

  dat <- do.call(rbind,out)

  dat$var1 <- as.integer(dat$role=="mother")
  dat$var2 <- as.integer(dat$role=="father")
  dat$var3 <- as.integer(grepl("sib", dat$role))
  dat
}

dat <- simulate_families()

AE  <- ACDE(y~1, dat, "AE")
ACE <- ACDE(y~1, dat, "ACE")
ADE <- ACDE(y~1, dat, "ADE")

anova(AE$fit, ACE$fit, ADE$fit)

#############################################################
# Create rectangular variance table (important!)
#############################################################

summary(AE)
summary(ACE)
summary(ADE)

require(gap.datasets)
model <- bwt ~ male + first + midage + highage + birthyr
AE <- ACDE(model,mfblong)
ACE <- ACDE(model,mfblong,type="ACE")
ADE <- ACDE(model,mfblong,type="ADE")
anova(AE$fit,ACE$fit,ADE$fit)
```

`AE3` *AE model using nuclear family trios*

Description

AE model using nuclear family trios

Usage

```
AE3(model, random, data, seed = 1234, n.sim = 50000, verbose = TRUE)
```

Arguments

`model`	a linear mixed model formula, see example below.
`random`	random effect, see exampe below.
`data`	data to be analyzed.
`seed`	random number seed.
`n.sim`	number of simulations.
`verbose`	a flag for printing out results.

Details

This function is adapted from example 7.1 of Rabe-Hesketh et al. (2008). It also procides heritability estimate and confidence intervals.

Value

The returned value is a list containing:

- lme.result the linear mixed model result.
- h2 the heritability estimate.
- CL confidence intervals.

Note

Adapted from f.mbf.R from the paper.

Author(s)

Jing Hua Zhao

References

Rabe-Hesketh S, Skrondal A, Gjessing HK (2008). "Biometrical modeling of twin and family data using standard mixed model software." *Biometrics*, **64**(1), 280-8. doi:10.1111/j.15410420.2007.00803.x.

Examples

```
## Not run:
require(gap.datasets)
AE3(bwt ~ male + first + midage + highage + birthyr,
    list(familyid = pdIdent(~var1 + var2 + var3 -1)), mfblong)

## End(Not run)
```

allele.recode *Allele recoding*

Description

Allele recoding

Usage

```
allele.recode(a1, a2, miss.val = NA)
```

Arguments

a1	first allele.
a2	second allele.
miss.val	missing value.

asplot *Regional association plot*

Description

Regional association plot

Usage

```
asplot(
  locus,
  map,
  genes,
  flanking = 1000,
  best.pval = NULL,
  sf = c(4, 4),
  logpmax = 10,
  pch = 21
)
```

Arguments

locus	Data frame with columns c("CHR", "POS", "NAME", "PVAL", "RSQR") containing association results.
map	Genetic map, i.e, c("POS","THETA","DIST").
genes	Gene annotation with columns c("START", "STOP", "STRAND", "GENE").
flanking	Flanking length.

best.pval	Best p value for the locus of interest.
sf	scale factors for p values and recombination rates, smaller values are necessary for gene dense regions.
logpmax	Maximum value for -log10(p).
pch	Plotting character for the SNPs to be highlighted, e.g., 21 and 23 refer to circle and diamond.

Details

This function obtains regional association plot for a particular locus, based on the information about recombinatino rates, linkage disequilibria between the SNP of interest and neighbouring ones, and single-point association tests p values.

Note that the best p value is not necessarily within locus in the original design.

Author(s)

Paul de Bakker, Jing Hua Zhao, Shengxu Li

References

Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, Roix JJ, Kathiresan S, Hirschhorn JN, Daly MJ, Hughes TE, Groop L, Altshuler D, Almgren P, Florez JC, Meyer J, Ardlie K, Bengtsson Boström K, Isomaa B, Lettre G, Lindblad U, Lyon HN, Melander O, Newton-Cheh C, Nilsson P, Orho-Melander M, Råstam L, Speliotes EK, Taskinen MR, Tuomi T, Guiducci C, Berglund A, Carlson J, Gianniny L, Hackett R, Hall L, Holmkvist J, Laurila E, Sjögren M, Sterner M, Surti A, Svensson M, Svensson M, Tewhey R, Blumenstiel B, Parkin M, Defelice M, Barry R, Brodeur W, Camarata J, Chia N, Fava M, Gibbons J, Handsaker B, Healy C, Nguyen K, Gates C, Sougnez C, Gage D, Nizzari M, Gabriel SB, Chirn GW, Ma Q, Parikh H, Richardson D, Ricke D, Purcell S (2007). "Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels." *Science*, **316**(5829), 1331-6. doi:10.1126/science.1142358.

Examples

```
## Not run:
require(gap.datasets)
asplot(CDKNlocus, CDKNmap, CDKNgenes)
title("CDKN2A/CDKN2B Region")
asplot(CDKNlocus, CDKNmap, CDKNgenes, best.pval=5.4e-8, sf=c(3,6))

## NCBI2R

options(stringsAsFactors=FALSE)
p <- with(CDKNlocus,data.frame(SNP=NAME,PVAL))
hit <- subset(p,PVAL==min(PVAL,na.rm=TRUE))$SNP

library(NCBI2R)
# LD under build 36
chr_pos <- GetSNPInfo(with(p,SNP))[c("chr","chrpos")]
l <- with(chr_pos,min(as.numeric(chrpos),na.rm=TRUE))
u <- with(chr_pos,max(as.numeric(chrpos),na.rm=TRUE))
```

```
LD <- with(chr_pos,GetLDInfo(unique(chr),l,u))
# We have complaints; a possibility is to get around with
# https://ftp.ncbi.nlm.nih.gov/hapmap/
hit_LD <- subset(LD,SNPA==hit)
hit_LD <- within(hit_LD,{RSQR=r2})
info <- GetSNPInfo(p$SNP)
haldane <- function(x) 0.5*(1-exp(-2*x))
locus <- with(info, data.frame(CHR=chr,POS=chrpos,NAME=marker,
                    DIST=(chrpos-min(chrpos))/1000000,
                    THETA=haldane((chrpos-min(chrpos))/100000000)))
locus <- merge.data.frame(locus,hit_LD,by.x="NAME",by.y="SNPB",all=TRUE)
locus <- merge.data.frame(locus,p,by.x="NAME",by.y="SNP",all=TRUE)
locus <- subset(locus,!is.na(POS))
ann <- AnnotateSNPList(p$SNP)
genes <- with(ann,data.frame(ID=locusID,CLASS=fxn_class,PATH=pathways,
                             START=GeneLowPoint,STOP=GeneHighPoint,
                             STRAND=ori,GENE=genesymbol,BUILD=build,CYTO=cyto))
attach(genes)
ugenes <- unique(GENE)
ustart <- as.vector(as.table(by(START,GENE,min))[ugenes])
ustop <- as.vector(as.table(by(STOP,GENE,max))[ugenes])
ustrand <- as.vector(as.table(by(as.character(STRAND),GENE,max))[ugenes])
detach(genes)
genes <- data.frame(START=ustart,STOP=ustop,STRAND=ustrand,GENE=ugenes)
genes <- subset(genes,START!=0)
rm(l,u,ugenes,ustart,ustop,ustrand)
# Assume we have the latest map as in CDKNmap
asplot(locus,CDKNmap,genes)

## End(Not run)
```

---

b2r *Obtain correlation coefficients and their variance-covariances*

Description

Obtain correlation coefficients and their variance-covariances

Usage

```
b2r(b, s, rho, n)
```

Arguments

b	the vector of linear regression coefficients.
s	the corresponding vector of standard errors.
rho	triangular array of between-SNP correlation.
n	the sample size.

Details

This function converts linear regression coefficients of phenotype on single nucleotide polymorphisms (SNPs) into Pearson correlation coefficients with their variance-covariance matrix. It is useful as a preliminary step for meta-analyze SNP-trait associations at a given region. Between-SNP correlations (e.g., from HapMap) are required as auxiliary information.

Value

The returned value is a list containing:

- r the vector of correlation coefficients.
- V the variance-covariance matrix of correlations.

Author(s)

Jing Hua Zhao

References

Elston RC (1975). "On the correlation between correlations." *Biometrika*, **62**(1), 133-140. doi:10.1093/biomet/62.1.133.

Becker BJ (2000). "Multivariate meta-analysis." In Tinsley HE, Brown SD (eds.), *Handbook of Applied Multivariate Statistics and Mathematical Modeling*, chapter 17, 499-525. Academic Press, San Diego. ISBN 978-0126913606.

Casella G, Berger RL (2002). *Statistical Inference*, 2 edition. Duxbury. ISBN 978-0-534-24312-8.

See Also

mvmeta, LD22

Examples

```
## Not run:
n <- 10
r <- c(1,0.2,1,0.4,0.5,1)
b <- c(0.1,0.2,0.3)
s <- c(0.4,0.3,0.2)
bs <- b2r(b,s,r,n)

## End(Not run)
```

BFDP *Bayesian false-discovery probability*

Description

Bayesian false-discovery probability

Usage

```
BFDP(a, b, pi1, W, logscale = FALSE)
```

Arguments

a	parameter value at which the power is to be evaluated.
b	the variance for a, or the uppoer point (RR_{hi}) of a 95%CI if logscale=FALSE.
pi1	the prior probabiility of a non-null association.
W	the prior variance.
logscale	FALSE=the orginal scale, TRUE=the log scale.

Details

This function calculates BFDP, the approximate $P(H_0|\hat{\theta})$, given an estiamte of the log relative risk, $\hat{\theta}$, the variance of this estimate, V, the prior variance, W, and the prior probability of a non-null association. When logscale=TRUE, the function accepts an estimate of the relative risk, $\hat{RR}$, and the upper point of a 95% confidence interval RR_{hi}.

Value

The returned value is a list with the following components: PH0. probability given a,b). PH1. probability given a,b,W). BF. Bayes factor, P_{H_0}/P_{H_1}. BFDP. Bayesian false-discovery probability. ABF. approxmiate Bayes factor. ABFDP. approximate Bayesian false-discovery probability.

Note

Adapted from BFDP functions by Jon Wakefield on 17th April, 2007.

Author(s)

Jon Wakefield, Jing Hua Zhao

References

Wakefield J (2007). "A Bayesian measure of the probability of false discovery in genetic epidemiology studies." *Am J Hum Genet*, **81**(2), 208-27. doi:10.1086/519024.

See Also

FPRP

Examples

```
## Not run:
# Example from BDFP.xls by Jon Wakefield and Stephanie Monnier
# Step 1 - Pre-set an BFDP-level threshold for noteworthiness: BFDP values below this
#          threshold are noteworthy
# The threshold is given by R/(1+R) where R is the ratio of the cost of a false
# non-discovery to the cost of a false discovery

T <- 0.8

# Step 2 - Enter up values for the prior that there is an association

pi0 <- c(0.7,0.5,0.01,0.001,0.00001,0.6)

# Step 3 - Enter the value of the OR that is the 97.5% point of the prior, for example
#          if we pick the value 1.5 we believe that the prior probability that the
#          odds ratio is bigger than 1.5 is 0.025.

ORhi <- 3

W <- (log(ORhi)/1.96)^2
W

# Step 4 - Enter OR estimate and 95% confidence interval (CI) to obtain BFDP

OR <- 1.316
OR_L <- 1.10
OR_U <- 2.50
logOR <- log(OR)
selogOR <- (log(OR_U)-log(OR))/1.96
r <- W/(W+selogOR^2)
r
z <- logOR/selogOR
z
ABF <- exp(-z^2*r/2)/sqrt(1-r)
ABF
FF <- (1-pi0)/pi0
FF
BFDPex <- FF*ABF/(FF*ABF+1)
BFDPex
pi0[BFDPex>T]

## now turn to BFDP

pi0 <- c(0.7,0.5,0.01,0.001,0.00001,0.6)
ORhi <- 3
OR <- 1.316
OR_U <- 2.50
```

```
W <- (log(ORhi)/1.96)^2
z <- BFDP(OR,OR_U,pi0,W)
z

## End(Not run)
```

---

bt *Bradley-Terry model for contingency table*

Description

Bradley-Terry model for contingency table

Usage

```
bt(x)
```

Arguments

x	the data table.

Details

This function calculates statistics under Bradley-Terry model.

Value

The returned value is a list containing:

- y A column of 1.
- count the frequency count/weight.
- allele the design matrix.
- bt.glm a glm.fit object.
- etdt.dat a data table that can be used by ETDT.

Note

Adapted from a SAS macro for data in the example section.

Author(s)

Jing Hua Zhao

References

Bradley RA, Terry ME (1952). "Rank analysis of incomplete block designs." *Biometrika*, **39**, 324-335.

Sham PC, Curtis D (1995). "An extended transmission/disequilibrium test (TDT) for multi-allele marker loci." *Ann Hum Genet*, **59**(3), 323-36. doi:10.1111/j.14691809.1995.tb00751.x.

Copeman JB, Cucca F, Hearne CM, Cornall RJ, Reed PW, Rønningen KS, Undlien DE, Nisticò L, Buzzetti R, Tosi R, et al. (1995). "Linkage disequilibrium mapping of a type 1 diabetes susceptibility gene (IDDM7) to chromosome 2q31-q33." *Nat Genet*, **9**(1), 80-5. doi:10.1038/ng019580.

See Also

mtdt

Examples

```
## Not run:
x <- matrix(c(0,0, 0, 2, 0,0, 0, 0, 0, 0, 0, 0,
              0,0, 1, 3, 0,0, 0, 2, 3, 0, 0, 0,
              2,3,26,35, 7,0, 2,10,11, 3, 4, 1,
              2,3,22,26, 6,2, 4, 4,10, 2, 2, 0,
              0,1, 7,10, 2,0, 0, 2, 2, 1, 1, 0,
              0,0, 1, 4, 0,1, 0, 1, 0, 0, 0, 0,
              0,2, 5, 4, 1,1, 0, 0, 0, 2, 0, 0,
              0,0, 2, 6, 1,0, 2, 0, 2, 0, 0, 0,
              0,3, 6,19, 6,0, 0, 2, 5, 3, 0, 0,
              0,0, 3, 1, 1,0, 0, 0, 1, 0, 0, 0,
              0,0, 0, 2, 0,0, 0, 0, 0, 0, 0, 0,
              0,0, 1, 0, 0,0, 0, 0, 0, 0, 0, 0),nrow=12)

# Bradley-Terry model, only deviance is available in glm
# (SAS gives score and Wald statistics as well)
bt.ex<-bt(x)
anova(bt.ex$bt.glm)
summary(bt.ex$bt.glm)

## End(Not run)
```

---

ccsize *Power and sample size for case-cohort design*

Description

Power and sample size for case-cohort design

Usage

```
ccsize(n, q, pD, p1, theta, alpha, beta = 0.2, power = TRUE, verbose = FALSE)
```

Arguments

n	the total number of subjects in the cohort.
q	the sampling fraction of the subcohort.
pD	the proportion of the failures in the full cohort.
p1	proportions of the two groups (p2=1-p1).
theta	log-hazard ratio for two groups.
alpha	type I error – significant level.
beta	type II error.
power	if specified, the power for which sample size is calculated.
verbose	error messages are explicitly printed out.

Details

The power of the test is according to

$$\Phi\left(Z_\alpha + m^{1/2}\theta\sqrt{\frac{p_1 p_2 p_D}{q+(1-q)p_D}}\right)$$

where α is the significance level, θ is the log-hazard ratio for two groups, p_j, j=1, 2, are the proportion of the two groups in the population. m is the total number of subjects in the subcohort, p_D is the proportion of the failures in the full cohort, and q is the sampling fraction of the subcohort.

Alternatively, the sample size required for the subcohort is

$$m = nBp_D/(n - B(1-p_D))$$

where $B = (Z_{1-\alpha} + Z_\beta)^2/(\theta^2 p_1 p_2 p_D)$, and n is the size of cohort.

When infeaisble configurations are specified, a sample size of -999 is returned.

Value

a value indicating the power or required sample size.

Note

Programmed for EPIC study. keywords misc

Author(s)

Jing Hua Zhao

References

Cai J, Zeng D (2004). "Sample size/power calculation for case-cohort studies." *Biometrics*, **60**(4), 1015-24. doi:10.1111/j.0006341X.2004.00257.x.

See Also

pbsize

Examples

```
## Not run:
# Table 1 of Cai & Zeng (2004).
alpha <- 0.05
table1 <- rbind(
  transform(
    within(expand.grid(
      pD = c(0.10, 0.05),
      p1 = c(0.3, 0.5),
      theta = c(0.5, 1.0),
      q = c(0.1, 0.2)
    ), {
      n <- 1000
      power <- mapply(ccsize,
        n = n, q = q, pD = pD, p1 = p1, theta = theta,
        MoreArgs = list(alpha = alpha)
      )
    }),
    power = signif(power, 3)
  ),
  transform(
    within(expand.grid(
      pD = c(0.05, 0.01),
      p1 = c(0.3, 0.5),
      theta = c(0.5, 1.0),
      q = c(0.01, 0.02)
    ), {
      n <- 5000
      power <- mapply(ccsize,
        n = n, q = q, pD = pD, p1 = p1, theta = theta,
        MoreArgs = list(alpha = alpha)
      )
    }),
    power = signif(power, 3)
  )
)

# ARIC study
aric <- within(
  data.frame(
    n = 15792,
    pD = 0.03,
    p1 = 0.25,
    hr = c(1.35, 1.40, 1.45),
    q = c(1463, 722, 468) / 15792
  ), {
    alpha <- 0.05
    beta <- 0.2
    power <- mapply(ccsize,
      n = n, q = q, pD = pD, p1 = p1, theta = log(hr),
      MoreArgs = list(alpha = alpha)
    )
```

```
    ssize <- mapply(ccsize,
      n = n, q = q, pD = pD, p1 = p1, theta = log(hr),
      MoreArgs = list(alpha = alpha, beta = beta, power = FALSE)
    )
    power <- signif(power, 3)
  }
)

# EPIC study
epic <- within(
  expand.grid(
    pD = c(0.3, 0.2, 0.1, 0.05),
    p1 = seq(0.1, 0.5, by = 0.1),
    hr = seq(1.1, 1.4, by = 0.1)
  ), {
    n <- 25000
    q <- 0.1
    alpha <- 5e-8
    beta <- 0.2
    ssize <- mapply(ccsize,
      n = n, q = q, pD = pD, p1 = p1, theta = log(hr),
      MoreArgs = list(alpha = alpha, beta = beta, power = FALSE)
    )
  }
)
epic <- subset(epic, !is.na(ssize) & ssize > 0)

# exhaustive search
search <- within(
  expand.grid(
    pD = c(0.3, 0.2, 0.1, 0.05),
    p1 = seq(0.1, 0.5, by = 0.1),
    hr = seq(1.1, 1.4, by = 0.1),
    q  = seq(0.01, 0.5, by = 0.01)
  ), {
    n <- 25000
    alpha <- 5e-8
    power <- mapply(ccsize,
      n = n, q = q, pD = pD, p1 = p1, theta = log(hr),
      MoreArgs = list(alpha = alpha)
    )
    nq <- n * q
  }
)

## End(Not run)
```

`chow.test` *Chow's test for heterogeneity in two regressions*

Description

Chow's test for heterogeneity in two regressions

Usage

```
chow.test(y1, x1, y2, x2, x = NULL)
```

Arguments

y1	a vector of dependent variable.
x1	a matrix of independent variables.
y2	a vector of dependent variable.
x2	a matrix of independent variables.
x	a known matrix of independent variables.

Details

Chow's test is for differences between two or more regressions. Assuming that errors in regressions 1 and 2 are normally distributed with zero mean and homoscedastic variance, and they are independent of each other, the test of regressions from sample sizes n_1 and n_2 is then carried out using the following steps. 1. Run a regression on the combined sample with size $n = n_1 + n_2$ and obtain within group sum of squares called S_1. The number of degrees of freedom is $n_1 + n_2 - k$, with k being the number of parameters estimated, including the intercept. 2. Run two regressions on the two individual samples with sizes n_1 and n_2, and obtain their within group sums of square $S_2 + S_3$, with $n_1 + n_2 - 2k$ degrees of freedom. 3. Conduct an $F_{(k,n_1+n_2-2k)}$ test defined by

$$F = \frac{[S_1 - (S_2 + S_3)]/k}{[(S_2 + S_3)/(n_1 + n_2 - 2k)]}$$

If the F statistic exceeds the critical F, we reject the null hypothesis that the two regressions are equal.

In the case of haplotype trend regression, haplotype frequencies from combined data are known, so can be directly used.

Value

The returned value is a vector containing (please use subscript to access them):

- F the F statistic.
- df1 the numerator degree(s) of freedom.
- df2 the denominator degree(s) of freedom.
- p the p value for the F test.

Note

adapted from chow.R.

Author(s)

Shigenobu Aoki, Jing Hua Zhao

References

Chow GC (1960). "Tests of Equality Between Sets of Coefficients in Two Linear Regressions." *Econometrica*, **28**(3), 591-605. doi:10.2307/1910133.

See Also

`htr`

Examples

```
## Not run:
dat1 <- matrix(c(
     1.2, 1.9, 0.9,
     1.6, 2.7, 1.3,
     3.5, 3.7, 2.0,
     4.0, 3.1, 1.8,
     5.6, 3.5, 2.2,
     5.7, 7.5, 3.5,
     6.7, 1.2, 1.9,
     7.5, 3.7, 2.7,
     8.5, 0.6, 2.1,
     9.7, 5.1, 3.6), byrow=TRUE, ncol=3)

dat2 <- matrix(c(
     1.4, 1.3, 0.5,
     1.5, 2.3, 1.3,
     3.1, 3.2, 2.5,
     4.4, 3.6, 1.1,
     5.1, 3.1, 2.8,
     5.2, 7.3, 3.3,
     6.5, 1.5, 1.3,
     7.8, 3.2, 2.2,
     8.1, 0.1, 2.8,
     9.5, 5.6, 3.9), byrow=TRUE, ncol=3)

y1<-dat1[,3]
y2<-dat2[,3]
x1<-dat1[,1:2]
x2<-dat2[,1:2]
chow.test.r<-chow.test(y1,x1,y2,x2)
# from http://aoki2.si.gunma-u.ac.jp/R/

## End(Not run)
```

`chr_pos_a1_a2` *SNP id by chr:pos+a1/a2*

Description

SNP id by chr:pos+a1/a2

Usage

```
chr_pos_a1_a2(
  chr,
  pos,
  a1,
  a2,
  prefix = "chr",
  seps = c(":", "_", "_"),
  uppercase = TRUE
)
```

Arguments

`chr`	Chromosome.
`pos`	Position.
`a1`	Allele 1.
`a2`	Allele 2.
`prefix`	Prefix of the identifier.
`seps`	Delimiters.
`uppercase`	A flag to return in upper case.

Details

This function generates unique identifiers for variants

Value

Identifier.

Examples

```
# rs12075
chr_pos_a1_a2(1,159175354,"A","G",prefix="chr",seps=c(":","_","_"),uppercase=TRUE)
```

ci2ms *Effect size and standard error from confidence interval*

Description

Effect size and standard error from confidence interval

Usage

```
ci2ms(ci, logscale = TRUE, alpha = 0.05)
```

Arguments

`ci`	confidence interval (CI). The delimiter between lower and upper limit is either a hyphen (-) or en dash (–).
`logscale`	a flag indicating the confidence interval is based on a log-scale.
`alpha`	Type 1 error.

Details

Effect size is a measure of strength of the relationship between two variables in a population or parameter estimate of that population. Without loss of generality, denote `m` and `s` to be the mean and standard deviation of a sample from $N(\mu, \sigma^2)$). Let $z \sim N(0, 1)$ with cutoff point z_α, confidence limits `L`, `U` in a CI are defined as follows,

$$L = m - z_\alpha s$$
$$U = m + z_\alpha s$$

$\Rightarrow U + L = 2m, U - L = 2z_\alpha s$. Consequently,

$$m = \frac{U + L}{2}$$
$$s = \frac{U - L}{2z_\alpha}$$

Effect size in epidemiological studies on a binary outcome is typically reported as odds ratio from a logistic regression or hazard ratio from a Cox regression, $L \equiv \log(L), U \equiv \log(U)$.

Value

Based on CI, the function provides a list containing estimates

- m effect size (log(OR))
- s standard error
- direction a decrease/increase (-/+) sign such that `sign(m)`=-1, 0, 1, is labelled "-", "0", "+", respectively as in PhenoScanner.

Examples

```
# rs3784099 and breast cancer recurrence/mortality
ms <- ci2ms("1.28-1.72")
print(ms)
# Vector input
ci2 <- c("1.28-1.72","1.25-1.64")
ms2 <- ci2ms(ci2)
print(ms2)
```

---

circos.cis.vs.trans.plot

circos plot of cis/trans classification

Description

circos plot of cis/trans classification

Usage

```
circos.cis.vs.trans.plot(hits, panel, id, radius = 1e+06)
```

Arguments

`hits`	A text file as input data with varibles named "CHR","BP","SNP","prot".
`panel`	Protein panel with prot(ein), uniprot (id) and "chr","start","end","gene".
`id`	Identifier.
`radius`	The flanking distance as cis.

Details

The function implements a circos plot at the early stage of SCALLOP-INF meta-analysis.

Value

None.

Examples

```
## Not run:
  circos.cis.vs.trans.plot(hits="INF1.merge", panel=inf1, id="uniprot")

## End(Not run)
```

`circos.cnvplot` *circos plot of CNVs.*

Description

circos plot of CNVs.

Usage

```
circos.cnvplot(data)
```

Arguments

`data`	CNV data containing chromosome, start, end and freq.

Details

The function plots frequency of CNVs.

Value

None.

Examples

```
## Not run:
circos.cnvplot(cnv)

## End(Not run)
```

`circos.mhtplot` *circos Manhattan plot with gene annotation*

Description

circos Manhattan plot with gene annotation

Usage

```
circos.mhtplot(data, glist)
```

Arguments

`data`	Data to be used.
`glist`	A gene list.

Details

The function generates circos Manhattan plot with gene annotation.

Value

None.

Examples

```
## Not run:
require(gap.datasets)
glist <- c("IRS1","SPRY2","FTO","GRIK3","SNED1","HTR1A","MARCH3","WISP3",
           "PPP1R3B","RP1L1","FDFT1","SLC39A14","GFRA1","MC4R")
circos.mhtplot(mhtdata,glist)

## End(Not run)
```

---

circos.mhtplot2 *Another circos Manhattan plot*

Description

Another circos Manhattan plot

Usage

```
circos.mhtplot2(dat, labs, species = "hg18", ticks = 0:3 * 10, ymax = 30)
```

Arguments

dat	Data to be plotted with variables chr, pos, log10p.
labs	Data on labels.
species	Genome build.
ticks	Tick positions.
ymax	maximum value for y-axis.

Details

This is adapted from work for a recent publication. It enables a y-axis to the -log10(P) for association statistics

Value

There is no return value but a plot.

Examples

```
## Not run:
require(gap.datasets)
library(dplyr)
glist <- c("IRS1","SPRY2","FTO","GRIK3","SNED1","HTR1A","MARCH3","WISP3",
           "PPP1R3B","RP1L1","FDFT1","SLC39A14","GFRA1","MC4R")
testdat <- mhtdata[c("chr","pos","p","gene","start","end")] %>%
           rename(log10p=p) %>%
           mutate(chr=paste0("chr",chr),log10p=-log10(log10p))
dat <- mutate(testdat,start=pos,end=pos) %>%
       select(chr,start,end,log10p)
labs <- subset(testdat,gene %in% glist) %>%
        group_by(gene,chr,start,end) %>%
        summarize() %>%
        mutate(cols="blue") %>%
        select(chr,start,end,gene,cols)
labs[2,"cols"] <- "red"
ticks <- 0:3*5
circos.mhtplot2(dat,labs,ticks=ticks,ymax=max(ticks))
# https://www.rapidtables.com/web/color/RGB_Color.html

## End(Not run)
```

`cis.vs.trans.classification` *A cis/trans classifier*

Description

A cis/trans classifier

Usage

```
cis.vs.trans.classification(hits, panel, id, radius = 1e+06)
```

Arguments

`hits`	Data to be used, which contains prot, Chr, bp, id and/or other information such as SNPid.
`panel`	Panel data.
`id`	Identifier.
`radius`	The flanking distance for variants.

Details

The function classifies variants into cis/trans category according to a panel which contains id, chr, start, end, gene variables.

Value

The cis/trans classification.

Author(s)

James Peters

Examples

```
cis.vs.trans.classification(hits=jma.cojo, panel=inf1, id="uniprot")
## Not run:
INF <- Sys.getenv("INF")
f <- file.path(INF,"work","INF1.merge")
clumped <- read.delim(f,as.is=TRUE)
hits <- merge(clumped[c("CHR","POS","MarkerName","prot","log10p")],
              inf1[c("prot","uniprot")],by="prot")
names(hits) <- c("prot","Chr","bp","SNP","log10p","uniprot")
cistrans <- cis.vs.trans.classification(hits,inf1,"uniprot")
cis.vs.trans <- with(cistrans,data)
knitr::kable(with(cistrans,table),caption="Table 1. cis/trans classification")
with(cistrans,total)

## End(Not run)
```

---

cnvplot *genomewide plot of CNVs*

Description

genomewide plot of CNVs

Usage

```
cnvplot(data)
```

Arguments

`data`	Data to be used.

Details

The function generates a plot containing genomewide copy number variants (CNV) chr, start, end, freq(uencies).

Value

None.

Examples

```
knitr::kable(cnv,caption="A CNV dataset")
cnvplot(cnv)
```

`comp.score` *score statistics for testing genetic linkage of quantitative trait*

Description

score statistics for testing genetic linkage of quantitative trait

Usage

```
comp.score(
  ibddata = "ibd_dist.out",
  phenotype = "pheno.dat",
  mean = 0,
  var = 1,
  h2 = 0.3
)
```

Arguments

`ibddata`	The output file from GENEHUNTER using command "dump ibd". The default file name is $ibd_dist.out$.
`phenotype`	The file of pedigree structure and trait value. The default file name is "pheno.dat". Columns (no headings) are: family ID, person ID, father ID, mother ID, gender, trait value, where Family ID and person ID must be numbers, not characters. Use character "NA" for missing phenotypes.
`mean`	(population) mean of the trait, with a default value of 0.
`var`	(population) variance of the trait, with a default value of 1.
`h2`	heritability of the trait, with a default value of 0.3.

Details

The function empirically estimate the variance of the score functions. The variance-covariance matrix consists of two parts: the additive part and the part for the individual-specific environmental effect. Other reasonable decompositions are possible.

This program has the following improvement over "score.r":

1. It works with selected nuclear families
2. Trait data on parents (one parent or two parents), if available, are utilized.
3. Besides a statistic assuming no locus-specific dominance effect, it also computes a statistic that allows for such effect. It computes two statistics instead of one.

Function "merge" is used to merge the IBD data for a pair with the transformed trait data (i.e., $w_k w_l$).

Value

a matrix with each row containing the location and the statistics and their p-values.

Note

Adapt from score2.r.

Author(s)

Yingwei Peng, Kai Wang

References

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996). "Parametric and nonparametric linkage analysis: a unified multipoint approach." *Am J Hum Genet*, **58**(6), 1347-63.

Kruglyak L, Lander ES (1998). "Faster multipoint linkage analysis using Fourier transforms." *J Comput Biol*, **5**(1), 1-7. doi:10.1089/cmb.1998.5.1.

Wang K (2005). "A likelihood approach for quantitative-trait-locus mapping with selected pedigrees." *Biometrics*, **61**(2), 465-73. doi:10.1111/j.15410420.2005.031213.x.

Examples

```
## Not run:
# An example based on GENEHUNTER version 2.1, with quantitative trait data in file
# "pheno.dat" generated from the  standard normal distribution. The following
# exmaple shows that it is possible to automatically call GENEHUNTER using R
# function "system".

cwd <- getwd()
cs.dir <- file.path(find.package("gap"),"tests/comp.score")
setwd(cs.dir)
dir()
# system("gh < gh.inp")
cs.default <- comp.score()
setwd(cwd)

## End(Not run)
```

---

cs *Credible set from summary statistics*

Description

Computes a Bayesian credible set from GWAS summary statistics using Wakefield-style approximate Bayes factors.

Usage

```
cs(tbl, b = "Effect", se = "StdErr", log_p = NULL, cutoff = 0.95)
```

Arguments

`tbl`	A data.frame containing summary statistics.
`b`	Name of column containing effect sizes.
`se`	Name of column containing standard errors.
`log_p`	Optional column name containing log p-values. If supplied, z-scores are derived from p-values instead of effect sizes and standard errors.
`cutoff`	Cumulative posterior probability threshold. Default is 0.95 (95% credible set).

Details

Credible set is often used in fine-mapping.

Posterior probabilities are computed from z-statistics using a numerically stable log-sum-exp implementation from matrixStats.

Value

A subset of `tbl` containing variants in the credible set, ordered by decreasing posterior probability of association.

Examples

```
## Not run:
\preformatted{
  zcat ~/rds/results/private/proteomics/scallop-inf1/4E.BP1-1.tbl.gz | \
  awk 'NR==1 || ($1==4 && $2 >= 187158034 - 1e6 && $2 < 187158034 + 1e6)' > 4E.BP1.z
}
tbl <- within(read.delim("4E.BP1.z"),{logp <- logp(Effect/StdErr)})
z <- cs(tbl)
l <- cs(tbl,log_p="logp")

## End(Not run)
```

ESplot *Effect-size / Odds-ratio forest plot*

Description

The function accepts parameter estimates and their standard errors from one or more models and produces a horizontal forest plot with confidence intervals.

Two plotting modes are supported:

- `transform="none"` (default): plots estimates on the linear scale (typical for GWAS or Mendelian randomisation beta coefficients).
- `transform="exp"`: plots exponentiated estimates on a log10 axis (typical for odds ratios or hazard ratios). Confidence intervals are computed on the log scale and back-transformed.

Usage

```
ESplot(
  ESdat,
  alpha = 0.05,
  fontsize = 12,
  transform = c("none", "exp"),
  xlab = NULL
)
```

Arguments

`ESdat`	Data frame with **three columns**: • id Model or trait label • b Effect estimate (beta or log(OR)/log(HR)) • se Standard error of the estimate
`alpha`	Type-I error rate for the confidence interval (default 0.05 for 95% CI).
`fontsize`	Base font size used in the plot.
`transform`	Either `"none"` (linear scale) or `"exp"` (exponentiated scale).
`xlab`	Optional x-axis label. If `NULL`, a sensible default is used.

Details

Create a publication-ready forest plot for model effect estimates. The function supports both linear effect sizes (e.g. regression betas) and exponentiated effects (e.g. odds ratios or hazard ratios).

Confidence intervals are computed as

$$estimate \pm z_{\alpha/2} \times SE$$

When `transform="exp"`, estimates are interpreted as log(OR) or log(HR) and are exponentiated before plotting. The x-axis is displayed on a log10 scale and the reference line is placed at 1.

This function replaces an earlier base-R implementation and provides a consistent interface for GWAS, Mendelian randomisation, and epidemiological regression analyses.

Value

A `ggplot2` plot object.

Author(s)

Jing Hua Zhao

Examples

```
## Example 1: Linear effect sizes (GWAS / MR)
rs12075 <- data.frame(
  id=c("CCL2","CCL7","CCL8","CCL11","CCL13","CXCL6","Monocytes"),
  b=c(0.1694,-0.0899,-0.0973,0.0749,0.189,0.0816,0.0338387),
  se=c(0.0113,0.013,0.0116,0.0114,0.0114,0.0115,0.00713386)
)
ESplot(rs12075)

## Example 2: Odds ratios
dat <- data.frame(
  id=c("Basic","Adjusted","Moderate","Heavy","Other"),
  b=log(c(4.5,3.5,2.5,1.5,1)),
  se=c(0.2,0.1,0.2,0.3,0.2)
)
ESplot(dat, transform="exp")
```

---

fbsize *Sample size for family-based linkage and association design*

Description

Sample size for family-based linkage and association design

Usage

```
fbsize(
  gamma,
  p,
  alpha = c(1e-04, 1e-08, 1e-08),
  beta = 0.2,
  debug = 0,
  error = 0
)
```

Arguments

gamma	genotype relative risk assuming multiplicative model.
p	frequency of disease allele.
alpha	Type I error rates for ASP linkage, TDT and ASP-TDT.
beta	Type II error rate.
debug	verbose output.
error	0=use the correct formula,1=the original paper.

Details

This function implements Risch and Merikangas (1996) statistics evaluating power for family-based linkage (affected sib pairs, ASP) and association design. They are potentially useful in the prospect of genome-wide association studies.

The function calls auxiliary functions sn() and strlen; `sn()` contains the necessary thresholds for power calculation while `strlen()` evaluates length of a string (generic).

Value

The returned value is a list containing:

- gamma input gamma.
- p input p.
- n1 sample size for ASP.
- n2 sample size for TDT.
- n3 sample size for ASP-TDT.
- lambdao lambda o.
- lambdas lambda s.

Note

extracted from rm.c.

Author(s)

Jing Hua Zhao

References

Risch N, Merikangas K (1996). “The Future of Genetic Studies of Complex Human Diseases.” *Science*, **273**(5281), 1516-1517. doi:10.1126/science.273.5281.1516. Risch N, Merikangas K (1996). “The Future of Genetic Studies of Complex Human Diseases.” *Science*, **273**(5281), 1516-1517. doi:10.1126/science.273.5281.1516.Risch N, Merikangas K (1997). “Reply to Scott el al.” *Science*, **275**, 1329-1330.Scott WK, Pericak-Vance MA, Haines JL (1997). “Genetic analysis of complex diseases.” *Science*, **275**(5304), 1327; author reply 1329-30.

See Also

`pbsize`

Examples

```
models <- matrix(c(
   4.0, 0.01,
   4.0, 0.10,
   4.0, 0.50,
   4.0, 0.80,
   2.0, 0.01,
```

```
    2.0, 0.10,
    2.0, 0.50,
    2.0, 0.80,
    1.5, 0.01,
    1.5, 0.10,
    1.5, 0.50,
    1.5, 0.80), ncol=2, byrow=TRUE)
outfile <- "fbsize.txt"
cat("gamma","p","Y","N_asp","P_A","H1","N_tdt","H2","N_asp/tdt","L_o","L_s\n",
    file=outfile,sep="\t")
for(i in 1:12) {
  g <- models[i,1]
  p <- models[i,2]
  z <- fbsize(g,p)
  cat(z$gamma,z$p,z$y,z$n1,z$pA,z$h1,z$n2,z$h2,z$n3,z$lambdao,z$lambdas,file=outfile,
      append=TRUE,sep="\t")
  cat("\n",file=outfile,append=TRUE)
}
table1 <- read.table(outfile,header=TRUE,sep="\t")
nc <- c(4,7,9)
table1[,nc] <- ceiling(table1[,nc])
dc <- c(3,5,6,8,10,11)
table1[,dc] <- round(table1[,dc],2)
unlink(outfile)
# APOE-4, Scott WK, Pericak-Vance, MA & Haines JL
# Genetic analysis of complex diseases 1327
g <- 4.5
p <- 0.15
cat("\nAlzheimer's:\n\n")
fbsize(g,p)
# note to replicate the Table we need set alpha=9.961139e-05,4.910638e-08 and
# beta=0.2004542 or reset the quantiles in fbsize.R
```

FPRP *False-positive report probability*

Description

False-positive report probability

Usage

```
FPRP(a, b, pi0, ORlist, logscale = FALSE)
```

Arguments

a	parameter value at which the power is to be evaluated.
b	the variance for a, or the uppoer point of a 95%CI if logscale=FALSE.

`pi0`	the prior probabiility that H_0 is true.
`ORlist`	a vector of ORs that is most likely.
`logscale`	FALSE=a,b in orginal scale, TRUE=a, b in log scale.

Details

The function calculates the false positive report probability (FPRP), the probability of no true association beteween a genetic variant and disease given a statistically significant finding, which depends not only on the observed P value but also on both the prior probability that the assocition is real and the statistical power of the test. An associate result is the false negative reported probability (FNRP). See example for the recommended steps.

The FPRP and FNRP are derived as follows. Let H_0=null hypothesis (no association), H_A=alternative hypothesis (association). Since classic frequentist theory considers they are fixed, one has to resort to Bayesian framework by introduing prior, $\pi = P(H_0 = TRUE) = P(association)$. Let T=test statistic, and $P(T > z_\alpha|H_0 = TRUE) = P(rejecting\ H_0|H_0 = TRUE) = \alpha$, $P(T > z_\alpha|H_0 = FALSE) = P(rejecting\ H_0|H_A = TRUE) = 1 - \beta$. The joint probability of test and truth of hypothesis can be expressed by α, β and π.

Joint probability of significance of test and truth of hypothesis

Truth of H_A	significant	nonsignificant	Total
TRUE	$(1-\beta)\pi$	$\beta\pi$	π
FALSE	$\alpha(1-\pi)$	$(1-\alpha)(1-\pi)$	$1-\pi$
Total	$(1-\beta)\pi+\alpha(1-\pi)$	$\beta\pi+(1-\alpha)(1-\pi)$	1

We have $FPRP = P(H_0 = TRUE|T > z_\alpha) = \alpha(1-\pi)/[\alpha(1-\pi)+(1-\beta)\pi] = \{1+\pi/(1-\pi)][(1-\beta)/\alpha]\}^{-1}$ and similarly $FNRP = \{1+[(1-\alpha)/\beta][(1-\pi)/\pi]\}^{-1}$.

Value

The returned value is a list with compoents, p p value corresponding to a,b. power the power corresponding to the vector of ORs. FPRP False-positive report probability. FNRP False-negative report probability.

Author(s)

Jing Hua Zhao

References

Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N (2004). “Assessing the probability that a positive report is false: an approach for molecular epidemiology studies.” *J Natl Cancer Inst*, **96**(6), 434-42. doi:10.1093/jnci/djh075.

See Also

BFDP

Examples

```
## Not run:
# Example by Laure El ghormli & Sholom Wacholder on 25-Feb-2004
# Step 1 - Pre-set an FPRP-level criterion for noteworthiness

T <- 0.2

# Step 2 - Enter values for the prior that there is an association

pi0 <- c(0.25,0.1,0.01,0.001,0.0001,0.00001)

# Step 3 - Enter values of odds ratios (OR) that are most likely, assuming that
#          there is a non-null association

ORlist <- c(1.2,1.5,2.0)

# Step 4 - Enter OR estimate and 95% confidence interval (CI) to obtain FPRP

OR <- 1.316
ORlo <- 1.08
ORhi <- 1.60

logOR <- log(OR)
selogOR <- abs(logOR-log(ORhi))/1.96
p <- ifelse(logOR>0,2*(1-pnorm(logOR/selogOR)),2*pnorm(logOR/selogOR))
p
q <- qnorm(1-p/2)
POWER <- ifelse(log(ORlist)>0,1-pnorm(q-log(ORlist)/selogOR),
                pnorm(-q-log(ORlist)/selogOR))
POWER
FPRPex <- t(p*(1-pi0)/(p*(1-pi0)+POWER\
row.names(FPRPex) <- pi0
colnames(FPRPex) <- ORlist
FPRPex
FPRPex>T

## now turn to FPRP
OR <- 1.316
ORhi <- 1.60
ORlist <- c(1.2,1.5,2.0)
pi0 <- c(0.25,0.1,0.01,0.001,0.0001,0.00001)
z <- FPRP(OR,ORhi,pi0,ORlist,logscale=FALSE)
z

## End(Not run)
```

---

g2a *Conversion of a genotype identifier to alleles*

Description

Conversion of a genotype identifier to alleles

Usage

```
g2a(g)
```

Arguments

g	a genotype identifier.

---

gc.em *Gene counting for haplotype analysis*

Description

Gene counting for haplotype analysis

Usage

```
gc.em(
  data,
  locus.label = NA,
  converge.eps = 1e-06,
  maxiter = 500,
  handle.miss = 0,
  miss.val = 0,
  control = gc.control()
)
```

Arguments

data	Matrix of alleles, such that each locus has a pair of adjacent columns of alleles, and the order of columns corresponds to the order of loci on a chromosome. If there are K loci, then ncol(data) = 2*K. Rows represent alleles for each subject.
locus.label	Vector of labels for loci, of length K (see definition of data matrix).
converge.eps	Convergence criterion, based on absolute change in log likelihood (lnlike).
maxiter	Maximum number of iterations of EM.
handle.miss	a flag for handling missing genotype data, 0=no, 1=yes.
miss.val	missing value.
control	a function, see genecounting.

Details

Gene counting for haplotype analysis with missing data, adapted for hap.score

Value

List with components:

- converge Indicator of convergence of the EM algorithm (1=converged, 0 = failed).
- niter Number of iterations completed in the EM alogrithm.
- locus.info A list with a component for each locus. Each component is also a list, and the items of a locus- specific list are the locus name and a vector for the unique alleles for the locus.
- locus.label Vector of labels for loci, of length K (see definition of input values).
- haplotype Matrix of unique haplotypes. Each row represents a unique haplotype, and the number of columns is the number of loci.
- hap.prob Vector of mle's of haplotype probabilities. The ith element of hap.prob corresponds to the ith row of haplotype.
- hap.prob.noLD Similar to hap.prob, but assuming no linkage disequilibrium.
- lnlike Value of lnlike at last EM iteration (maximum lnlike if converged).
- lr Likelihood ratio statistic to test no linkage disequilibrium among all loci.
- indx.subj Vector for index of subjects, after expanding to all possible pairs of haplotypes for each person. If indx=i, then i is the ith row of input matrix data. If the ith subject has n possible pairs of haplotypes that correspond to their marker phenotype, then i is repeated n times.
- nreps Vector for the count of haplotype pairs that map to each subject's marker genotypes.
- hap1code Vector of codes for each subject's first haplotype. The values in hap1code are the row numbers of the unique haplotypes in the returned matrix haplotype.
- hap2code Similar to hap1code, but for each subject's second haplotype.
- post Vector of posterior probabilities of pairs of haplotypes for a person, given thier marker phenotypes.
- htrtable A table which can be used in haplotype trend regression.

Note

Adapted from GENECOUNTING.

Author(s)

Jing Hua Zhao

References

Zhao JH, Lissarrague S, Essioux L, Sham PC (2002). "GENECOUNTING: haplotype analysis with missing genotypes." *Bioinformatics*, **18**(12), 1694-5. doi:10.1093/bioinformatics/18.12.1694.

Zhao JH, Sham PC (2003). "Generic number systems and haplotype analysis." *Comput Methods Programs Biomed*, **70**(1), 1-9. doi:10.1016/s01692607(01)001936.

See Also

genecounting, LDkl

Examples

```
## Not run:
data(hla)
gc.em(hla[,3:8],locus.label=c("DQR","DQA","DQB"),control=gc.control(assignment="t"))

## End(Not run)
```

`gc.lambda` *Estimation of the genomic control inflation statistic (lambda)*

Description

Estimation of the genomic control inflation statistic (lambda)

Usage

```
gc.lambda(x, logscale = FALSE, z = FALSE)
```

Arguments

`x`	A real vector (p or z).
`logscale`	A logical variable such that x as -log10(p).
`z`	A flag to indicate x as a vector of z values.

Value

Estimate of inflation factor.

Examples

```
set.seed(12345)
p <- runif(100)
gc.lambda(p)
lp <- -log10(p)
gc.lambda(lp,logscale=TRUE)
z <- qnorm(p/2)
gc.lambda(z,z=TRUE)
```

`gcontrol` *genomic control*

Description

genomic control

Usage

```
gcontrol(
  data,
  zeta = 1000,
  kappa = 4,
  tau2 = 1,
  epsilon = 0.01,
  ngib = 500,
  burn = 50,
  idum = 2348
)
```

Arguments

`data`	the data matrix.
`zeta`	program constant with default value 1000.
`kappa`	multiplier in prior for mean with default value 4.
`tau2`	multiplier in prior for variance with default value 1.
`epsilon`	prior probability of marker association with default value 0.01.
`ngib`	number of Gibbs steps, with default value 500.
`burn`	number of burn-ins with default value 50.
`idum`	seed for pseudorandom number sequence.

Details

The Bayesian genomic control statistics with the following parameters,

n	number of loci under consideration
lambdahat	median(of the n trend statistics)/0.46
	Prior for noncentrality parameter Ai is
	Normal(sqrt(lambdahat)kappa,lambdahat*tau2)
kappa	multiplier in prior above, set at 1.6 * sqrt(log(n))
tau2	multiplier in prior above
epsilon	prior probability a marker is associated, set at 10/n
ngib	number of cycles for the Gibbs sampler after burn in
burn	number of cycles for the Gibbs sampler to burn in

Armitage's trend test along with the posterior probability that each marker is associated with the disorder is given. The latter is not a p-value but any value greater than 0.5 (pout) suggests association.

Value

The returned value is a list containing:

- deltot the probability of being an outlier.
- x2 the χ^2 statistic.
- A the A vector.

Note

Adapted from gcontrol by Bobby Jones and Kathryn Roeder, use -Dexecutable for standalone program, function getnum in the original code needs \

Author(s)

Bobby Jones, Jing Hua Zhao

References

Devlin B, Roeder K (1999). "Genomic control for association studies." *Biometrics*, **55**(4), 997-1004. doi:10.1111/j.0006341x.1999.00997.x.

Examples

```
## Not run:
test<-c(1,2,3,4,5,6,  1,2,1,23,1,2, 100,1,2,12,1,1,
        1,2,3,4,5,61, 1,2,11,23,1,2, 10,11,2,12,1,11)
test<-matrix(test,nrow=6,byrow=T)
gcontrol(test)

## End(Not run)
```

`gcontrol2` *genomic control based on p values*

Description

genomic control based on p values

Usage

```
gcontrol2(p, col = palette()[4], lcol = palette()[2], ...)
```

Arguments

`p`	a vector of observed p values.
`col`	colour for points in the Q-Q plot.
`lcol`	colour for the diagonal line in the Q-Q plot.
`...`	other options for plot.

Details

The function obtains 1-df χ^2 statistics (observed) according to a vector of p values, and the inflation factor (lambda) according to medians of the observed and expected statistics. The latter is based on the empirical distribution function (EDF) of 1-df χ^2 statstics.

It would be appropriate for genetic association analysis as of 1-df Armitage trend test for case-control data; for 1-df additive model with continuous outcome one has to consider the compatibility with p values based on z-/t- statistics.

Value

A list containing:

- x the expected χ^2 statistics.
- y the observed χ^2 statistics.
- lambda the inflation factor.

Author(s)

Jing Hua Zhao

References

Devlin B, Roeder K (1999) Genomic control for association studies. Biometrics 55:997-1004

Examples

```
## Not run:
x2 <- rchisq(100,1,.1)
p <- pchisq(x2,1,lower.tail=FALSE)
r <- gcontrol2(p)
print(r$lambda)

## End(Not run)
```

gcp *Permutation tests using GENECOUNTING*

Description

Permutation tests using GENECOUNTING

Usage

```
gcp(
  y,
  cc,
  g,
  handle.miss = 1,
  miss.val = 0,
  n.sim = 0,
  locus.label = NULL,
  quietly = FALSE
)
```

Arguments

y	A column of 0/1 indicating cases and controls.
cc	analysis indicator, 0 = marker-marker, 1 = case-control.
g	the multilocus genotype data.
handle.miss	a flag with value 1 indicating missing data are allowed.
miss.val	missing value.
n.sim	the number of permutations.
locus.label	label of each locus.
quietly	a flag if TRUE will suppress the screen output.

Details

This function is a R port of the GENECOUNTING/PERMUTE program which generates EHPLUS-type statistics including z-tests for individual haplotypes

Value

The returned value is a list containing (p.sim and ph when n.sim > 0):

- x2obs the observed chi-squared statistic.
- pobs the associated p value.
- zobs the observed z value for individual haplotypes.
- p.sim simulated p value for the global chi-squared statistic.
- ph simulated p values for individual haplotypes.

Note

Built on gcp.c.

Author(s)

Jing Hua Zhao

References

Zhao JH, Curtis D, Sham PC (2000). "Model-free analysis and permutation tests for allelic associations." *Hum Hered*, **50**(2), 133-9. doi:10.1159/000022901.

Zhao JH (2004). "2LD. GENECOUNTING and HAP: computer programs for linkage disequilibrium analysis." *Bioinformatics*, **20**(8), 1325-6. doi:10.1093/bioinformatics/bth071.

Zhao JH, Qian WD (2003) Association analysis of unrelated individuals using polymorphic genetic markers – methods, implementation and application, Royal Statistical Society, Hassallt-Diepenbeek, Belgium.

See Also

`genecounting`

Examples

```
## Not run:
data(fsnps)
y<-fsnps$y
cc<-1
g<-fsnps[,3:10]

gcp(y,cc,g,miss.val="Z",n.sim=5)
hap.score(y,g,method="hap",miss.val="Z")

## End(Not run)
```

`genecounting` *Gene counting for haplotype analysis*

Description

Gene counting for haplotype analysis

Usage

```
genecounting(data, weight = NULL, loci = NULL, control = gc.control())
```

Arguments

`data`	genotype table.
`weight`	a column of frequency weights.
`loci`	an array containing number of alleles at each locus.
`control`	is a function with the following arguments:

- xdata. a flag indicating if the data involves X chromosome, if so, the first column of data indicates sex of each subject: 1=male, 2=female. The marker data are no different from the autosomal version for females, but for males, two copies of the single allele present at a given locus.
- convll. set convergence criteria according to log-likelihood, if its value set to 1
- handle.miss. to handle missing data, if its value set to 1
- eps. the actual convergence criteria, with default value 1e-5
- tol. tolerance for genotype probabilities with default value 1e-8
- maxit. maximum number of iterations, with default value 50
- pl. criteria for trimming haplotypes according to posterior probabilities
- assignment. filename containing haplotype assignment
- verbose. If TRUE, yields print out from the C routine

Details

Gene counting for haplotype analysis with missing data.

Value

The returned value is a list containing:

- h haplotype frequency estimates under linkage disequilibrium (LD).
- h0 haplotype frequency estimates under linkage equilibrium (no LD).
- prob genotype probability estimates.
- l0 log-likelihood under linkage equilibrium.
- l1 log-likelihood under linkage disequilibrium.
- hapid unique haplotype identifier (defunct, see `gc.em`).
- npusr number of parameters according user-given alleles.
- npdat number of parameters according to observed.
- htrtable design matrix for haplotype trend regression (defunct, see `gc.em`).
- iter number of iterations used in gene counting.
- converge a flag indicating convergence status of gene counting.
- di0 haplotype diversity under no LD, defined as $1 - \sum(h_0^2)$.
- di1 haplotype diversity under LD, defined as $1 - \sum(h^2))$.
- resid residuals in terms of frequency weights = o - e.

Note

adapted from GENECOUNTING.

Author(s)

Jing Hua Zhao

References

Zhao JH, Lissarrague S, Essioux L, Sham PC (2002). "GENECOUNTING: haplotype analysis with missing genotypes." *Bioinformatics*, **18**(12), 1694-5. doi:10.1093/bioinformatics/18.12.1694.

Zhao JH, Sham PC (2003). "Generic number systems and haplotype analysis." *Comput Methods Programs Biomed*, **70**(1), 1-9. doi:10.1016/s01692607(01)001936.

Zhao JH (2004). "2LD. GENECOUNTING and HAP: computer programs for linkage disequilibrium analysis." *Bioinformatics*, **20**(8), 1325-6. doi:10.1093/bioinformatics/bth071.

See Also

gc.em, LDkl

Examples

```
## Not run:
require(gap.datasets)
# HLA data
data(hla)
hla.gc <- genecounting(hla[,3:8])
summary(hla.gc)
hla.gc$l0
hla.gc$l1

# ALDH2 data
data(aldh2)
control <- gc.control(handle.miss=1,assignment="ALDH2.out")
aldh2.gc <- genecounting(aldh2[,3:6],control=control)
summary(aldh2.gc)
aldh2.gc$l0
aldh2.gc$l1

# Chromosome X data
# assuming allelic data have been extracted in columns 3-13
# and column 3 is sex
filespec <- system.file("tests/genecounting/mao.dat")
mao2 <- read.table(filespec)
dat <- mao2[,3:13]
loci <- c(12,9,6,5,3)
contr <- gc.control(xdata=TRUE,handle.miss=1)
mao.gc <- genecounting(dat,loci=loci,control=contr)
mao.gc$npusr
mao.gc$npdat
```

```
## End(Not run)
```

`geno.recode` *Genotype recoding*

Description

Genotype recoding

Usage

```
geno.recode(geno, miss.val = 0)
```

Arguments

`geno`	genotype.
`miss.val`	missing value.

`get_b_se` *Get b and se from AF, n, and z*

Description

The function obtains effect size and its standard error.

Usage

```
get_b_se(f, n, z)
```

Arguments

`f`	Allele frequency.
`n`	Sample size.
`z`	z-statistics.

Value

b and se.

Examples

```
## Not run:
  library(dplyr)
  # eQTLGen
  cis_pQTL <- merge(read.delim('eQTLGen.lz') %>%
              filter(GeneSymbol=="LTBR"),read.delim("eQTLGen.AF"),by="SNP") %>%
              mutate(data.frame(get_b_se(AlleleB_all,NrSamples,Zscore)))
  head(cis_pQTL,1)
        SNP    Pvalue SNPChr  SNPPos AssessedAllele OtherAllele Zscore
  rs1003563 2.308e-06     12 6424577              A           G 4.7245
             Gene GeneSymbol GeneChr GenePos NrCohorts NrSamples         FDR
  ENSG00000111321       LTBR      12 6492472        34     23991 0.006278872
  BonferroniP hg19_chr hg19_pos AlleleA AlleleB allA_total allAB_total
            1       12  6424577       A       G       2574        8483
  allB_total AlleleB_all          b          se
        7859   0.6396966 0.04490488 0.009504684

## End(Not run)
```

`get_pve_se` *Get pve and its standard error from n, z*

Description

Get pve and its standard error from n, z

Usage

```
get_pve_se(n, z, correction = TRUE)
```

Arguments

`n`	Sample size.
`z`	z-statistic, i.e., b/se when they are available instead.
`correction`	if TRUE an correction based on t-statistic is applied.

Details

This function obtains proportion of explained variance of a continuous outcome.

Value

pve and its se.

get_sdy *Get sd(y) from AF, n, b, se*

Description

Get sd(y) from AF, n, b, se

Usage

```
get_sdy(f, n, b, se, method = "mean", ...)
```

Arguments

f	Allele frequency.
n	Sample size.
b	effect size.
se	standard error.
method	method of averaging: "mean" or "median".
...	argument(s) passed to method

Details

This function obtains standard error of a continuous outcome.

Value

sd(y).

Examples

```
## Not run:
set.seed(1)
X1 <- matrix(rbinom(1200,1,0.4),ncol=2)
X2 <- matrix(rbinom(1000,1,0.6),ncol=2)
colnames(X1) <- colnames(X2) <- c("f1","f2")
Y1 <- rnorm(600,apply(X1,1,sum),2)
Y2 <- rnorm(500,2*apply(X2,1,sum),5)
summary(lm1 <- lm(Y1~f1+f2,data=as.data.frame(X1)))
summary(lm2 <- lm(Y2~f1+f2,data=as.data.frame(X2)))
b1 <- coef(lm1)
b2 <- coef(lm2)
v1 <- vcov(lm1)
v2 <- vcov(lm2)
require(coloc)
## Bayesian approach, esp. when only p values are available
abf <- coloc.abf(list(beta=b1, varbeta=diag(v1), N=nrow(X1), sdY=sd(Y1), type="quant"),
                 list(beta=b2, varbeta=diag(v2), N=nrow(X2), sdY=sd(Y2), type="quant"))
```

```
abf
# sdY
cat("sd(Y)=",sd(Y1),"==> Estimates:",sqrt(diag(var(X1)*b1[-1]^2+var(X1)*v1[-1,-1]*nrow(X1))),"\n")
for(k in 1:2)
{
  k1 <- k + 1
 cat("Based on b",k," sd(Y1) = ",sqrt(var(X1[,k])*(b1[k1]^2+nrow(X1)*v1[k1,k1])),"\n",sep="")
}
cat("sd(Y)=",sd(Y2),"==> Estimates:",sqrt(diag(var(X2)*b2[-1]^2+var(X2)*v2[-1,-1]*nrow(X2))),"\n")
for(k in 1:2)
{
  k1 <- k + 1
 cat("Based on b",k," sd(Y2) = ",sqrt(var(X2[,k])*(b2[k1]^2+nrow(X2)*v2[k1,k1])),"\n",sep="")
}
get_sdy(0.6396966,23991,0.04490488,0.009504684)

## End(Not run)
```

`gif` *Kinship coefficient and genetic index of familiality*

Description

Kinship coefficient and genetic index of familiality

Usage

```
gif(data, gifset)
```

Arguments

`data`	the trio data of a pedigree.
`gifset`	a subgroup of pedigree members.

Details

The genetic index of familality is defined as the mean kinship between all pairs of individuals in a set multiplied by 100,000. Formally, it is defined in (Gholami and Thomas 1994) as

$$100,000 \times \frac{2}{n(n-1)} \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} k_{ij}$$

where n is the number of individuals in the set and k_{ij} is the kinship coefficient between individuals i and j.

The scaling is purely for convenience of presentation.

Value

The returned value is a list containing:

- gifval the genetic index of familiarity.

Note

Adapted from gif.c, testable with -Dexecutable as standalone program, which can be use for any pair of indidivuals

Author(s)

Alun Thomas, Jing Hua Zhao

References

Gholami K, Thomas A (1994). "A linear time algorithm for calculation of multiple pairwise kinship coefficients and the genetic index of familiality." *Comput Biomed Res*, **27**(5), 342-50. doi:10.1006/cbmr.1994.1026.

See Also

pfc

Examples

```
## Not run:
test<-c(
 5,      0,      0,
 1,      0,      0,
 9,      5,      1,
 6,      0,      0,
10,      9,      6,
15,      9,      6,
21,     10,     15,
 3,      0,      0,
18,      3,     15,
23,     21,     18,
 2,      0,      0,
 4,      0,      0,
 7,      0,      0,
 8,      4,      7,
11,      5,      8,
12,      9,      6,
13,      9,      6,
14,      5,      8,
16,     14,      6,
17,     10,      2,
19,      9,     11,
20,     10,     13,
22,     21,     20)
test<-matrix(test,ncol=3,byrow=TRUE)
```

```
gif(test,gifset=c(20,21,22))

# all individuals
gif(test,gifset=1:23)

## End(Not run)
```

---

grid2d *Two-dimensional grid*

Description

This function build 2-d grids

Usage

```
grid2d(
  chrlen,
  plot = TRUE,
  cex.labels = 0.6,
  xlab = "QTL position",
  ylab = "Gene position"
)
```

Arguments

chrlen	Lengths of chromosomes; e.g., hg18, hg19 or hg38.
plot	A flag for plot.
cex.labels	A scaling factor for labels.
xlab	X-axis title.
ylab	Y-axis title.

Value

A list with two variables:

- n Number of chromosomes.
- CM Cumulative lengths starting from 0.

h2.jags — *Heritability estimation based on genomic relationship matrix using JAGS*

Description

Heritability estimation based on genomic relationship matrix using JAGS

Usage

```
h2.jags(
  y,
  x,
  G,
  eps = 1e-04,
  sigma.p = 0,
  sigma.r = 1,
  parms = c("b", "p", "r", "h2"),
  ...
)
```

Arguments

y	outcome vector.
x	covariate matrix.
G	genomic relationship matrix.
eps	a positive diagonal perturbation to G.
sigma.p	initial parameter values.
sigma.r	initial parameter values.
parms	monitored parmeters.
...	parameters passed to jags, e.g., n.chains, n.burnin, n.iter.

Details

This function performs Bayesian heritability estimation using genomic relationship matrix.

Value

The returned value is a fitted model from jags().

Author(s)

Jing Hua Zhao keywords htest

References

Zhao JH, Luan JA, Congdon P (2018). "Bayesian Linear Mixed Models with Polygenic Effects." *Journal of Statistical Software*, **85**(6), 1 - 27. doi:10.18637/jss.v085.i06.

Examples

```
## Not run:
require(gap.datasets)
set.seed(1234567)
meyer <- within(meyer,{
    y[is.na(y)] <- rnorm(length(y[is.na(y)]),mean(y,na.rm=TRUE),sd(y,na.rm=TRUE))
    g1 <- ifelse(generation==1,1,0)
    g2 <- ifelse(generation==2,1,0)
    id <- animal
    animal <- ifelse(!is.na(animal),animal,0)
    dam <- ifelse(!is.na(dam),dam,0)
    sire <- ifelse(!is.na(sire),sire,0)
})
G <- kin.morgan(meyer)$kin.matrix*2
library(regress)
r <- regress(y~-1+g1+g2,~G,data=meyer)
r
with(r,h2G(sigma,sigma.cov))
eps <- 0.001
y <- with(meyer,y)
x <- with(meyer,cbind(g1,g2))
ex <- h2.jags(y,x,G,sigma.p=0.03,sigma.r=0.014)
print(ex)
require(coda)
ex.mcmc <- as.mcmc(ex)
traceplot(ex.mcmc)
densplot(ex.mcmc)

## End(Not run)
```

---

h2G *Heritability and its variance*

Description

Heritability and its variance

Usage

```
h2G(V, VCOV, verbose = TRUE)
```

Arguments

`V`	Variance estimates.
`VCOV`	Variance-covariance matrix.
`verbose`	Detailed output.

Value

A list of phenotypic variance/heritability estimates and their variances.

`h2GE` *Heritability and its variance when there is an environment component*

Description

Heritability and its variance when there is an environment component

Usage

```
h2GE(V, VCOV, verbose = TRUE)
```

Arguments

`V`	Variance estimates.
`VCOV`	Variance-covariance matrix.
`verbose`	Detailed output.

Value

A list of phenotypic variance/heritability/GxE interaction esimates and their variances.

`h2l` *Heritability under the liability threshold model*

Description

Heritability under the liability threshold model

Usage

```
h2l(K = 0.05, P = 0.5, h2, se, verbose = TRUE)
```

Arguments

K	Disease prevalence.
P	Phenotypeic variance.
h2	Heritability estimate.
se	Standard error.
verbose	Detailed output.

Value

A list of the input heritability estimate/standard error and their counterpart under liability threshold model, the normal deviate..

---

h2_mzdz *Heritability estimation according to twin correlations*

Description

Heritability estimation according to twin correlations

Usage

```
h2_mzdz(
  mzDat = NULL,
  dzDat = NULL,
  rmz = NULL,
  rdz = NULL,
  nmz = NULL,
  ndz = NULL,
  selV = NULL
)
```

Arguments

mzDat	a data frame for monzygotic twins (MZ).
dzDat	a data frame for dizygotic twins (DZ).
rmz	correlation for MZ twins.
rdz	correlation for DZ twins.
nmz	sample size for MZ twins.
ndz	sample size for DZ twins.
selV	names of variables for twin and cotwin.

Details

Given MZ/DZ data or their correlations and sample sizes, it obtains heritability and variance estimates under an ACE model as in doi:10.1038/s4156202301530y and Keeping (1995).

Value

A data.frame with variables h2, c2, e2, vh2, vc2, ve2.

References

Elks CE, den Hoed M, Zhao JH, Sharp SJ, Wareham NJ, Loos RJ, Ong KK (2012). "Variability in the heritability of body mass index: a systematic review and meta-regression." *Front Endocrinol (Lausanne)*, **3**, 29. doi:10.3389/fendo.2012.00029.

Keeping ES (1995). *Introduction to statistical inference*, Dover books on mathematics, Dover edition. Dover Publications, New York. ISBN 9780486685021.

Examples

```
## Not run:
library(mvtnorm)
set.seed(12345)
mzm <- as.data.frame(rmvnorm(195, c(22.75,22.75),
                     matrix(2.66^2*c(1, 0.67, 0.67, 1), 2)))
dzm <- as.data.frame(rmvnorm(130, c(23.44,23.44),
                     matrix(2.75^2*c(1, 0.32, 0.32, 1), 2)))
mzw <- as.data.frame(rmvnorm(384, c(21.44,21.44),
                     matrix(3.08^2*c(1, 0.72, 0.72, 1), 2)))
dzw <- as.data.frame(rmvnorm(243, c(21.72,21.72),
                     matrix(3.12^2*c(1, 0.33, 0.33, 1), 2)))
selVars <- c('bmi1','bmi2')
names(mzm) <- names(dzm) <- names(mzw) <- names(dzw) <- selVars
ACE_CI <- function(mzData,dzData,n.sim=5,selV=NULL,verbose=TRUE)
{
  ACE_obs <- h2_mzdz(mzDat=mzData,dzDat=dzData,selV=selV)
  cat("\n\nheritability according to correlations\n\n")
  print(format(ACE_obs,digits=3),row.names=FALSE)
  nmz <- nrow(mzData)
  ndz <- nrow(dzData)
  r <- data.frame()
  for(i in 1:n.sim)
  {
    cat("\rRunning # ",i,"/", n.sim,"\r",sep="")
    sampled_mz <- sample(1:nmz, replace=TRUE)
    sampled_dz <- sample(1:ndz, replace=TRUE)
    mzDat <- mzData[sampled_mz,]
    dzDat <- dzData[sampled_dz,]
    ACE_i <- h2_mzdz(mzDat=mzDat,dzDat=dzDat,selV=selV)
    if (verbose) print(ACE_i)
    r <- rbind(r,ACE_i)
  }
  m <- apply(r,2,mean,na.rm=TRUE)
  s <- apply(r,2,sd,na.rm=TRUE)
  allr <- data.frame(mean=m,sd=s,lcl=m-1.96*s,ucl=m+1.96*s)
  print(format(allr,digits=3))
}
ACE_CI(mzm,dzm,n.sim=500,selV=selVars,verbose=FALSE)
```

```
ACE_CI(mzw,dzw,n.sim=500,selV=selVars,verbose=FALSE)

## End(Not run)
```

`hap` *Haplotype reconstruction*

Description

Haplotype reconstruction

Usage

```
hap(
  id,
  data,
  nloci,
  loci = rep(2, nloci),
  names = paste("loci", 1:nloci, sep = ""),
  control = hap.control()
)
```

Arguments

`id`	a column of subject id.
`data`	genotype table.
`nloci`	number of loci.
`loci`	number of alleles at all loci.
`names`	locus names.
`control`	is a call to hap.control().

Details

Haplotype reconstruction using sorting and trimming algorithms.

The package can hanlde much larger number of multiallelic loci. For large sample size with relatively small number of multiallelic loci, genecounting should be used.

Value

The returned value is a list containing:

- ll log-likelihood assuming linkage disequilibrium.
- converge convergence status, 0=failed, 1=succeeded.
- niter number of iterations.

Note

adapted from hap.

References

Clayton DG (2001) SNPHAP. https://github.com/chr1swallace/snphap.

Zhao JH and W Qian (2003) Association analysis of unrelated individuals using polymorphic genetic markers. RSS 2003, Hassalt, Belgium

Zhao JH (2004). "2LD. GENECOUNTING and HAP: computer programs for linkage disequilibrium analysis." *Bioinformatics*, **20**(8), 1325-6. doi:10.1093/bioinformatics/bth071.

See Also

`genecounting`

Examples

```
## Not run:
require(gap.datasets)
# 4 SNP example, to generate hap.out and assign.out alone
data(fsnps)
hap(id=fsnps[,1],data=fsnps[,3:10],nloci=4)
dir()

# to generate results of imputations
control <- hap.control(ss=1,mi=5,hapfile="h",assignfile="a")
hap(id=fsnps[,1],data=fsnps[,3:10],nloci=4,control=control)
dir()

## End(Not run)
```

`hap.control` *Control for haplotype reconstruction*

Description

Control for haplotype reconstruction

Usage

```
hap.control(
  mb = 0,
  pr = 0,
  po = 0.001,
  to = 0.001,
  th = 1,
  maxit = 100,
```

```
    n = 0,
    ss = 0,
    rs = 0,
    rp = 0,
    ro = 0,
    rv = 0,
    sd = 0,
    mm = 0,
    mi = 0,
    mc = 50,
    ds = 0.1,
    de = 0,
    q = 0,
    hapfile = "hap.out",
    assignfile = "assign.out"
  )
```

Arguments

mb	Maximum dynamic storage to be allocated, in Mb.
pr	Prior (ie population) probability threshold.
po	Posterior probability threshold.
to	Log-likelihood convergence tolerance.
th	Posterior probability threshold for output.
maxit	Maximum EM iteration.
n	Force numeric allele coding (1/2) on output (off).
ss	Tab-delimited speadsheet file output (off).
rs	Random starting points for each EM iteration (off).
rp	Restart from random prior probabilities.
ro	Loci added in random order (off).
rv	Loci added in reverse order (off).
sd	Set seed for random number generator (use date+time).
mm	Repeat final maximization multiple times.
mi	Create multiple imputed datasets. If set >0.
mc	Number of MCMC steps between samples.
ds	Starting value of Dirichlet prior parameter.
de	Finishing value of Dirichlet prior parameter.
q	Quiet operation (off).
hapfile	a file for haplotype frequencies.
assignfile	a file for haplotype assignment.

Value

A list containing the parameter specifications to the function.

`hap.em` *Gene counting for haplotype analysis*

Description

Gene counting for haplotype analysis

Usage

```
hap.em(
  id,
  data,
  locus.label = NA,
  converge.eps = 1e-06,
  maxiter = 500,
  miss.val = 0
)
```

Arguments

`id`	a vector of individual IDs.
`data`	Matrix of alleles, such that each locus has a pair of adjacent columns of alleles, and the order of columns corresponds to the order of loci on a chromosome. If there are K loci, then ncol(data) = 2*K. Rows represent alleles for each subject.
`locus.label`	Vector of labels for loci, of length K (see definition of data matrix).
`converge.eps`	Convergence criterion, based on absolute change in log likelihood (lnlike).
`maxiter`	Maximum number of iterations of EM.
`miss.val`	missing value.

Details

Gene counting for haplotype analysis with missing data, adapted for `hap.score`.

Value

List with components:

- converge Indicator of convergence of the EM algorithm (1=converged, 0 = failed).
- niter Number of iterations completed in the EM alogrithm.
- locus.info A list with a component for each locus. Each component is also a list, and the items of a locus- specific list are the locus name and a vector for the unique alleles for the locus.
- locus.label Vector of labels for loci, of length K (see definition of input values).
- haplotype Matrix of unique haplotypes. Each row represents a unique haplotype, and the number of columns is the number of loci.

- hap.prob Vector of mle's of haplotype probabilities. The ith element of hap.prob corresponds to the ith row of haplotype.
- lnlike Value of lnlike at last EM iteration (maximum lnlike if converged).
- indx.subj Vector for index of subjects, after expanding to all possible pairs of haplotypes for each person. If indx=i, then i is the ith row of input matrix data. If the ith subject has n possible pairs of haplotypes that correspond to their marker phenotype, then i is repeated n times.
- nreps Vector for the count of haplotype pairs that map to each subject's marker genotypes.
- hap1code Vector of codes for each subject's first haplotype. The values in hap1code are the row numbers of the unique haplotypes in the returned matrix haplotype.
- hap2code Similar to hap1code, but for each subject's second haplotype.
- post Vector of posterior probabilities of pairs of haplotypes for a person, given thier marker phenotypes.

Note

Adapted from HAP.

Author(s)

Jing Hua Zhao

See Also

hap, LDkl

Examples

```
## Not run:
data(hla)
hap.em(id=1:length(hla[,1]),data=hla[,3:8],locus.label=c("DQR","DQA","DQB"))

## End(Not run)
```

---

hap.score — *Score statistics for association of traits with haplotypes*

Description

Score statistics for association of traits with haplotypes

Usage

```
hap.score(
  y,
  geno,
  trait.type = "gaussian",
  offset = NA,
  x.adj = NA,
  skip.haplo = 0.005,
  locus.label = NA,
  miss.val = 0,
  n.sim = 0,
  method = "gc",
  id = NA,
  handle.miss = 0,
  mloci = NA,
  sexid = NA
)
```

Arguments

y	Vector of trait values. For trait.type = "binomial", y must have values of 1 for event, 0 for no event.
geno	Matrix of alleles, such that each locus has a pair of adjacent columns of alleles, and the order of columns corresponds to the order of loci on a chromosome. If there are K loci, then ncol(geno) = 2*K. Rows represent alleles for each subject.
trait.type	Character string defining type of trait, with values of "gaussian", "binomial", "poisson", "ordinal".
offset	Vector of offset when trait.type = "poisson".
x.adj	Matrix of non-genetic covariates used to adjust the score statistics. Note that intercept should not be included, as it will be added in this function.
skip.haplo	Skip score statistics for haplotypes with frequencies < skip.haplo.
locus.label	Vector of labels for loci, of length K (see definition of geno matrix).
miss.val	Vector of codes for missing values of alleles.
n.sim	Number of simulations for empirical p-values. If n.sim=0, no empirical p-values are computed.
method	method of haplotype frequency estimation, "gc" or "hap".
id	an added option which contains the individual IDs.
handle.miss	flag to handle missing genotype data, 0=no, 1=yes.
mloci	maximum number of loci/sites with missing data to be allowed in the analysis.
sexid	flag to indicator sex for data from X chromosome, i=male, 2=female.

Details

Compute score statistics to evaluate the association of a trait with haplotypes, when linkage phase is unknown and diploid marker phenotypes are observed among unrelated subjects. For now, only autosomal loci are considered. This package haplo.score which this function is based is greatly acknowledged.

This is a version which substitutes haplo.em.

Value

List with the following components:

- score.global Global statistic to test association of trait with haplotypes that have frequencies >= skip.haplo.
- df Degrees of freedom for score.global.
- score.global.p P-value of score.global based on chi-square distribution, with degrees of freedom equal to df.
- score.global.p.sim P-value of score.global based on simulations (set equal to NA when n.sim=0).
- score.haplo Vector of score statistics for individual haplotypes that have frequencies >= skip.haplo.
- score.haplo.p Vector of p-values for score.haplo, based on a chi-square distribution with 1 df.
- score.haplo.p.sim Vector of p-values for score.haplo, based on simulations (set equal to NA when n.sim=0).
- score.max.p.sim P-value of maximum score.haplo, based on simulations (set equal to NA when n.sim=0).
- haplotype Matrix of hapoltypes analyzed. The ith row of haplotype corresponds to the ith item of score.haplo, score.haplo.p, and score.haplo.p.sim.
- hap.prob Vector of haplotype probabilies, corresponding to the haplotypes in the matrix haplotype.
- locus.label Vector of labels for loci, of length K (same as input argument).
- n.sim Number of simulations.
- n.val.global Number of valid simulated global statistics.
- n.val.haplo Number of valid simulated score statistics (score.haplo) for individual haplotypes.

References

Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA (2002). "Score tests for association between traits and haplotypes when linkage phase is ambiguous." *Am J Hum Genet*, **70**(2), 425-34. doi:10.1086/338688.

Examples

```
## Not run:
data(hla)
y<-hla[,2]
geno<-hla[,3:8]
# complete data
```

```
hap.score(y,geno,locus.label=c("DRB","DQA","DQB"))
# incomplete genotype data
hap.score(y,geno,locus.label=c("DRB","DQA","DQB"),handle.miss=1,mloci=1)
unlink("assign.dat")

### note the differences in p values in the following runs
data(aldh2)
# to subset the data since hap doesn't handle one allele missing
deleted<-c(40,239,256)
aldh2[deleted,]
aldh2<-aldh2[-deleted,]
y<-aldh2[,2]
geno<-aldh2[,3:18]
# only one missing locus
hap.score(y,geno,handle.miss=1,mloci=1,method="hap")
# up to seven missing loci and with 10,000 permutations
hap.score(y,geno,handle.miss=1,mloci=7,method="hap",n.sim=10000)

# hap.score takes considerably longer time and does not handle missing data
hap.score(y,geno,n.sim=10000)

## End(Not run)
```

---

hg18 *Chromosomal lengths for build 36*

Description

Data are used in other functions.

Usage

```
data(hg18)
```

Format

A vector containing lengths of chromosomes.

Details

generated from GRCh.R.

hg19 *Chromosomal lengths for build 37*

Description

Data are used in other functions.

Usage

```
data(hg19)
```

Format

A vector containing lengths of chromosomes.

hg38 *Chromosomal lengths for build 38*

Description

Data are used in other functions.

Usage

```
data(hg38)
```

Format

A vector containing lengths of chromosomes.

hmht.control *Controls for highlighted regions in mhtplot*

Description

Helper function defining highlighted markers or genomic regions to be emphasised in `mhtplot()`.

Usage

```
hmht.control(
  data = NULL,
  colors = "red",
  yoffset = 0.25,
  cex = 1.2,
  boxed = FALSE
)
```

Arguments

data	Data frame with **four columns**: chromosome, position, value and label (e.g. gene name).
colors	Character vector of colours used for highlighted regions. Colours are recycled if multiple labels are present.
yoffset	Numeric vertical offset added to the highest highlighted point before placing the label.
cex	Numeric scaling factor for label text.
boxed	Logical. If TRUE, labels are drawn inside a white box with black border.

Value

A list of highlight control parameters for mhtplot().

See Also

mhtplot(), mht.control()

Examples

```
## Example highlight specification
hdata <- data.frame(
  chr  = c(1,3,5),
  pos  = c(10000,50000,90000),
  p    = c(1e-8,1e-7,1e-9),
  gene = c("GENE1","GENE2","GENE3")
)
hmht.control(data = hdata, cex=0.8, colors = "red", boxed = TRUE)
```

---

htr *Haplotype trend regression*

Description

Haplotype trend regression

Usage

```
htr(y, x, n.sim = 0)
```

Arguments

y	a vector of phenotype.
x	a haplotype table.
n.sim	the number of permutations.

Details

Haplotype trend regression (with permutation)

Value

The returned value is a list containing:

- f the F statistic for overall association.
- p the p value for overall association.
- fv the F statistics for individual haplotypes.
- pi the p values for individual haplotypes.

Note

adapted from emgi.cpp, a pseudorandom number seed will be added on.

Author(s)

Dimitri Zaykin, Jing Hua Zhao

References

Zaykin DV, Westfall PH, Young SS, Karnoub MA, Wagner MJ, Ehm MG (2002). “Testing association of statistically inferred haplotypes with discrete and continuous traits in samples of unrelated individuals.” *Hum Hered*, **53**(2), 79-91. doi:10.1159/000057986.

Xie R, Stram DO (2005). “Asymptotic equivalence between two score tests for haplotype-specific risk in general linear models.” *Genetic Epidemiology*, **29**(2), 166-170. doi:10.1002/gepi.20087.

See Also

hap.score

Examples

```
## Not run:
# 26-10-03
# this is now part of demo
test2<-read.table("test2.dat")
y<-test2[,1]
x<-test2[,-1]
y<-as.matrix(y)
x<-as.matrix(x)
htr.test2<-htr(y,x)
htr.test2
htr.test2<-htr(y,x,n.sim=10)
htr.test2

# 13-11-2003
require(gap.datasets)
data(apoeapoc)
```

```
apoeapoc.gc<-gc.em(apoeapoc[,5:8])
y<-apoeapoc$y
for(i in 1:length(y)) if(y[i]==2) y[i]<-1
htr(y,apoeapoc.gc$htrtable)

# 20-8-2008
# part of the example from useR!2008 tutorial by Andrea Foulkes
# It may be used beyond the generalized linear model (GLM) framework
HaploEM <- haplo.em(Geno,locus.label=SNPnames)
HapMat <- HapDesign(HaploEM)
m1 <- lm(Trait~HapMat)
m2 <- lm(Trait~1)
anova(m2,m1)

## End(Not run)
```

---

hwe *Hardy-Weinberg Equilibrium Test (Multiallelic, Unified Interface)*

Description

Unified Hardy-Weinberg equilibrium (HWE) testing procedure for multiallelic loci. All input formats are internally converted to a single genotype count matrix, ensuring identical inference across representations.

Usage

```
hwe(
  data,
  type = c("alleles", "genotypes", "counts"),
  verbose = TRUE,
  yates.correct = FALSE,
  B = 1e+05,
  seed = 123
)
```

Arguments

`data`	genotype data in one of three formats: • alleles two-column allele pairs • genotypes integer genotype IDs (triangular encoding) • counts symmetric genotype count matrix
`type`	input format: "alleles", "genotypes", or "counts"
`verbose`	logical; if TRUE, prints full test output
`yates.correct`	logical; if TRUE applies Yates continuity correction to Pearson chi-square statistic only
`B`	number of Monte Carlo replicates for exact test
`seed`	random seed for Monte Carlo exact test

Details

Let allele frequencies be:

$$p_i = \frac{c_i}{2n}$$

Under Hardy–Weinberg equilibrium:

$$P_{ii} = p_i^2, \quad P_{ij} = 2p_i p_j \ (i \neq j)$$

Expected genotype counts:

$$E_{ij} = nP_{ij}$$

All input formats are mapped to the same genotype matrix, ensuring algebraic equivalence.

Pearson chi-square

$$X^2 = \sum_{i \leq j} \frac{(O_{ij} - E_{ij})^2}{E_{ij}}$$

With optional Yates correction:

$$X^2 = \sum \frac{(|O_{ij} - E_{ij}| - 0.5)^2}{E_{ij}}$$

Likelihood ratio test

$$G^2 = 2 \sum_{i \leq j} O_{ij} \log(O_{ij}/E_{ij})$$

with convention 0log(0) = 0.

Inbreeding coefficient

$$F = \frac{H_{obs} - H_{exp}}{1 - H_{exp}}$$

where:

$$H_{obs} = \sum_i O_{ii}/n, \quad H_{exp} = \sum_i p_i^2$$

Under:

$$X \sim \text{Multinomial}(n, P)$$

the p-value is:

$$p = \Pr(\ell(X^{sim}) \leq \ell(X^{obs}))$$

where:

$$\ell(x) = \sum x_i \log p_i + \log \frac{n!}{\prod x_i!}$$

$$\text{alleles} \equiv \text{genotype IDs} \equiv \text{count matrix} \to M_{ij}$$

Hence all statistics are identical up to Monte Carlo variation.

Value

Named list containing:

- `source` — input representation used ("alleles", "genotypes", or "counts")
- `X2` — Pearson chi-square statistic
- `p_X2` — asymptotic p-value of Pearson chi-square test
- `LRT` — likelihood ratio statistic
- `p_LRT` — asymptotic p-value of likelihood ratio test
- `p_exact` — Monte Carlo exact test p-value
- `freq` — allele frequency vector
- `rho` — inbreeding coefficient

Note

Note that

- Zero-frequency alleles are removed automatically
- Exact test is Monte Carlo (fixed seed for reproducibility)
- All statistics are computed on the same standardized genotype matrix

Examples

```
## Not run:
a1 <- c(1,1,1,1,2,2,2,3,3,1,2,3,1,2,3,1,2,3)
a2 <- c(1,2,3,1,2,3,2,3,1,2,3,1,1,1,2,3,2,3)
r1 <- hwe(cbind(a1,a2), "alleles", FALSE)
g <- a2g(a1,a2)
r2 <- hwe(g, "genotypes", FALSE)
g_tab <- table(g)
pairs <- g2a(as.integer(names(g_tab)))
k <- max(pairs)
M <- matrix(0, k, k)
for(i in seq_len(nrow(pairs))) {
  M[pairs[i,1], pairs[i,2]] <- g_tab[i]
}
r3 <- hwe(M, "counts", FALSE)
r <- lapply(list(r1, r2, r3), \(x) within(as.data.frame(x), {
     freq <- paste(round(as.numeric(freq), 3), collapse=";")})[1,])
do.call(rbind,r)

## End(Not run)
```

hwe.cc — *A likelihood ratio test of population Hardy-Weinberg equilibrium for case-control studies*

Description

A likelihood ratio test of population Hardy-Weinberg equilibrium for case-control studies

Usage

```
hwe.cc(model, case, ctrl, k0, initial1, initial2)
```

Arguments

`model`	model specification, dominant, recessive.
`case`	a vector of genotype counts in cases.
`ctrl`	a vector of genotype counts in controls.
`k0`	prevalence of disease in the population.
`initial1`	initial values for beta, gamma, and q.
`initial2`	initial values for logit(p) and log(gamma).

Details

A likelihood ratio test of population Hardy-Weinberg equilibrium for case-control studies

This is a collection of utility functions. The null hypothesis declares that the proportions of genotypes are according to Hardy-Weinberg law, while under the alternative hypothesis, the expected genotype counts are according to the probabilities that particular genotypes are obtained conditional on the prevalence of disease in the population. In so doing, Hardy-Weinberg equilibrium is considered using both case and control samples but pending on the disease model such that 2-parameter multiplicative model is built on baseline genotype α, $\alpha\beta$ and $\alpha\gamma$.

Value

The returned value is a list with the following components.

- Cox statistics under a general model.
- t2par under the null hypothesis.
- t3par under the alternative hypothesis.
- lrt.stat the log-likelihood ratio statistic.
- pval the corresponding p value.

Author(s)

Chang Yu, Li Wang, Jing Hua Zhao

References

Yu C, Zhang S, Zhou C, Sile S (2009). "A likelihood ratio test of population Hardy-Weinberg equilibrium for case-control studies." *Genet Epidemiol*, **33**(3), 275-80. doi:10.1002/gepi.20381.

See Also

hwe

Examples

```
## Not run:
### Saba Sile, email of Jan 26, 2007, data always in order of GG AG AA, p=Pr(G),
### q=1-p=Pr(A)
case=c(155,27,4)
ctrl=c(408,55,15)
k0=.2
initial1=c(1.0,0.94,0.0904)
initial2=c(logit(1-0.0904),log(0.94))
hwe.cc("recessive",case,ctrl,k0, initial1, initial2)

### John Phillips III, TGFb1 data codon 10: TT CT CC, CC is abnormal and increasing
### TGFb1 activity
case=c(29,78,13)
ctrl=c(17,28,6)
k0 <- 1e-5
initial1 <- c(2.45,2.45,0.34)
initial2 <- c(logit(1-0.34),log(2.45))
hwe.cc("dominant",case,ctrl,k0,initial1,initial2)

## End(Not run)
```

---

hwe.hardy *Hardy-Weinberg equilibrium test using MCMC*

Description

Hardy-Weinberg equilibrium test using MCMC

Usage

```
hwe.hardy(a, alleles = 3, seed = 3000, sample = c(1000, 1000, 5000))
```

Arguments

a	an array containing the genotype counts, as integer.
alleles	number of allele at the locus, greater than or equal to 3, as integer.
seed	pseudo-random number seed, as integer.
sample	optional, parameters for MCMC containing number of chunks, size of a chunk and burn-in steps, as integer.

Details

Hardy-Weinberg equilibrium test by MCMC

Value

The returned value is a list containing:

- method Hardy-Weinberg equilibrium test using MCMC.
- data.name name of used data if x is given.
- p.value Monte Carlo p value.
- p.value.se standard error of Monte Carlo p value.
- switches percentage of switches (partial, full and altogether).

Note

Codes are commented for taking x a genotype object, as genotype to prepare `a` and `alleles` on the fly.

Adapted from HARDY, testable with -Dexecutable as standalone program.

keywords htest

Author(s)

Sun-Wei Guo, Jing Hua Zhao, Gregor Gorjanc

Source

https://sites.stat.washington.edu/thompson/Genepi/pangaea.shtml

References

Guo SW, Thompson EA (1992). "Performing the exact test of Hardy-Weinberg proportion for multiple alleles." *Biometrics*, **48**(2), 361-72.

See Also

`hwe`, `genetics::HWE.test`, `genetics::genotype`

Examples

```
## Not run:
 # example 2 from hwe.doc:
   a<-c(
   3,
   4, 2,
   2, 2, 2,
   3, 3, 2, 1,
   0, 1, 0, 0, 0,
   0, 0, 0, 0, 0, 1,
   0, 0, 1, 0, 0, 0, 0,
```

```
    0, 0, 0, 2, 1, 0, 0, 0)
    ex2 <- hwe.hardy(a=a,alleles=8)

    # example using HLA
    data(hla)
    x <- hla[,3:4]
    y <- pgc(x,handle.miss=0,with.id=1)
    n.alleles <- max(x,na.rm=TRUE)
    z <- vector("numeric",n.alleles*(n.alleles+1)/2)
    z[y$idsave] <- y$wt
    hwe.hardy(a=z,alleles=n.alleles)

    # with use of class 'genotype'
    # this is to be fixed
    library(genetics)
    hlagen <- genotype(a1=x$DQR.a1, a2=x$DQR.a2,
                       alleles=sort(unique(c(x$DQR.a1, x$DQR.a2))))
    hwe.hardy(hlagen)

    # comparison with hwe
    hwe(z,data.type="count")

    # to create input file for HARDY
    print.tri<-function (xx,n) {
        cat(n,"\n")
        for(i in 1:n) {
            for(j in 1:i) {
                cat(xx[i,j]," ")
            }
        cat("\n")
        }
        cat("100 170 1000\n")
    }
    xx<-matrix(0,n.alleles,n.alleles)
    xxx<-lower.tri(xx,diag=TRUE)
    xx[xxx]<-z
    sink("z.dat")
    print.tri(xx,n.alleles)
    sink()
    # now call as: hwe z.dat z.out

## End(Not run)
```

`hwe.jags` *Hardy-Weinberg equlibrium test for a multiallelic marker using JAGS*

Description

Hardy-Weinberg equlibrium test for a multiallelic marker using JAGS

Usage

```
hwe.jags(
  k,
  n,
  delta = rep(1/k, k),
  lambda = 0,
  lambdamu = -1,
  lambdasd = 1,
  parms = c("p", "f", "q", "theta", "lambda"),
  ...
)
```

Arguments

`k`	number of alleles.
`n`	a vector of k(k+1)/2 genotype counts.
`delta`	initial parameter values.
`lambda`	initial parameter values.
`lambdamu`	initial parameter values.
`lambdasd`	initial parameter values.
`parms`	monitored parmeters.
`...`	parameters passed to jags, e.g., n.chains, n.burnin, n.iter.

Details

Hardy-Weinberg equilibrium test.

This function performs Bayesian Hardy-Weinberg equilibrium test, which mirrors hwe.hardy, another implementation for highly polymorphic markers when asymptotic results do not hold.

Value

The returned value is a fitted model from jags().

Author(s)

Jing Hua Zhao, Jon Wakefield

References

Wakefield J (2010). "Bayesian methods for examining Hardy-Weinberg equilibrium." *Biometrics*, **66**(1), 257-65. doi:10.1111/j.15410420.2009.01267.x.

See Also

`hwe.hardy`

Examples

```
## Not run:
ex1 <- hwe.jags(4,c(5,6,1,7,11,2,8,19,26,15))
print(ex1)
ex2 <- hwe.jags(2,c(49,45,6))
print(ex2)
ex3 <- hwe.jags(4,c(0,3,1,5,18,1,3,7,5,2),lambda=0.5,lambdamu=-2.95,lambdasd=1.07)
print(ex3)
ex4 <- hwe.jags(9,c(1236,120,3,18,0,0,982,55,7,249,32,1,0,12,0,2582,132,20,1162,29,
                    1312,6,0,0,4,0,4,0,2,0,0,0,0,0,0,0,115,5,2,53,1,149,0,0,4),
                delta=c(1,1,1,1,1,1,1,1,1),lambdamu=-4.65,lambdasd=0.21)
print(ex4)
ex5 <- hwe.jags(8,n=c(
         3,
         4, 2,
         2, 2, 2,
         3, 3, 2, 1,
         0, 1, 0, 0, 0,
         0, 0, 0, 0, 0, 1,
         0, 0, 1, 0, 0, 0, 0,
         0, 0, 0, 2, 1, 0, 0, 0))
print(ex5)

# Data and code accordining to the following URL,
# http://darwin.eeb.uconn.edu/eeb348-notes/testing-hardy-weinberg.pdf
hwe.jags.ABO <- function(n,...)
{
  hwe <- function() {
     # likelihood
     pi[1] <- p.a*p.a + 2*p.a*p.o
     pi[2] <- 2*p.a*p.b
     pi[3] <- p.b*p.b + 2*p.b*p.o
     pi[4] <- p.o*p.o
     n[1:4] ~ dmulti(pi[],N)
     # priors
     a1 ~ dexp(1)
     b1 ~ dexp(1)
     o1 ~ dexp(1)
     p.a <- a1/(a1 + b1 + o1)
     p.b <- b1/(a1 + b1 + o1)
     p.o <- o1/(a1 + b1 + o1)
  }
  hwd <- function() {
     # likelihood
     pi[1] <- p.a*p.a + f*p.a*(1-p.a) + 2*p.a*p.o*(1-f)
     pi[2] <- 2*p.a*p.b*(1-f)
     pi[3] <- p.b*p.b + f*p.b*(1-p.b) + 2*p.b*p.o*(1-f)
     pi[4] <- p.o*p.o + f*p.o*(1-p.o)
     n[1:4] ~ dmulti(pi[],N)
     # priors
     a1 ~ dexp(1)
     b1 ~ dexp(1)
```

```
    o1 ~ dexp(1)
    p.a <- a1/(a1 + b1 + o1)
    p.b <- b1/(a1 + b1 + o1)
    p.o <- o1/(a1 + b1 + o1)
    f ~ dunif(0,1)
  }
  N <- sum(n)
  ABO.hwe <- R2jags::jags(list(n=n,N=N),,c("pi","p.a","p.b","p.o"),hwe,...)
  ABO.hwd <- R2jags::jags(list(n=n,N=N),,c("pi","p.a","p.b","p.o","f"),hwd,...)
  invisible(list(hwe=ABO.hwe,hwd=ABO.hwd))
}
hwe.jags.ABO.results <- hwe.jags.ABO(n=c(862, 131, 365, 702))
hwe.jags.ABO.results

## End(Not run)
```

`invnormal` *Inverse normal transformation*

Description

Inverse normal transformation

Usage

```
invnormal(x)
```

Arguments

x	Data with missing values.

Value

Transformed value.

Examples

```
x <- 1:10
z <- invnormal(x)
plot(z,x,type="b")
```

`inv_chr_pos_a1_a2` *Retrieval of chr:pos+a1/a2 according to SNP id*

Description

This function obtains information embedded in unique identifiers.

Usage

```
inv_chr_pos_a1_a2(chr_pos_a1_a2, prefix = "chr", seps = c(":", "_", "_"))
```

Arguments

`chr_pos_a1_a2`	SNP id.
`prefix`	Prefix of the identifier.
`seps`	Delimiters of fields.

Value

A data.frame with the following variables:

- chr Chromosome.
- pos Position.
- a1 Allele 1.
- a2 Allele 2.

Examples

```
# rs12075
inv_chr_pos_a1_a2("chr1:159175354_A_G",prefix="chr",seps=c(":","_","_"))
```

`ixy` *Conversion of chrosome name from strings*

Description

This function converts 1:22, X, Y back to 1:24.

Usage

```
ixy(x)
```

Arguments

`x`	Chromosome name in strings

Value

As indicated.

KCC *Disease prevalences in cases and controls*

Description

Disease prevalences in cases and controls

Usage

```
KCC(model, GRR, p1, K)
```

Arguments

model	disease model (one of "multiplicative","additive","recessive","dominant","overdominant").
GRR	genotype relative risk.
p1	disease allele frequency.
K	disease prevalence in the whole population.

Details

KCC calculates disease prevalences in cases and controls for a given genotype relative risk, allele frequency and prevalencen of the disease in the whole population. It is used by tscc and pbsize2.

Value

A list of two elements:

- pprime prevlence in cases.
- p prevalence in controls.

kin.morgan — *kinship matrix for simple pedigree*

Description

kinship matrix for simple pedigree

Usage

```
kin.morgan(ped, verbose = FALSE)
```

Arguments

`ped`	A matrix with columns on individual's id, father's id and mother's id.
`verbose`	an option to print out the original pedigree.

Details

kinship matrix according to Morgan v2.1.

Value

The returned value is a list containing:

- kin the kinship matrix in vector form.
- kin.matrix the kinship matrix.

Note

The input data is required to be sorted so that parents preceed their children.

Author(s)

Morgan development team, Jing Hua Zhao

References

Morgan V2.1, https://faculty.washington.edu/eathomp/Genepi/MORGAN/Morgan.shtml

See Also

`gif`

Examples

```
## Not run:
# Werner syndrome pedigree
werner<-c(
 1, 0,  0,  1,
 2, 0,  0,  2,
 3, 0,  0,  2,
 4, 1,  2,  1,
 5, 0,  0,  1,
 6, 1,  2,  2,
 7, 1,  2,  2,
 8, 0,  0,  1,
 9, 4,  3,  2,
10, 5,  6,  1,
11, 5,  6,  2,
12, 8,  7,  1,
13,10,  9,  2,
14,12, 11,  1,
15,14, 13,  1)
werner<-t(matrix(werner,nrow=4))
kin.morgan(werner[,1:3])

## End(Not run)
```

---

klem — *Haplotype frequency estimation based on a genotype table of two multiallelic markers*

Description

Haplotype frequency estimation using expectation-maximization algorithm based on a table of genotypes of two multiallelic markers.

Usage

```
klem(obs, k = 2, l = 2)
```

Arguments

`obs`	a table of genotype counts.
`k`	number of alleles at marker 1.
`l`	number of alleles at marker 2. The dimension of the genotype table should be k*(k+1)/2 x l*(l+1)/2. Modified from 2ld.c.

Value

The returned value is a list containing:

- h haplotype Frequencies.
- l0 log-likelihood under linkage equilibrium.
- l1 log-likelihood under linkage disequilibrium.

Author(s)

Jing Hua Zhao

See Also

genecounting

Examples

```
## Not run:
# an example with known genotype counts
z <- klem(obs=1:9)
# an example with imputed genotypes at SH2B1
source(file.path(find.package("gap"),"scripts","SH2B1.R"),echo=TRUE)

## End(Not run)
```

---

labelManhattan *Annotate Manhattan or Miami Plot*

Description

Annotate Manhattan or Miami Plot

Usage

```
labelManhattan(
  chr,
  pos,
  name,
  gwas,
  gwasChrLab = "chr",
  gwasPosLab = "pos",
  gwasPLab = "p",
  gwasZLab = "NULL",
  chrmaxpos,
  textPos = 4,
  angle = 0,
  miamiBottom = FALSE
)
```

Arguments

- `chr` A vector of chromosomes for the markers to be labelled.
- `pos` A vector of positions on the chromosome for the markers to be labelled. These must correspond to markers in the GWAS dataset used to make the manhattan plot.
- `name` A vector of labels to be added next to the points specified by `chr` and `pos`.
- `gwas` The same GWAS dataset used to plot the existing Manhattan or Miami plot to be annotated.
- `gwasChrLab` The name of the column in `gwas` containing chromosome number. Defaults to ‘"chr"’.
- `gwasPosLab` The name of the column in `gwas` containing position. Defaults to ‘"pos"’.
- `gwasPLab` The name of the column in `gwas` containing p-values. Defaults to ‘"p"’.
- `gwasZLab` The name of the column in `gwas` containing z-values. Defaults to ‘"NULL"’.
- `chrmaxpos` Data frame containing x coordinates for chromosome start positions, generated by `labelManhattan`.
- `textPos` An integer or vector dictating where the label should be plotted relative to each point. Good for avoiding overlapping labels. Provide an integer to plot all points in the same relative position or use a vector to specify position for each label. Passed to the ‘`pos`’ option of `graphics::text`. Defaults to ‘`4`’.
- `angle` An integer or vector dictating the plot angle of the label for each point. rovide an integer to plot all points in the same relative position or use a vector to specify position for each label.Passed to the ‘`srt`’ option of `graphics::text`. Defaults to ‘`0`’.
- `miamiBottom` If ‘`TRUE`’, labels will be plotted on the lower region of a Miami plot. If ‘`FALSE`’, labels will be plotted on the upper region. Defaults to ‘`FALSE`’.

Details

Add labels beside specified points on a Manhattan or Miami plot. Ideal for adding locus names to peaks. Currently only designed to work with `miamiplot2`.

Value

Adds annotation to existing Manhattan or Miami plot

Note

Extended to handle extreme P values.

Author(s)

Jonathan Marten

Examples

```
## Not run:
labelManhattan(c(4,5,11,19),c(9994215,16717922,45538760,51699256),
               c("GENE1","GENE2","GENE3","GENE4"),
               gwas1,chrmaxpos=chrmaxpos)
labelManhattan(geneLabels$chr,geneLabel$pos,geneLabel$geneName,gwas1,chrmaxpos=chrmaxpos)

## End(Not run)
```

`LD22` *LD statistics for two diallelic markers*

Description

LD statistics for two diallelic markers

Usage

```
LD22(h, n)
```

Arguments

`h`	a vector of haplotype frequencies.
`n`	number of haplotypes.

Details

It is possible to perform permutation test of r^2 by re-ordering the genotype through R's sample function, obtaining the haplotype frequencies by `gc.em` or `genecounting`, supplying the estimated haplotype frequencies to the current function and record x2, and comparing the observed x2 and that from the replicates.

Value

The returned value is a list containing:

- h the original haplotype frequency vector.
- n the number of haplotypes.
- D the linkage disequilibrium parameter.
- VarD the variance of D.
- Dmax the maximum of D.
- VarDmax the variance of Dmax.
- Dprime the scaled disequilibrium parameter.
- VarDprime the variance of Dprime.
- x2 the Chi-squared statistic.
- lor the log(OR) statistic.
- vlor the var(log(OR)) statistic.

Note

extracted from 2ld.c, worked 28/6/03, tables are symmetric do not fix, see kbyl below

Author(s)

Jing Hua Zhao

References

Zabetian CP, Buxbaum SG, Elston RC, Köhnke MD, Anderson GM, Gelernter J, Cubells JF (2003). "The structure of linkage disequilibrium at the DBH locus strongly influences the magnitude of association between diallelic markers and plasma dopamine beta-hydroxylase activity." *Am J Hum Genet*, **72**(6), 1389-400. doi:10.1086/375499.

Zapata C, Alvarez G, Carollo C (1997). "Approximate variance of the standardized measure of gametic disequilibrium D'." *Am J Hum Genet*, **61**(3), 771-4. doi:10.1016/s00029297(07)643420.

See Also

`LDkl`

Examples

```
## Not run:
h <- c(0.442356,0.291532,0.245794,0.020319)
n <- 481*2
t <- LD22(h,n)

## End(Not run)
```

LDkl *LD statistics for two multiallelic markers*

Description

LD statistics for two multiallelic loci. For two diallelic makers, the familiar r^2 has standard error seX2.

Usage

```
LDkl(n1 = 2, n2 = 2, h, n, optrho = 2, verbose = FALSE)
```

Arguments

n1	number of alleles at marker 1.
n2	number of alleles at marker 2.
h	a vector of haplotype frequencies.
n	number of haplotypes.
optrho	type of contingency table association, 0=Pearson, 1=Tschuprow, 2=Cramer (default).
verbose	detailed output of individual statistics.

Value

The returned value is a list containing:

- n1 the number of alleles at marker 1.
- n2 the number of alleles at marker 2.
- h the haplotype frequency vector.
- n the number of haplotypes.
- Dp D'.
- VarDp variance of D'.
- Dijtable table of Dij.
- VarDijtable table of variances for Dij.
- Dmaxtable table of Dmax.
- Dijptable table of Dij'.
- VarDijptable table of variances for Dij'.
- X2table table of Chi-squares (based on Dij).
- ptable table of p values.
- x2 the Chi-squared statistic.
- seX2 the standard error of x2/n.
- rho the measure of association.
- seR the standard error of rho.
- optrho the method for calculating rho.
- klinfo the Kullback-Leibler information.

Note

adapted from 2ld.c.

Author(s)

Jing Hua Zhao

References

Bishop YMM, Fienberg SE, Holland PW (1975). *Discrete multivariate analysis: theory and practice*. MIT Press, Cambridge, Mass. ISBN 9780262021135.

Cramer H (1946). *Mathematical Methods of Statistics*. Princeton Univ. Press.

Zapata C, Carollo C, Rodriguez S (2001). "Sampling variance and distribution of the D' measure of overall gametic disequilibrium between multiallelic loci." *Ann Hum Genet*, **65**(Pt 4), 395-406. doi:10.1017/s0003480001008697.

Zhao JH (2004). "2LD. GENECOUNTING and HAP: computer programs for linkage disequilibrium analysis." *Bioinformatics*, **20**(8), 1325-6. doi:10.1093/bioinformatics/bth071.

See Also

LD22

Examples

```
## Not run:
# two examples in the C program 2LD:
# two SNPs as in 2by2.dat
# this can be compared with output from LD22

h <- c(0.442356,0.291532,0.245794,0.020319)
n <- 481*2
t <- LDkl(2,2,h,n)
t

# two multiallelic markers as in kbyl.dat
# the two-locus haplotype vector is in file "kbyl.dat"
# The data is now available from 2ld in Haplotype-Analysis

filespec <- system.file("kbyl.dat")
h <- scan(filespec,skip=1)
t <- LDkl(9,5,h,213*2,verbose=TRUE)

## End(Not run)
```

`log10p` *log10(p) for a normal deviate z*

Description

log10(p) for a normal deviate z

Usage

```
log10p(z)
```

Arguments

z	normal deviate.

Value

`log10(P)`

Author(s)

James Peters

Examples

```
log10p(100)
```

`log10pvalue` *log10(p) for a P value including its scientific format*

Description

log10(p) for a P value including its scientific format

Usage

```
log10pvalue(p = NULL, base = NULL, exponent = NULL)
```

Arguments

p	value.
base	base part in scientific format.
exponent	exponent part in scientific format.

Value

`log10(P)`

Examples

```
log10pvalue(1e-323)
log10pvalue(base=1,exponent=-323)
```

logp *log(p) for a normal deviate z*

Description

log(p) for a normal deviate z

Usage

```
logp(z)
```

Arguments

z	normal deviate.

Value

log(P)

Examples

```
logp(100)
```

makeped *A function to prepare pedigrees in post-MAKEPED format*

Description

A function to prepare pedigrees in post-MAKEPED format

Usage

```
makeped(
  pifile = "pedfile.pre",
  pofile = "pedfile.ped",
  auto.select = 1,
  with.loop = 0,
  loop.file = NA,
  auto.proband = 1,
  proband.file = NA
)
```

Arguments

`pifile`	input filename.
`pofile`	output filename.
`auto.select`	no loops in pedigrees and probands are selected automatically? 0=no, 1=yes.
`with.loop`	input data with loops? 0=no, 1=yes.
`loop.file`	filename containing pedigree id and an individual id for each loop, set if with.loop=1.
`auto.proband`	probands are selected automatically? 0=no, 1=yes.
`proband.file`	filename containing pedigree id and proband id, set if auto.proband=0 (not implemented).

Details

Many computer programs for genetic data analysis requires pedigree data to be in the so-called "post-MAKEPED" format. This function performs this translation and allows for some inconsistences to be detected.

The first four columns of the input file contains the following information:

pedigree ID, individual ID, father's ID, mother's ID, sex

Either father's or mother's id is set to 0 for founders, i.e. individuals with no parents. Numeric coding for sex is 0=unknown, 1=male, 2=female. These can be followed by satellite information such as disease phenotype and marker information.

The output file has extra information extracted from data above.

Before invoking makeped, input file, loop file and proband file have to be prepared.

By default, auto.select=1, so translation proceeds without considering loops and proband statuses. If there are loops in the pedigrees, then set auto.select=0, with.loop=1, loop.file="filespec".

There may be several versions of makeped available, but their differences with this port should be minor.

Note

adapted from makeped.c by W Li and others. keywords datagen

Examples

```
## Not run:
cwd <- getwd()
cs.dir <- file.path(find.package("gap.examples"),"tests","kinship")
setwd(cs.dir)
dir()
makeped("ped7.pre","ped7.ped",0,1,"ped7.lop")
setwd(cwd)
# https://lab.rockefeller.edu/ott/

## End(Not run)
```

masize	*Sample size calculation for mediation analysis*

Description

The function computes sample size for regression problems where the goal is to assess mediation of the effects of a primary predictor by an intermediate variable or mediator.

Usage

```
masize(model, opts, alpha = 0.025, gamma = 0.2)
```

Arguments

`model`	"lineari", "logisticj", "poissonk", "coxl", where i,j,k,l range from 1 to 4,5,9,9, respectively.
`opts`	A list specific to the model

b1	regression coefficient for the primary predictor X1
b2	regression coefficient for the mediator X2
rho	correlation between X1 and X2
sdx1, sdx2	standard deviations (SDs) of X1 and X2
f1, f2	prevalence of binary X1 and X2
sdy	residual SD of the outcome for the linear model
p	marginal prevalence of the binary outcome in the logistic model
m	marginal mean of the count outcome in a Poisson model
f	proportion of uncensored observations for the Cox model
fc	proportion of observations censored early
alpha	one-sided type-I error rate
gamma	type-II error rate
ns	number of observations to be simulated
seed	random number seed

For linear model, the arguments are b2, rho, sdx2, sdy, alpha, and gamma. For cases CpBm and BpBm, set sdx2 = $\sqrt{f2(1-f2)}$. Three alternative functions are included for the linear model. These functions make it possible to supply other combinations of input parameters affecting mediation:

b1*	coefficient for the primary predictor in the reduced model excluding the mediator (b1star)
b1	coefficient for the primary predictor in the full model including the mediator
PTE	proportion of the effect of the primary predictor explained by the mediator, defined as (b1*-b1)/b1*

These alternative functions for the linear model require specification of an extra parameter, but are provided for convenience, along with two utility files for computing PTE and b1* from the other parameters. The required arguments are explained in comments within the R code.

`alpha` Type-I error rate, one-sided.

`gamma` Type-II error rate.

Details

Mediation has been thought of in terms of the proportion of effect explained, or the relative attenuation of b1, the coefficient for the primary predictor X1, when the mediator, X2, is added to the model. The goal is to show that b1*, the coefficient for X1 in the reduced model (i.e., the model with only X1, differs from b1, its coefficient in the full model (i.e., the model with both X1 and the mediator X2. If X1 and X2 are correlated, then showing that b2, the coefficient for X2, differs from zero is equivalent to showing b1* differs from b1. Thus the problem reduces to detecting an effect of X2, controlling for X1. In short, it amounts to the more familiar problem of inflating sample size to account for loss of precision due to adjustment for X1.

The approach here is to approximate the expected information matrix from the regression model including both X1 and X2, to obtain the expected standard error of the estimate of b2, evaluated at the MLE. The sample size follows from comparing the Wald test statistic (i.e., the ratio of the estimate of b2 to its SE) to the standard normal distribution, with the expected value of the numerator and denominator of the statistic computed under the alternative hypothesis. This reflects the Wald test for the statistical significance of a coefficient implemented in most regression packages.

The function provides methods to calculate sample sizes for the mediation problem for linear, logistic, Poisson, and Cox regression models in four cases for each model:

CpCm	continuous primary predictor, continuous mediator
BpCm	binary primary predictor, continuous mediator
CpBm	continuous primary predictor, binary mediator
BpBm	binary primary predictor, binary mediator

The function is also generally applicable to the analogous problem of calculating sample size adequate to detect the effect of a primary predictor in the presence of confounding. Simply treat X2 as the primary predictor and consider X1 the confounder.

For linear model, a single function, linear, implements the analytic solution for all four cases, based on Hsieh et al., is to inflate sample size by a variance inflation factor, $1/(1 - rho^2)$, where rho is the correlation of X1 and X2. This also turns out to be the analytic solution in cases CpCm and BpCm for the Poisson model, and underlies approximate solutions for the logistic and Cox models. An analytic solution is also given for cases CpBm and BpBm for the Poisson model. Since analytic solutions are not available for the logistic and Cox models, a simulation approach is used to obtain the expected information matrix instead.

For logistic model, the approximate solution due to Hsieh is implemented in the function logistic.approx, and can be used for all four cases. Arguments are p, b2, rho, sdx2, alpha, and gamma. For a binary mediator with prevalence f2, sdx2 should be reset to $\sqrt{f2(1 - f2)}$. Simulating the information matrix of the logistic model provides somewhat more accurate sample size estimates than the Hsieh approximation. The functions for cases CpCm, BpCm, CpBm, and BpBm are respectively logistic.ccs, logistic.bcs, logistic.cbs, and logistic.bbs, as for the Poisson and Cox models.

Arguments for these functions include p, b1, sdx1 or f1, b2, sdx2 or f2, rho, alpha, gamma, and ns. As in other functions, sdx1, sdx2, alpha, and gamma are set to the defaults listed above. These four functions call two utility functions, getb0 (to calculate the intercept parameter from the others) and antilogit, which are supplied.

For Poisson model, The function implementing the approximate solution based on the variance inflation factor is poisson.approx, and can be used for all four cases. Arguments are EY (the marginal mean of the Poisson outcome), b2, sdx2, rho, alpha and gamma, with sdx2, alpha and gamma set to the usual defaults; use sdx2=$\sqrt{f2(1-f2)}$ for a binary mediator with prevalence f2 (cases CpBm and BpBm). For cases CpCm and BpCm (continuous mediators), the approximate formula is also the analytic solution. For these cases, we supply redundant functions poisson.cc and poisson.bc, with the same arguments and defaults as for poisson.approx (it's the same function). For the two cases with binary mediators, the functions are poisson.cb and poisson.bb. In addition to m, b2, f2, rho, alpha, and gamma, b1 and sdx1 or f1 must be specified. Defaults are as usual. Functions using simulation for the Poisson model are available: poisson.ccs, poisson.bcs, poisson.cbs, and poisson.bbs. As in the logistic case, these require arguments b1 and sdx1 or f1. For this case, however, the analytic functions are faster, avoid simulation error, and should be used. We include these functions as templates that could be adapted to other joint predictor distributions. For Cox model, the function implementing the approximate solution, using the variance inflation factor and derived by Schmoor et al., is cox.approx, and can be used for all four cases. Arguments are b2, sdx2, rho, alpha, gamma, and f. For binary X2 set sdx2 = $\sqrt{f2(1-f2)}$. The approximation works very well for cases CpCm and BpCm (continuous mediators), but is a bit less accurate for cases CpBm and BpBm (binary mediators). We get some improvement for those cases using the simulation approach. This approach is implemented for all four, as functions cox.ccs, cox.bcs, cox.cbs, and cox.bbs. Arguments are b1, sdx1 or f1, b2, sdx2 or f2, rho, alpha, gamma, f, and ns, with defaults as described above. Slight variants of these functions, cox.ccs2, cox.bcs2, cox.cbs2, and cox.bbs2, make it possible to allow for early censoring of a fraction fc of observations; but in our experience this has virtually no effect, even with values of fc of 0.5. The default for fc is 0.

A summary of the argumentss is as follows, noting that additional parameter seed can be supplied for simulation-based method.

model	arguments	description
linear1	b2, rho, sdx2, sdy	linear
linear2	b1star, PTE, rho, sdx1, sdy	lineara
linear3	b1star, b2, PTE, sdx1, sdx2, sdy	linearb
linear4	b1star, b1, b2, sdx1, sdx2, sdy	linearc
logistic1	p, b2, rho, sdx2	logistic.approx
logistic2	p, b1, b2, rho, sdx1, sdx2, ns	logistic.ccs
logistic3	p, b1, f1, b2, rho, sdx2, ns	logistic.bcs
logistic4	p, b1, b2, f2, rho, sdx1, ns	logistic.cbs
logistic5	p, b1, f1, b2, f2, rho, ns	logistic.bbs
poisson1	m, b2, rho, sdx2	poisson.approx
poisson2	m, b2, rho, sdx2	poisson.cc
poisson3	m, b2, rho, sdx2	poisson.bc
poisson4	m, b1, b2, f2, rho, sdx1	poisson.cb
poisson5	m, b1, f1, b2, f2, rho	poisson.bb

poisson6	m, b1, b2, rho, sdx1, sdx2, ns	poisson.ccs
poisson7	m, b1, f1, b2, rho, sdx2, ns	poisson.bcs
poisson8	m, b1, b2, f2, rho, sdx1, ns	poisson.cbs
poisson9	m, b1, f1, b2, f2, rho, ns	poisson.bbs
cox1	b2, rho, f, sdx2	cox.approx
cox2	b1, b2, rho, f, sdx1, sdx2, ns	cox.ccs
cox3	b1, f1, b2, rho, f, sdx2, ns	cox.bcs
cox4	b1, b2, f2, rho, f, sdx1, ns	cox.cbs
cox5	b1, f1, b2, f2, rho, f, ns	cox.bbs
cox6	b1, b2, rho, f, fc, sdx1, sdx2, ns	cox.ccs2
cox7	b1, f1, b2, rho, f, fc, sdx2, ns	cox.bcs2
cox8	b1, b2, f2, rho, f, fc, sdx1, ns	cox.cbs2
cox9	b1, f1, b2, f2, rho, f, fc, ns	cox.bbs2

Value

A short description of model (desc, b=binary, c=continuous, s=simulation) and sample size (n). In the case of Cox model, number of events (d) is also indicated.

References

Hsieh FY, Bloch DA, Larsen MD (1998). "A simple method of sample size calculation for linear and logistic regression." *Stat Med*, **17**(14), 1623-34. doi:10.1002/(sici)10970258(19980730)17:14<1623::aid-sim871>3.0.co;2s.

Schmoor C, Sauerbrei W, Schumacher M (2000). "Sample size considerations for the evaluation of prognostic factors in survival analysis." *Stat Med*, **19**(4), 441-52. doi:10.1002/(sici)1097-0258(20000229)19:4<441::aidsim349>3.0.co;2n.

Vittinghoff E, Sen S, McCulloch CE (2009). "Sample size calculations for evaluating mediation." *Stat Med*, **28**(4), 541-57. doi:10.1002/sim.3491.

See Also

ab

Examples

```
## Not run:
## linear model
# CpCm
opts <- list(b2=0.5, rho=0.3, sdx2=1, sdy=1)
masize("linear1",opts)
# BpBm
opts <- list(b2=0.75, rho=0.3, f2=0.25, sdx2=sqrt(0.25*0.75), sdy=3)
masize("linear1",opts,gamma=0.1)

## logistic model
# CpBm
```

```
opts <- list(p=0.25, b2=log(0.5), rho=0.5, sdx2=0.5)
masize("logistic1",opts)
opts <- list(p=0.25, b1=log(1.5), sdx1=1, b2=log(0.5), f2=0.5, rho=0.5, ns=10000,
             seed=1234)
masize("logistic4",opts)
opts <- list(p=0.25, b1=log(1.5), sdx1=1, b2=log(0.5), f2=0.5, rho=0.5, ns=10000,
             seed=1234)
masize("logistic4",opts)
opts <- list(p=0.25, b1=log(1.5), sdx1=4.5, b2=log(0.5), f2=0.5, rho=0.5, ns=50000,
             seed=1234)
masize("logistic4",opts)

## Poisson model
# BpBm
opts <- list(m=0.5, b2=log(1.25), rho=0.3, sdx2=sqrt(0.25*0.75))
masize("poisson1",opts)
opts <- list(m=0.5, b1=log(1.4), f1=0.25, b2=log(1.25), f2=0.25, rho=0.3)
masize("poisson5",opts)
opts <- c(opts,ns=10000, seed=1234)
masize("poisson9",opts)

## Cox model
# BpBm
opts <- list(b2=log(1.5), rho=0.45, f=0.2, sdx2=sqrt(0.25*0.75))
masize("cox1",opts)
opts <- list(b1=log(2), f1=0.5, b2=log(1.5), f2=0.25, rho=0.45, f=0.2, seed=1234)
masize("cox5",c(opts, ns=10000))
masize("cox5",c(opts, ns=50000))

## End(Not run)
```

`MCMCgrm` *Mixed modeling with genetic relationship matrices*

Description

Mixed modeling with genetic relationship matrices

Usage

```
MCMCgrm(
  model,
  prior,
  data,
  GRM,
  eps = 0,
  n.thin = 10,
  n.burnin = 3000,
```

```
  n.iter = 13000,
  ...
)
```

Arguments

`model`	statistical model.
`prior`	a list of priors for parameters in the model above.
`data`	a data.frame containing outcome and covariates.
`GRM`	a relationship matrix.
`eps`	a small number added to the diagonal of the a nonpositive definite GRM.
`n.thin`	thinning parameter in the MCMC.
`n.burnin`	the number of burn-in's.
`n.iter`	the number of iterations.
`...`	other options as appropriate for MCMCglmm.

Details

Mixed modeling with genomic relationship matrix. This is appropriate with relationship matrix derived from family structures or unrelated individuals based on whole genome data.

The function was created to address a number of issues involving mixed modelling with family data or population sample with whole genome data. First, the implementaiton will shed light on the uncertainty involved with polygenic effect in that posterior distributions can be obtained. Second, while the model can be used with the MCMCglmm package there is often issues with the specification of pedigree structures but this is less of a problem with genetic relationship matrices. We can use established algorithms to generate kinship or genomic relationship matrix as input to the MCMCglmm function. Third, it is more intuitive to specify function arguments in line with other packages such as R2OpenBUGS, R2jags or glmmBUGS. In addition, our experiences of tuning the model would help to reset the input and default values.

Value

The returned value is an object as generated by MCMCglmm.

Author(s)

Jing Hua Zhao

References

Hadfield JD (2010). “MCMC Methods for Multi-Response Generalized Linear Mixed Models: The MCMCglmm R Package.” *Journal of Statistical Software*, **33**(2), 1 - 22. doi:10.18637/jss.v033.i02.

Examples

```
## Not run:
### with kinship

# library(kinship)
# fam <- with(l51,makefamid(id,fid,mid))
# s <-with(l51, makekinship(fam, id, fid, mid))
# K <- as.matrix(s)*2

### with gap

s <- kin.morgan(l51)
K <- with(s,kin.matrix*2)
prior <- list(R=list(V=1, nu=0.002), G=list(G1=list(V=1, nu=0.002)))
m <- MCMCgrm(qt~1,prior,l51,K)
save(m,file="l51.m")
pdf("l51.pdf")
plot(m)
dev.off()

# A real analysis on bats
## data
bianfu.GRM <- read.table("bianfu.GRM.txt", header = TRUE)
bianfu.GRM[1:5,1:6]
Data <- read.table(file = "PHONE.txt", header = TRUE,
                   colClasses=c(rep("factor",3),rep("numeric",7)))
## MCMCgrm
library("MCMCglmm")
GRM <- as.matrix(bianfu.GRM[,-1])
colnames(GRM) <- rownames(GRM) <- bianfu.GRM[,1]
library(gap)
names(Data)[1] <- "id"
prior <- list(G = list(G1 = list(V = 1, nu = 0.002)), R = list(V = 1, nu = 0.002))
model1.1 <- MCMCgrm(WEIGTHT ~ 1, prior, Data, GRM, n.burnin=100, n.iter=1000, verbose=FALSE)
## an alternative
names(Data)[1] <- "animal"
N <- nrow(Data)
i <- rep(1:N, rep(N, N))
j <- rep(1:N, N)
s <- Matrix::spMatrix(N, N, i, j, as.vector(GRM))
Ginv <- Matrix::solve(s)
class(Ginv) <- "dgCMatrix"
rownames(Ginv) <- Ginv@Dimnames[[1]] <- with(Data, animal)
model1.2 <- MCMCglmm(WEIGTHT ~ 1, random= ~ animal, data = Data,
  ginverse=list(animal=Ginv), prior = prior, burnin=100, nitt=1000, verbose=FALSE)
## without missing data
model1.3 <- MCMCglmm(Peak_Freq ~ WEIGTHT, random = ~ animal,
  data=subset(Data,!is.na(Peak_Freq)&!is.na(WEIGTHT)),
  ginverse=list(animal=Ginv), prior = prior, burnin=100, nitt=1000, verbose=FALSE)

## End(Not run)
```

`METAL_forestplot` *forest plot as R/meta's forest for METAL outputs*

Description

forest plot as R/meta's forest for METAL outputs

Usage

```
METAL_forestplot(
  tbl,
  all,
  rsid,
  flag = "",
  package = "meta",
  method = "REML",
  split = FALSE,
  ...
)
```

Arguments

`tbl`	Meta-anslysis summary statistics.
`all`	statistics from all contributing studies.
`rsid`	SNPID-rsid mapping file.
`flag`	a variable in tbl such as cis/trans type.
`package`	"meta" or "metafor" package.
`method`	an explcit flag for fixed/random effects model.
`split`	when TRUE, individual prot-MarkerName.pdf will be generated.
`...`	Additional arguments to `meta::forest` or `metafor::forest`.

Details

This functions takes a meta-data from METAL (tbl) and data from contributing studies (all) for forest plot. It also takes a SNPID-rsid mapping (rsid) as contributing studies often involve discrepancies in rsid so it is appropriate to use SNPID, i.e., chr:pos_A1_A2 (A1<=A2).

The study-specific and total sample sizes (`N`) can be customised from METAL commands. By default, the input triplets each contain a `MarkerName` variable which is the unique SNP identifier (e.g., chr:pos:a1:a2) and the `tbl` argument has variables `A1` and `A2` as produced by METAL while the `all` argument has `EFFECT_ALLELE` and `REFERENCE_ALLELE` as with a `study` variable indicating study name. Another variable common the `tbl` and `all` is `prot` variable as the function was developed in a protein based meta-analysis. As noted above, the documentation example also has variable `N`. From these all information is in place for generation of a list of forest plots through a batch run.

CUSTOMVARIABLE N
LABEL N as N
WEIGHTLABEL N

Value

It will generate a forest plot specified by pdf for direction-adjusted effect sizes.

Author(s)

Jing Hua Zhao

References

Schwarzer G (2007). “meta: An R package for meta-analysis.” *R News*, **7**, 40-45. https://cran.r-project.org/doc/Rnews/Rnews_2007-3.pdf. Willer CJ, Li Y, Abecasis GR (2010). “METAL: fast and efficient meta-analysis of genomewide association scans.” *Bioinformatics*, **26**(17), 2190-1. doi:10.1093/bioinformatics/btq340.

Examples

```
## Not run:
 data(OPG, package="gap.datasets")
 meta::settings.meta(method.tau="DL")
 METAL_forestplot(OPGtbl,OPGall,OPGrsid,width=8.75,height=5,digits.TE=2,digits.se=2,
                  col.diamond="black",col.inside="black",col.square="black")
 METAL_forestplot(OPGtbl,OPGall,OPGrsid,package="metafor",method="FE",xlab="Effect",
                  showweights=TRUE)

## End(Not run)
```

---

metap — *Meta-analysis of p-values with heterogeneity and random effects*

Description

Performs GWAS-style meta-analysis by combining p-values across studies. Implements Fisher’s method, fixed-effect weighted Stouffer Z, and random-effects Z meta-analysis with heterogeneity statistics.

Usage

```
metap(
  data,
  N,
  sided = c("two", "one"),
  verbose = TRUE,
  prefixp = "p",
  prefixn = "n",
  prefixbeta = NULL,
  prefixdir = NULL
)
```

Arguments

`data`	data.frame containing study results.
`N`	number of studies.
`sided`	`"two"` (default) or `"one"` for one-sided p-values.
`verbose`	logical; print summary output.
`prefixp`	prefix for p-value columns (default `"p"`).
`prefixn`	prefix for sample-size columns (default `"n"`).
`prefixbeta`	optional prefix for beta columns (used for direction).
`prefixdir`	optional prefix for sign columns (+1/-1).

Details

This function implements the meta-analysis approach used in the Genetic Investigation of ANThropometric Traits (GIANT) consortium.

Missing studies are automatically excluded per row, so the number of contributing studies may vary across variants.

Fisher's method:

$$X^2 = -2\sum_{i=1}^{k} \log(p_i) \sim \chi^2_{2k}$$

Fixed-effect weighted Stouffer Z:

Convert p-values to Z:

$$z_i = \Phi^{-1}(1 - p_i/2)$$

Sample-size weights:

$$w_i = \sqrt{n_i}$$

$$Z_{FE} = \frac{\sum w_i z_i}{\sqrt{\sum w_i^2}}$$

Heterogeneity:

$$Q = \sum w_i (z_i - \bar{z})^2$$

$$I^2 = \max(0, (Q - (k-1))/Q)$$

Random-effects Z meta-analysis:

DerSimonian–Laird variance:

$$\tau^2 = \max\left(0, \frac{Q - (k-1)}{\sum w_i - \sum w_i^2 / \sum w_i}\right)$$

Random-effects weights:

$$w_i^* = 1/(1/w_i + \tau^2)$$

$$Z_{RE} = \frac{\sum w_i^* z_i}{\sqrt{\sum w_i^*}}$$

Value

data.frame with

- fisher_p Fisher combined p-value
- stouffer_FE Fixed-effect Z meta p-value
- stouffer_RE Random-effects Z meta p-value
- Q Cochran heterogeneity statistic
- I2 Proportion heterogeneity
- tau2 Between-study variance

Author(s)

ChatGPT (Jing Hua Zhao)

Examples

```
## Not run:
## -------------------------------------------------------------------
## Classic GIANT consortium example (historical demo)
## Speliotes, Elizabeth K., M.D. [ESPELIOTES@PARTNERS.ORG]
## 22-2-2008 MRC-Epid JHZ
## -------------------------------------------------------------------

s <- data.frame(
  p1 = 0.1^rep(8:2, each = 7),
  n1 = rep(32000, 49),
  p2 = 0.1^rep(8:2, times = 7),
  n2 = rep(8000, 49)
)

res <- metap(s, 2)
head(res)

## Visual comparison equal vs unequal N (original demo)

np <- 7
p  <- 0.1^((np + 1):2)
z  <- qnorm(1 - p/2)
n  <- c(32000, 8000)

grid <- expand.grid(i = seq_len(np), j = seq_len(np))
za <- z[grid$i]; zb <- z[grid$j]

metaz_equalN   <- (sqrt(n[1])*za + sqrt(n[1])*zb)/sqrt(n[1]+n[1])
metaz_unequalN <- (sqrt(n[1])*za + sqrt(n[2])*zb)/sqrt(n[1]+n[2])

q  <- -log10(sort(p, decreasing=TRUE))
t1 <- matrix(-log10(sort(2*pnorm(-abs(metaz_equalN))),   decreasing=TRUE), np, np)
t2 <- matrix(-log10(sort(2*pnorm(-abs(metaz_unequalN))), decreasing=TRUE), np, np)
```

```
par(mfrow=c(1,2), bg="white", mar=c(4.2,3.8,0.2,0.2))
persp(q,q,t1, main="Equal sample sizes")
persp(q,q,t2, main="Unequal sample sizes")

## --------------------------------------------------------------
## New example: missing studies + heterogeneity
## --------------------------------------------------------------

set.seed(1)
dat <- data.frame(
  p1 = runif(100,1e-6,0.05),
  n1 = sample(5000:20000,100,TRUE),
  p2 = runif(100,1e-6,0.05),
  n2 = sample(5000:20000,100,TRUE)
)

## simulate missing studies
dat$p2[sample(1:100,20)] <- NA

res <- metap(dat,2)
summary(res$I2)

## End(Not run)
```

`metareg` *Fixed and random effects meta-analysis (vectorised implementation)*

Description

Performs inverse-variance weighted fixed- and random-effects meta-analysis across multiple studies supplied in wide format.

Usage

```
metareg(data, N, verbose = FALSE, prefixb = "b", prefixse = "se")
```

Arguments

`data`	A data frame containing regression coefficients and standard errors in wide format.
`N`	Integer. Number of studies included in the meta-analysis.
`verbose`	Logical. If `TRUE`, prints a completion message.
`prefixb`	Character. Prefix for regression coefficients. Default is `"b"` (columns `b1, b2, ..., bN`).
`prefixse`	Character. Prefix for standard errors. Default is `"se"` (columns `se1, se2, ..., seN`).

Details

The function is designed for high-throughput settings (e.g. GWAS), where each row represents an independent meta-analysis.

The function accepts wide-format input with estimates $b_1, \ldots, b_N$ and standard errors $se_1, \ldots, se_N$. Missing values are automatically ignored on a per-row basis.

Fixed effects model:

For k studies, inverse-variance weights are defined as

$$w_i = 1/se_i^2$$

The pooled estimate is

$$\beta_f = \frac{\sum_i b_i w_i}{\sum_i w_i}$$

with standard error

$$se_f = \sqrt{1/\sum_i w_i}$$

and test statistic

$$z_f = \beta_f / se_f$$

with p-value

$$p_f = 2\,\Phi(-|z_f|)$$

.

Random effects model (DerSimonian–Laird):

Cochran's Q statistic:

$$Q = \sum_i w_i (b_i - \beta_f)^2$$

Between-study variance:

$$\tau^2 = \max\left(0, \frac{Q - (k-1)}{\sum w_i - \sum w_i^2 / \sum w_i}\right)$$

Corrected weights:

$$w_i^* = 1/(1/w_i + \tau^2)$$

Random-effects pooled estimate:

$$\beta_r = \frac{\sum_i b_i w_i^*}{\sum_i w_i^*}$$

with standard error

$$se_r = \sqrt{1/\sum_i w_i^*}$$

and p-value

$$p_r = 2\,\Phi(-|z_r|)$$

.

Heterogeneity p-value:

$$p_{heter} = P(\chi^2_{k-1} > Q)$$

.

The heterogeneity statistic is reported as

$$I^2 = \max(0, (Q - (k-1))/Q)$$

.

Value

A data frame with one row per meta-analysis containing:

- beta_f Fixed-effects pooled estimate
- se_f Standard error of fixed-effects estimate
- z_f Z statistic (fixed effects)
- p_f P value (fixed effects)
- beta_r Random-effects pooled estimate
- se_r Standard error of random-effects estimate
- z_r Z statistic (random effects)
- p_r P value (random effects)
- p_heter Cochran's Q heterogeneity test p-value
- i2 I^2 heterogeneity statistic
- k Number of studies contributing to each row
- eps Smallest double-precision number used for stability

Author(s)

ChatGPT

References

Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003). "Measuring inconsistency in meta-analyses." *BMJ*, **327**(7414), 557-60. doi:10.1136/bmj.327.7414.557.

Examples

```
## Not run:
df <- data.frame(
  b1 = 1,  se1 = 2,
  b2 = 2,  se2 = 6,
  b3 = 3,  se3 = 8
)
metareg(df, 3)

df2 <- data.frame(
  b1 = c(1,2), se1 = c(2,4),
```

```
  b2 = c(2,3), se2 = c(4,6),
  b3 = c(3,4), se3 = c(6,8)
)
metareg(df2, 3)

## End(Not run)
```

---

mht.control *Controls for Manhattan plot*

Description

Parameter specification helper for `mhtplot()`. This function creates a list of graphical and behavioural settings used when generating Manhattan plots.

Usage

```
mht.control(
  type = "p",
  usepos = FALSE,
  logscale = TRUE,
  base = 10,
  cutoffs = NULL,
  colors = NULL,
  labels = NULL,
  gap = NULL,
  cex = 0.4,
  lab.cex = 1,
  axis.cex = 1.2,
  axis.lwd = 1.2,
  axis.tck = -0.02,
  yline = 3,
  xline = 3,
  verbose = FALSE
)
```

Arguments

`type`	Character. Either `"p"` (points) or `"l"` (lines).
`usepos`	Logical. Use real chromosomal positions instead of ordinal marker order.
`logscale`	Logical. If `TRUE`, values are transformed using `-log(base)(value)` before plotting.
`base`	Numeric. Base of logarithm used when `logscale = TRUE`.
`cutoffs`	Numeric vector of horizontal reference lines to draw.
`colors`	Vector of chromosome colours. Recycled as needed.
`labels`	Optional chromosome labels for the x-axis.

`gap`	Numeric. Gap inserted between chromosomes on the x-axis.
`cex`	Numeric. Scaling factor for plotted points.
`lab.cex`	Numeric. Scaling factor for chromosome labels on the x-axis.
`axis.cex`	Numeric. Scaling factor for axis tick labels. Increase when exporting high-resolution figures.
`axis.lwd`	Numeric. Line width for axes and tick marks.
`axis.tck`	Numeric. Length and direction of tick marks. Negative values draw ticks outward (recommended for publication plots).
`yline`	Numeric. Margin line for the y-axis label.
`xline`	Numeric. Margin line for the x-axis label.
`verbose`	Logical. Print plotting progress messages.

Value

a named list of control parameters for `mhtplot()`.

See Also

`mhtplot()`, `hmht.control()`

Examples

```
mht.control()
```

`mhtplot` *Manhattan plot*

Description

Draw a Manhattan plot for genome-wide association studies (GWAS) or any genome-indexed numeric score.

Usage

```
mhtplot(data, control = mht.control(), hcontrol = hmht.control(), ...)
```

Arguments

`data` A matrix or data frame with at least three columns. The first three columns are interpreted as:

1. chromosome
2. position
3. value (typically p-value) Column names are ignored. Factors are automatically converted.

`control` A list produced by `mht.control()` controlling plot behaviour.

hcontrol — A list produced by `hmht.control()` defining highlighted markers or regions and labels.

... — Additional graphical arguments passed to `graphics::plot()` (e.g. `pch`, `bg`, `xlab`, `ylab`, `ylim`). If `mar` is supplied, the default margins are not modified.

Details

Produces a Manhattan plot in which genomic markers are arranged along the x-axis by chromosome and position.

By default the y-axis shows `-log10(p)`, the standard GWAS significance scale. Set `logscale = FALSE` in `mht.control()` to plot raw values instead.

Rows containing missing values are removed automatically before plotting.

Chromosome handling:

Chromosomes may be numeric or character. The prefix `"chr"` is removed automatically. Chromosomes are ordered numerically first, followed by character chromosomes (e.g. X, Y, MT).

X-axis spacing:

- `usepos = FALSE` (default): markers are spaced evenly within chromosomes.
- `usepos = TRUE`: real chromosomal positions are used.
- `gap` inserts spacing between chromosomes when using real positions.

Colours:

Chromosome colours alternate by default. Custom colours can be supplied via `colors` in `mht.control()`; colours are recycled as needed.

Axis tuning:

Axis appearance can be controlled using:

- `axis.cex` — tick label size
- `axis.lwd` — axis and tick thickness
- `axis.tck` — tick length and direction

These settings are particularly useful when exporting high-resolution figures.

Horizontal thresholds:

Horizontal reference lines can be drawn using the `cutoffs` parameter.

Highlighting regions:

Highlighted regions are defined using `hmht.control()`. Matching markers are recoloured, labelled, and optionally boxed. Matching is performed by chromosome and position range.

Value

invisibly returns `NULL`.

Mathematical background

A Manhattan plot visualises genome-wide association statistics by mapping genetic markers to a two-dimensional coordinate system.

Y-axis transformation

P-values are transformed to improve visibility of small values:

$$y = -\log_{10}(p)$$

Small p-values therefore appear as large positive values and form the characteristic peaks used to identify strong associations.

Genome linearisation

Markers originate from multiple chromosomes and must be mapped onto a single continuous axis. For chromosome c:

$$x_i = pos_i + offset_c$$

where the chromosome offset is

$$offset_c = \sum_{k<c} \max(pos_k)$$

This produces a continuous genome coordinate system in which chromosomes appear sequentially without overlap.

Chromosome label placement

Chromosome labels are positioned at the midpoint of each chromosome:

$$mid_c = (\min(x_c) + \max(x_c))/2$$

This centres labels regardless of chromosome length.

Plot limits

The plotting region is defined using axis tick locations so that ticks and plotting limits coincide exactly.

Conceptually, a Manhattan plot is defined by two transformations:

$$x = \text{linearised genome coordinate}$$

$$y = -\log_{10}(p)$$

All other elements (colouring, thresholds, highlighting) are visual annotations applied to these transformed coordinates.

Author(s)

Jing Hua Zhao

See Also

mht.control(), hmht.control()

Examples

```
## -----------------------------------------------------------
## 1. Minimal example
## -----------------------------------------------------------
test <- matrix(c(
  1,1,4,
  1,1,6,
  1,10,3,
  2,1,5,
  2,2,6,
  2,4,8),
  byrow=TRUE, ncol=3)
mhtplot(test)
## Raw values instead of -log10
mhtplot(test, mht.control(logscale = FALSE))

## -----------------------------------------------------------
## 2. Simulated GWAS dataset
## -----------------------------------------------------------
set.seed(1)
affy <- c(40220,41400,33801,32334,32056,31470,25835,27457,22864,
          28501,26273,24954,19188,15721,14356,15309,11281,14881,
          6399,12400,7125,6207)
n.markers <- sum(affy)
n.chr <- length(affy)
gwas <- data.frame(
  chr = rep(1:n.chr, affy),
  pos = 1:n.markers,
  p   = runif(n.markers)
)
mhtplot(gwas)

## -----------------------------------------------------------
## 3. Publication-style figure
## -----------------------------------------------------------
ops <- mht.control(
  axis.cex = 1.4,
  axis.lwd = 2,
  axis.tck = -0.03
)
mhtplot(gwas, control = ops, pch = 19)

## -----------------------------------------------------------
## 4. Real positions + chromosome gaps
## -----------------------------------------------------------
ops2 <- mht.control(usepos = TRUE, gap = 10000)
mhtplot(gwas, control = ops2, pch = 19)
```

```
## ------------------------------------------------------------
## 5. Genome-wide significance thresholds
## ------------------------------------------------------------
ops3 <- mht.control(cutoffs = c(5, 7.3))
mhtplot(gwas, control = ops3, pch = 19)

## ------------------------------------------------------------
## 6. Highlight selected genes
## ------------------------------------------------------------
hdata <- data.frame(
  chr  = c(1,3,5),
  pos  = c(10000,50000,90000),
  p    = c(1e-8,1e-7,1e-9),
  gene = c("GENE1","GENE2","GENE3")
)
hops <- hmht.control(
  data = hdata,
  colors = "red",
  boxed = TRUE
)
mhtplot(gwas, control = ops, hcontrol = hops, pch = 19)
## A real study (data from gap.datasets package)
if (requireNamespace("gap.datasets", quietly = TRUE)) {
  data("mhtdata", package = "gap.datasets")

  data <- with(mhtdata, cbind(chr, pos, p))
  glist <- c("IRS1","SPRY2","FTO","GRIK3","SNED1","HTR1A","MARCH3",
             "WISP3","PPP1R3B","RP1L1","FDFT1","SLC39A14","GFRA1","MC4R")
  hdata <- subset(mhtdata, gene %in% glist)[c("chr","pos","p","gene")]

  ops  <- mht.control(colors = rep(c("lightgray","gray"),11),
                      labels = paste("chr",1:22,sep=""),
                      yline = 1.5, xline = 3)
  hops <- hmht.control(data = hdata, colors = "red", boxed = TRUE)

  mhtplot(data, ops, hops, pch = 19)
  title("Manhattan plot with genes highlighted")
}

## ------------------------------------------------------------
## 7. Export high-resolution PNG
## ------------------------------------------------------------
f <- tempfile(fileext = ".png")
png(f, height = 3600, width = 6000, res = 600)
opar <- par()
par(cex = 0.7)
mhtplot(gwas, control = ops, pch = 19)
par(opar)
dev.off()

## ------------------------------------------------------------
## 8. Miamiplot (see also vignette)
## ------------------------------------------------------------
```

```
if (requireNamespace("gap.datasets", quietly = TRUE)) {
  data("mhtdata", package = "gap.datasets")
  mhtdata <- within(mhtdata,{pr=p})
  miamiplot(mhtdata,chr="chr",bp="pos",p="p",pr="pr",snp="rsn")
}
```

mhtplot.trunc *Truncated Manhattan plot*

Description

Truncated Manhattan plot

Usage

```
mhtplot.trunc(
  x,
  chr = "CHR",
  bp = "BP",
  p = NULL,
  log10p = NULL,
  z = NULL,
  snp = "SNP",
  col = c("gray10", "gray60"),
  chrlabs = NULL,
  suggestiveline = -log10(1e-05),
  genomewideline = -log10(5e-08),
  highlight = NULL,
  annotatelog10P = NULL,
  annotateTop = FALSE,
  cex.mtext = 1.5,
  cex.text = 0.7,
  mtext.line = 2,
  y.ax.space = 5,
  y.brk1 = NULL,
  y.brk2 = NULL,
  trunc.yaxis = TRUE,
  cex.axis = 1.2,
  delta = 0.05,
  ...
)
```

Arguments

x A data.frame.

`chr`	Chromosome column name.
`bp`	Base-pair position column name.
`p`	P-value column name.
`log10p`	Column containing -log10(P).
`z`	Z-statistic column name.
`snp`	SNP/variant identifier column name.
`col`	Point colours alternating by chromosome.
`chrlabs`	Optional chromosome labels.
`suggestiveline`	Horizontal suggestive significance line.
`genomewideline`	Horizontal genome-wide significance line.
`highlight`	SNPs to highlight.
`annotatelog10P`	Threshold for annotation.
`annotateTop`	Annotate only top SNP per chromosome.
`cex.mtext`	Axis title size.
`cex.text`	SNP label size.
`mtext.line`	Axis title line offset.
`y.ax.space`	Y-axis tick spacing.
`y.brk1`	Lower truncation breakpoint.
`y.brk2`	Upper truncation breakpoint.
`trunc.yaxis`	Enable truncated y-axis.
`cex.axis`	Axis tick label size.
`delta`	Fractional window around highlighted SNPs.
`...`	Additional graphical parameters passed to points().

Details

Draws a Manhattan plot with optional y-axis truncation for extremely significant associations commonly observed in large-scale GWAS or protein GWAS analyses.

Value

Invisibly returns the processed plotting data.

Example FTO locus dataset and truncated Manhattan plot

This example demonstrates the use of `mhtplot.trunc()` on a single-chromosome FTO locus dataset with and without y-axis truncation.

Examples

```
txt <- "
CHR POS SNP Z log10P
16 53804965 rs10852521 -39.75000 344.8039
16 53805207 rs11075985 43.88235 419.8925
16 53819877 rs11075989 43.94118 421.0149
16 53819893 rs11075990 -43.94118 421.0149
16 53809247 rs1121980 43.76471 417.6523
16 53845487 rs11642841 38.52941 324.0426
16 53842908 rs12149832 42.23529 389.0756
16 53800954 rs1421085 -45.76471 456.5538
16 53803574 rs1558902 45.88235 458.8962
16 53813367 rs17817449 -46.87500 478.8994
16 53828066 rs17817964 44.29412 427.7808
16 53804340 rs1861866 39.81250 345.8844
16 53818460 rs3751812 44.41176 430.0480
16 53822651 rs7185735 -43.94118 421.0149
16 53810686 rs7193144 -44.29412 427.7808
16 53821862 rs7201850 42.35294 391.2377
16 53821615 rs7202116 -43.94118 421.0149
16 53813450 rs8043757 -42.22222 388.8357
16 53798523 rs8047395 37.76471 311.3650
16 53816275 rs8050136 46.75000 476.3569
16 53816752 rs8051591 -44.00000 422.1388
16 53803156 rs8055197 39.81250 345.8844
16 53812614 rs8057044 39.75000 344.8039
16 53806280 rs9922047 -39.62500 342.6480
16 53831771 rs9922619 43.37500 410.2743
16 53831146 rs9922708 43.25000 407.9218
16 53801549 rs9923147 43.82353 418.7716
16 53819198 rs9923233 43.94118 421.0149
16 53801985 rs9923544 43.82353 418.7716
16 53820503 rs9926289 40.66667 360.8208
16 53799905 rs9928094 -43.88235 419.8925
16 53799977 rs9930333 -44.00000 422.1388
16 53830452 rs9930501 -40.94118 365.6883
16 53830465 rs9930506 -43.31250 409.0972
16 53827179 rs9931494 -42.94118 402.1387
16 53830491 rs9932754 -41.00000 366.7356
16 53816838 rs9935401 46.81250 477.6273
16 53819169 rs9936385 -44.23529 426.6494
16 53799507 rs9937053 43.94118 421.0149
16 53820527 rs9939609 44.05882 423.2642
16 53800568 rs9939973 43.88235 419.8925
16 53800754 rs9940128 43.82353 418.7716
16 53800629 rs9940646 -43.82353 418.7716
16 53825488 rs9941349 42.58824 395.5801
"
FTO <- read.table(text = txt, header = TRUE, stringsAsFactors = FALSE)
par(mar = c(5, 6, 2, 1))
mhtplot.trunc(
  x = FTO,
```

```
  chr = "CHR",
  bp = "POS",
  log10p = "log10P",
  snp = "SNP",
  cex = 1.0,
  cex.axis = 1.2,
  cex.mtext = 1.5,
  col = "navy"
)
title("FTO locus without truncation")

par(mar = c(5, 6, 2, 1))
mhtplot.trunc(
  x = FTO,
  chr = "CHR",
  bp = "POS",
  log10p = "log10P",
  snp = "SNP",
  trunc.yaxis = TRUE,
  y.brk1 = 200,
  y.brk2 = 350,
  y.ax.space = 50,
  genomewideline = -log10(5e-8),
  suggestiveline = NULL,
  highlight = c("rs1421085", "rs1558902", "rs17817449",
                "rs8050136", "rs9939609"),
  annotatelog10P = 420,
  annotateTop = FALSE,
  cex = 1.2,
  cex.text = 0.9,
  cex.axis = 1.2,
  cex.mtext = 1.5,
  col = "steelblue4"
)
title("FTO locus with truncated y-axis")
```

`mhtplot2` *Manhattan plot with annotations*

Description

Manhattan plot with annotations

Usage

```
mhtplot2(data, control = mht.control(), hcontrol = hmht.control(), ...)
```

Arguments

`data`	a data frame with three columns representing chromosome, position and p values.
`control`	A list produced by `mht.control()` controlling plot behaviour.
`hcontrol`	A list produced by `hmht.control()` defining highlighted markers or regions and labels.
`...`	Additional graphical arguments passed to `graphics::plot()` (e.g. `pch`, `bg`, `xlab`, `ylab`, `ylim`). If `mar` is supplied, the default margins are not modified.

Details

To generate Manhattan plot with annotations. The function is generic and for instance could be used for genomewide p values or any random variable that is uniformly distributed. By default, a log10-transformation is applied. Note that with real chromosomal positions, it is also appropriate to plot and some but not all chromosomes.

It is possible to specify options such as xlab, ylim and font family when the plot is requested for data in other context. The example uses only chromosomes 14 and 20 of (den Hoed et al. 2013).

Value

shown on or saved to the appropriate device.

Author(s)

Jing Hua Zhao

References

den Hoed M, Eijgelsheim M, Esko T, Brundel BJ, Peal DS, Evans DM, Nolte IM, Segrè AV, Holm H, Handsaker RE, Westra HJ, Johnson T, Isaacs A, Yang J, Lundby A, Zhao JH, Kim YJ, Go MJ, Almgren P, Bochud M, Boucher G, Cornelis MC, Gudbjartsson D, Hadley D, van der Harst P, Hayward C, den Heijer M, Igl W, Jackson AU, Kutalik Z, Luan J, Kemp JP, Kristiansson K, Ladenvall C, Lorentzon M, Montasser ME, Njajou OT, O'Reilly PF, Padmanabhan S, St Pourcain B, Rankinen T, Salo P, Tanaka T, Timpson NJ, Vitart V, Waite L, Wheeler W, Zhang W, Draisma HH, Feitosa MF, Kerr KF, Lind PA, Mihailov E, Onland-Moret NC, Song C, Weedon MN, Xie W, Yengo L, Absher D, Albert CM, Alonso A, Arking DE, de Bakker PI, Balkau B, Barlassina C, Benaglio P, Bis JC, Bouatia-Naji N, Brage S, Chanock SJ, Chines PS, Chung M, Darbar D, Dina C, Dörr M, Elliott P, Felix SB, Fischer K, Fuchsberger C, de Geus EJ, Goyette P, Gudnason V, Harris TB, Hartikainen AL, Havulinna AS, Heckbert SR, Hicks AA, Hofman A, Holewijn S, Hoogstra-Berends F, Hottenga JJ, Jensen MK, Johansson A, Junttila J, Kääb S, Kanon B, Ketkar S, Khaw KT, Knowles JW, Kooner AS, others (2013). "Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders." *Nat Genet*, **45**(6), 621-31. doi:10.1038/ng.2610.

Examples

```
## Not run:
mdata <- within(hr1420,{
  c1<-colour==1
```

```
  c2<-colour==2
  c3<-colour==3
  colour[c1] <- 62
  colour[c2] <- 73
  colour[c3] <- 552
})
mdata <- mdata[,c("CHR","POS","P","gene","colour")]
ops <- mht.control(colors=rep(c("lightgray","gray"),11),yline=1.5,xline=2)
hops <- hmht.control(data=subset(mdata,!is.na(gene)),boxed=TRUE)
v <- "Verdana"
ifelse(Sys.info()['sysname']=="Windows", windowsFonts(ffamily=windowsFont(v)),
       ffamily <- v)
tiff("mh.tiff", width=.03937*189, height=.03937*189/2, units="in", res=1200,
     compress="lzw")
par(las=2, xpd=TRUE, cex.axis=1.8, cex=0.4)
mhtplot2(with(mdata,cbind(CHR,POS,P,colour)),ops,hops,pch=19,
         ylab=expression(paste(plain("-"),log[10],plain("p-value"),sep=" ")),
         family="ffamily")
axis(2,pos=2,at=seq(0,25,5),family="ffamily",cex=0.5,cex.axis=1.1)
dev.off()

# To exemplify the use of chr, pos and p without gene annotation
# in response to query from Vallejo, Roger <Roger.Vallejo@ARS.USDA.GOV>
opar <- par()
par(cex=0.4)
ops <- mht.control(colors=rep(c("lightgray","lightblue"),11),yline=2.5,xline=2)
mhtplot2(data.frame(mhtdata[,c("chr","pos","p")],gene=NA,color=NA),ops,xlab="",ylab="")
axis(2,at=1:16)
title("data in mhtplot used by mhtplot2")
par(opar)

## End(Not run)
```

---

mia *Multiple imputation analysis for hap*

Description

Multiple imputation analysis for hap

Usage

```
mia(
  hapfile = "hap.out",
  assfile = "assign.out",
  miafile = "mia.out",
  so = 0,
  ns = 0,
  mi = 0,
  allsnps = 0,
```

```
  sas = 0
)
```

Arguments

`hapfile`	hap haplotype output file name.
`assfile`	hap assignment output file name.
`miafile`	mia output file name.
`so`	to generate results according to subject order.
`ns`	do not sort in subject order.
`mi`	number of multiple imputations used in hap.
`allsnps`	all loci are SNPs.
`sas`	produce SAS data step program.

Details

This command reads outputs from hap session that uses multiple imputations, i.e. -mi# option. To simplify matters it assumes -ss option is specified together with -mi option there.

This is a very naive version of MIANALYZE, but can produce results for PROC MIANALYZE of SAS.

It simply extracts outputs from hap.

Value

The returned value is a list.

Note

adapted from hap, in fact cline.c and cline.h are not used. keywords utilities

References

Zhao JH and W Qian (2003) Association analysis of unrelated individuals using polymorphic genetic markers. RSS 2003, Hassalt, Belgium

Clayton DG (2001) SNPHAP. https://github.com/chr1swallace/snphap.

See Also

hap

Examples

```
## Not run:
# 4 SNP example, to generate hap.out and assign.out alone
data(fsnps)
hap(id=fsnps[,1],data=fsnps[,3:10],nloci=4)
```

```
# to generate results of imputations
control <- hap.control(ss=1,mi=5)
hap(id=fsnps[,1],data=fsnps[,3:10],nloci=4,control=control)

# to extract information from the second run above
mia(so=1,ns=1,mi=5)
file.show("mia.out")

## commands to check out where the output files are as follows:
## Windows
# system("command.com")
## Unix
# system("csh")

## End(Not run)
```

---

miamiplot *Miami plot*

Description

Miami plot

Usage

```
miamiplot(
  x,
  chr = "CHR",
  bp = "BP",
  p = "P",
  pr = "PR",
  snp = "SNP",
  col = c("midnightblue", "chartreuse4"),
  col2 = c("royalblue1", "seagreen1"),
  ymax = NULL,
  highlight = NULL,
  highlight.add = NULL,
  pch = 19,
  cex = 0.75,
  cex.lab = 1,
  xlab = "Chromosome",
  ylab = "-log10(P) [y>0]; log10(P) [y<0]",
  lcols = c("red", "black"),
  lwds = c(5, 2),
  ltys = c(1, 2),
  main = "",
  ...
)
```

Arguments

x	Input data.
chr	Chromsome.
bp	Position.
p	P value.
pr	P value of the other GWAS.
snp	Marker.
col	Colors.
col2	Colors.
ymax	Max y.
highlight	Highlight flag.
highlight.add	Highlight meta-data.
pch	Symbol.
cex	cex.
cex.lab	cex for labels.
xlab	Label for x-axis.
ylab	Label for y-axis.
lcols	Colors.
lwds	lwd.
ltys	lty.
main	Main title.
...	Additional options.

Details

The function allows for contrast of genomewide P values from two GWASs. It is conceptually simpler than at the first sight since it involves only one set of chromosomal positions.

Value

None.

Examples

```
## Not run:
  mhtdata <- within(mhtdata,{pr=p})
  miamiplot(mhtdata,chr="chr",bp="pos",p="p",pr="pr",snp="rsn")

## End(Not run)
```

`miamiplot2` *Miami Plot*

Description

Miami Plot

Usage

```
miamiplot2(
  gwas1,
  gwas2,
  name1 = "GWAS 1",
  name2 = "GWAS 2",
  chr1 = "chr",
  chr2 = "chr",
  pos1 = "pos",
  pos2 = "pos",
  p1 = "p",
  p2 = "p",
  z1 = NULL,
  z2 = NULL,
  sug = 1e-05,
  sig = 5e-08,
  pcutoff = 0.1,
  topcols = c("green3", "darkgreen"),
  botcols = c("royalblue1", "navy"),
  yAxisInterval = 5
)
```

Arguments

`gwas1`	The first of two GWAS datasets to plot, in the upper region.
`gwas2`	The second of two GWAS datasets to plot, in the lower region.
`name1`	The name of the first dataset, plotted above the upper plot region. Defaults to ‘`"GWAS 1"`’.
`name2`	The name of the second dataset, plotted below the lower plot region. Defaults to ‘`"GWAS 2"`’.
`chr1`	The name of the column containing chromosome number in `gwas1`. Defaults to ‘`"chr"`’.
`chr2`	The name of the column containing chromosome number in `gwas2`. Defaults to ‘`"chr"`’.
`pos1`	The name of the column containing SNP position in `gwas1`. Defaults to ‘`"pos"`’.
`pos2`	The name of the column containing SNP position in `gwas2`. Defaults to ‘`"pos"`’.
`p1`	The name of the column containing p-values in `gwas1`. Defaults to ‘`"p"`’.

p2	The name of the column containing p-values in gwas2. Defaults to '"p"'.
z1	The name of the column containing z-values in gwas1. Defaults to '"NULL"'.
z2	The name of the column containing z-values in gwas2. Defaults to '"NULL"'.
sug	The threshold for suggestive significance, plotted as a light grey dashed line.
sig	The threshold for genome-wide significance, plotted as a dark grey dashed line.
pcutoff	The p-value threshold below which SNPs will be ignored. Defaults to 0.1. It is not recommended to set this higher as it will narrow the central gap between the two plot region where the chromosome number is plotted.
topcols	A vector of two colours to plot alternating chromosomes in for the upper plot. Defaults to green3 and darkgreen.
botcols	A vector of two colours to plot alternating chromosomes in for the lower plot. Defaults to royalblue1 and navy.
yAxisInterval	The interval between tick marks on the y-axis. Defaults to 5, 2 may be more suitable for plots with larger minimum p-values.

Details

Creates a Miami plot to compare results from two genome-wide association analyses.

Value

In addition to creading a Miami plot, the function returns a data frame containing x coordinates for chromosome start positions (required for labelManhattan)

Note

Extended to handle extreme P values.

Author(s)

Jonathan Marten

Examples

```
## Not run:
# miamiplot2(gwas1, gwas2)
# chrmaxpos <- miamiplot2(gwas1, gwas2)
gwas <- within(mhtdata[c("chr","pos","p")], {z=qnorm(p/2)})
chrmaxpos <- miamiplot2(gwas,gwas,name1="Batch 2",name2="Batch 1",z1="z",z2="z")
labelManhattan(chr=c(2,16),pos=c(226814165,52373776),name=c("AnonymousGene","FTO"),
               gwas,gwasZLab="z",chrmaxpos=chrmaxpos)

## End(Not run)
```

mr — *Mendelian Randomization wrapper (IVW, Egger, Weighted Median, Penalised WM)*

Description

Mendelian Randomization wrapper (IVW, Egger, Weighted Median, Penalised WM)

Usage

```
mr(data, X, Y, alpha = 0.05, other_plots = FALSE)
```

Arguments

`data`	Data frame containing SNP summary statistics in wide format.
`X`	Character string. Exposure trait name.
`Y`	Character vector. Outcome trait names.
`alpha`	Significance level used for confidence intervals (default 0.05).
`other_plots`	Logical. If TRUE, produces metafor funnel and forest plots.

Details

Performs two–sample Mendelian Randomization using summary statistics stored in a wide data frame with columns named:

- SNP
- b.trait : effect estimate
- SE.trait : standard error

For each outcome in `Y`, the function:

1. Extracts instruments for exposure `X`
2. Computes IVW, MR-Egger, Weighted Median and Penalised Weighted Median estimates
3. Computes Cochran's Q heterogeneity statistic
4. Produces MR scatter plots

Methods implemented:

- IVW (inverse-variance weighted regression)
- MR-Egger regression
- Weighted median estimator
- Penalised weighted median
- Cochran's Q heterogeneity statistic (metafor)

Required packages: `metafor`, `ggplot2`, `cowplot`. Functions `weighted.median()` and `mr.boot()` must be available in the environment (e.g. from Mendelian randomization toolkits).

Value

Invisible list with components:

- r Matrix of MR estimates for each exposure–outcome pair.
- plots List of ggplot objects (MR scatter plots).

Examples

```
## Not run:
if (requireNamespace("metafor", quietly = TRUE) &&
    requireNamespace("ggplot2", quietly = TRUE) &&
    requireNamespace("cowplot", quietly = TRUE)) {
txt <- "
rs188743906  0.6804 0.1104  0.00177 0.01660        NA        NA
rs2289779   -0.0788 0.0134  0.00104 0.00261 -0.007543 0.0092258
rs117804300 -0.2281 0.0390 -0.00392 0.00855  0.109372 0.0362219
rs7033492   -0.0968 0.0147 -0.00585 0.00269  0.022793 0.0119903
rs10793962   0.2098 0.0212  0.00378 0.00536 -0.014567 0.0138196
rs635634    -0.2885 0.0153 -0.02040 0.00334  0.077157 0.0117123
rs176690    -0.0973 0.0142  0.00293 0.00306 -0.000007 0.0107781
rs147278971 -0.2336 0.0378 -0.01240 0.00792  0.079873 0.0397491
rs11562629   0.1155 0.0181  0.00960 0.00378 -0.010040 0.0151460
"
v <- c("SNP","b.LIF.R","SE.LIF.R","b.FEV1","SE.FEV1","b.CAD","SE.CAD")
mrdat <- setNames(as.data.frame(scan(text = txt,
                  what = list("",0,0,0,0,0,0), quiet=TRUE)), v)
res <- mr(mrdat, "LIF.R", c("CAD","FEV1"), other_plots=TRUE)
r <- as.data.frame(res$r, stringsAsFactors=FALSE)
rownames(r) <- r$IV
r$IV <- NULL
r[] <- lapply(r, function(x) as.numeric(as.character(x)))
b_cols  <- grep("^b[A-Z]", names(r), value=TRUE)
se_cols <- paste0("se", substring(b_cols, 2))
keep <- se_cols %in% names(r)
b_cols <- b_cols[keep]; se_cols <- se_cols[keep]
if(length(b_cols) > 0){
  pvals <- sapply(seq_along(b_cols), function(i)
    2 * pnorm(-abs(r[[b_cols[i]]] / r[[se_cols[i]]])))
  pvals <- as.data.frame(pvals)
  colnames(pvals) <- substring(b_cols, 2)
  pvals[] <- lapply(pvals, format.pval, digits=3, eps=1e-4)
  results_table <- cbind(round(r,3), pvals)
} else {
  results_table <- round(r,3)
}
results_table
res$plots
}

## End(Not run)
```

`mr_forestplot` *Mendelian Randomization forest plot*

Description

Mendelian Randomization forest plot

Usage

```
mr_forestplot(dat, sm = "", title = "", ...)
```

Arguments

`dat`	A data.frame with outcome id, effect size and standard error.
`sm`	Summary measure such as OR, RR, MD.
`title`	Title of the meta-analysis.
`...`	Additional arguments passed to meta::forest().

Details

Wrapper around meta::forest() for multi-outcome Mendelian Randomization. Works for binary and continuous outcomes, with or without summary statistics.

Examples

```
## Not run:
## Example data -----------------------------------------------------------
tnfb <- '
             "multiple sclerosis"  0.69058600 0.059270400
   "systemic lupus erythematosus"  0.76687500 0.079000500
         "sclerosing cholangitis"  0.62671500 0.075954700
  "juvenile idiopathic arthritis" -1.17577000 0.160293000
                      "psoriasis"  0.00582586 0.000800016
           "rheumatoid arthritis" -0.00378072 0.000625160
     "inflammatory bowel disease" -0.14334200 0.025272500
         "ankylosing spondylitis" -0.00316852 0.000626225
                 "hypothyroidism" -0.00432054 0.000987324
              "allergic rhinitis"  0.00393075 0.000926002
         "IgA glomerulonephritis" -0.32696600 0.105262000
                 "atopic eczema" -0.00204018 0.000678061
'

tnfb <- as.data.frame(scan(file = textConnection(tnfb), what = list("",0,0)))
names(tnfb) <- c("outcome","Effect","StdErr")
tnfb$outcome <- gsub("\\b(^[a-z])","\\U\\1", tnfb$outcome, perl = TRUE)


## 1) Default meta-style forest plot (b, SE, CI + weights) ----------------
```

```
mr_forestplot(
  tnfb,
  colgap.forest.left = "0.05cm",
  fontsize = 14,
  leftcols  = c("studlab","effect","seTE","ci"),
  leftlabs  = c("Outcome","b","SE","95% CI"),
  rightcols = c("w.common","w.random"),
  rightlabs = c("Weight (FE)","Weight (RE)"),
  common = FALSE, random = FALSE,
  print.I2 = FALSE, print.pval.Q = FALSE, print.tau2 = FALSE,
  spacing = 1.6, digits.TE = 2, digits.seTE = 2
)


## 2) MR summary (OR + CI only) -------------------------------------------
mr_forestplot(
  tnfb,
  sm = "OR",
  backtransf = TRUE,
  colgap.forest.left = "0.05cm",
  fontsize = 14,
  leftcols  = "studlab",
  leftlabs  = "Outcome",
  rightcols = c("effect","ci"),
  rightlabs = c("OR","95% CI"),
  sortvar = tnfb$Effect,
  common = FALSE, random = FALSE,
  print.I2 = FALSE, print.pval.Q = FALSE, print.tau2 = FALSE,
  spacing = 1.6
)


## 3) MR summary with P-values --------------------------------------------
mr_forestplot(
  tnfb,
  sm = "OR",
  backtransf = TRUE,
  colgap.forest.left = "0.05cm",
  fontsize = 14,
  leftcols  = "studlab",
  leftlabs  = "Outcome",
  rightcols = c("effect","ci","pval"),
  rightlabs = c("OR","95% CI","P"),
  digits = 3, digits.pval = 2, scientific.pval = TRUE,
  sortvar = tnfb$Effect,
  common = FALSE, random = FALSE,
  print.I2 = FALSE, print.pval.Q = FALSE, print.tau2 = FALSE,
  addrow = TRUE,
  spacing = 1.6
)

## End(Not run)
```

mtdt — *Transmission/disequilibrium test of a multiallelic marker*

Description

Transmission/disequilibrium test of a multiallelic marker

Usage

```
mtdt(x, n.sim = 0)
```

Arguments

x	the data table.
n.sim	the number of simulations.

Details

This function calculates transmission-disequilibrium statistics involving multiallelic marker. Inside the function are tril and triu used to obtain lower and upper triangular matrices.

Value

It returned list contains the following components:

- SE Spielman-Ewens Chi-square from the observed data.
- ST Stuart or score Statistic from the observed data.
- pSE the simulated p value.
- sSE standard error of the simulated p value.
- pST the simulated p value.
- sST standard error of the simulated p value.

Author(s)

Mike Miller, Jing Hua Zhao

References

Miller MB (1997). “Genomic scanning and the transmission/disequilibrium test: analysis of error rates.” *Genet Epidemiol*, **14**(6), 851-6. doi:10.1002/(sici)10982272(1997)14:6<854::aidgepi48>3.3.co;2-7.

Sham PC, Curtis D (1995). “An extended transmission/disequilibrium test (TDT) for multi-allele marker loci.” *Ann Hum Genet*, **59**(3), 323-36. doi:10.1111/j.14691809.1995.tb00751.x.

Spielman RS, Ewens WJ (1996). “The TDT and other family-based tests for linkage disequilibrium and association.” *Am J Hum Genet*, **59**(5), 983-9.

Zhao JH, Sham PC, Curtis D (1999). “A program for the Monte Carlo evaluation of significance of the extended transmission/disequilibrium test.” *Am J Hum Genet*, **64**, 1484-1485.

See Also

bt

Examples

```
## Not run:
x <- matrix(c(0,0, 0, 2, 0,0, 0, 0, 0, 0, 0, 0,
              0,0, 1, 3, 0,0, 0, 2, 3, 0, 0, 0,
              2,3,26,35, 7,0, 2,10,11, 3, 4, 1,
              2,3,22,26, 6,2, 4, 4,10, 2, 2, 0,
              0,1, 7,10, 2,0, 0, 2, 2, 1, 1, 0,
              0,0, 1, 4, 0,1, 0, 1, 0, 0, 0, 0,
              0,2, 5, 4, 1,1, 0, 0, 0, 2, 0, 0,
              0,0, 2, 6, 1,0, 2, 0, 2, 0, 0, 0,
              0,3, 6,19, 6,0, 0, 2, 5, 3, 0, 0,
              0,0, 3, 1, 1,0, 0, 0, 1, 0, 0, 0,
              0,0, 0, 2, 0,0, 0, 0, 0, 0, 0, 0,
              0,0, 1, 0, 0,0, 0, 0, 0, 0, 0, 0),nrow=12)

# See note to bt for the score test obtained by SAS

mtdt(x)

## End(Not run)
```

`mtdt2` *Transmission/disequilibrium test of a multiallelic marker by Bradley-Terry model*

Description

Transmission/disequilibrium test of a multiallelic marker by Bradley-Terry model

Usage

```
mtdt2(x, verbose = TRUE, n.sim = NULL, ...)
```

Arguments

`x`	the data table.
`verbose`	To print out test statistics if TRUE.
`n.sim`	Number of simulations.
`...`	other options compatible with the BTm function.

Details

This function calculates transmission-disequilibrium statistics involving multiallelic marker according to Bradley-Terry model.

Value

It returned list contains the following components:

- c2b A data frame in four-column format showing transmitted vs nontransmitted counts.
- BTm A fitted Bradley-Terry model object.
- X2 Allele-wise, genotype-wise and goodness-of-fit Chi-squared statistics.
- df Degrees of freedom.
- p P value.
- pn Monte Carlo p values when n.sim is specified.

Author(s)

Jing Hua Zhao keywords models keywords htest

References

Firth D (2005). "Bradley-Terry Models in R." *Journal of Statistical Software*, **12**(1), 1 - 12. doi:10.18637/jss.v012.i01.

Turner H, Firth D (2010) Bradley-Terry models in R: The BradleyTerry2 package. https://cran.r-project.org/web/packages/BradleyTerry2/vignettes/BradleyTerry.pdf.

See Also

mtdt

Examples

```
## Not run:
x <- matrix(c(0,0, 0, 2, 0,0, 0, 0, 0, 0, 0, 0,
              0,0, 1, 3, 0,0, 0, 2, 3, 0, 0, 0,
              2,3,26,35, 7,0, 2,10,11, 3, 4, 1,
              2,3,22,26, 6,2, 4, 4,10, 2, 2, 0,
              0,1, 7,10, 2,0, 0, 2, 2, 1, 1, 0,
              0,0, 1, 4, 0,1, 0, 1, 0, 0, 0, 0,
              0,2, 5, 4, 1,1, 0, 0, 0, 2, 0, 0,
              0,0, 2, 6, 1,0, 2, 0, 2, 0, 0, 0,
              0,3, 6,19, 6,0, 0, 2, 5, 3, 0, 0,
              0,0, 3, 1, 1,0, 0, 0, 1, 0, 0, 0,
              0,0, 0, 2, 0,0, 0, 0, 0, 0, 0, 0,
              0,0, 1, 0, 0,0, 0, 0, 0, 0, 0, 0),nrow=12)

xx <- mtdt2(x,refcat="12")

## End(Not run)
```

muvar	*Means and variances under 1- and 2- locus (biallelic) QTL model*

Description

Means and variances under 1- and 2- locus (biallelic) QTL model

Usage

```
muvar(
  n.loci = 1,
  y1 = c(0, 1, 1),
  y12 = c(1, 1, 1, 1, 1, 0, 0, 0, 0),
  p1 = 0.99,
  p2 = 0.9
)
```

Arguments

`n.loci`	number of loci, 1=single locus, 2=two loci.
`y1`	the genotypic means of aa, Aa and AA.
`y12`	the genotypic means of aa, Aa and AA at the first locus and bb, Bb and BB at the second locus.
`p1`	the frequency of the lower allele, or the that for the first locus under a 2-locus model.
`p2`	the frequency of the lower allele at the second locus.

Details

Function muvar() gives means and variances under 1-locus and 2-locus QTL model (simple); in the latter case it gives results from different avenues. This function is included for experimental purpose and yet to be generalized.

Value

Currently it does not return any value except screen output; the results can be kept via R's sink() command or via modifying the C/R codes.

Note

Adapted from an earlier C program written for the above book.

Author(s)

Jing Hua Zhao

References

Sham P (1997). *Statistics in Human Genetics*. Wiley. ISBN 978-0470689288.

Examples

```
## Not run:
# the default 1-locus model
muvar(n.loci=1,y1=c(0,1,1),p1=0.5)

# the default 2-locus model
muvar(n.loci=2,y12=c(1,1,1,1,1,0,0,0,0),p1=0.99,p2=0.9)

## End(Not run)
```

---

mvmeta *Multivariate fixed-effects meta-analysis via generalized least squares*

Description

Performs multivariate meta-analysis by pooling study-specific parameter estimates using generalized least squares (GLS) under a fixed-effects model.

Usage

```
mvmeta(b, V)
```

Arguments

b	Matrix of study estimates (studies × parameters).
V	may be supplied with • a matrix of upper-triangular rows • a list of covariance matrices • a 3D array (p × p × k)

Details

The function accepts a matrix of parameter estimates and the corresponding within-study covariance matrices (stored in upper-triangular vector form).

This approach is appropriate when combining correlated effect estimates, for example correlation coefficients of SNPs across studies.

The function fits a multivariate **fixed-effects meta-analysis** using generalized least squares (GLS).

For study $i = 1, \ldots, k$, let d_i be the vector of observed parameter estimates and Ψ_i the corresponding within-study covariance matrix:

$$d_i \sim N(\beta,\ \Psi_i)$$

where β is the vector of common (pooled) parameters.

The study estimates are stacked into a single vector

$$d = (d_1^T, \dots, d_k^T)^T$$

with block-diagonal covariance matrix

$$\Psi = \mathrm{blockdiag}(\Psi_1, \dots, \Psi_k).$$

The model can then be written in GLS regression form

$$d = X\beta + \varepsilon, \qquad \varepsilon \sim N(0, \Psi)$$

where X is a block design matrix that repeats an identity matrix for each study (intercept-only multivariate meta-analysis). Missing outcomes are automatically removed when constructing d, Ψ and X.

The pooled estimator is the GLS estimator

$$\hat{\beta} = (X^T \Psi^{-1} X)^{-1} X^T \Psi^{-1} d.$$

Heterogeneity is assessed using the multivariate Cochran Q statistic

$$Q = (d - X\hat{\beta})^T \Psi^{-1} (d - X\hat{\beta}),$$

which is asymptotically χ^2_{N-p}, where N is the number of observed estimates and p the number of pooled parameters.

This implementation corresponds to the multivariate fixed-effects model described in Hartung et al. (2008, Example 11.3).

Value

An object of class `"mvmeta"` with the following elements:

- beta: pooled estimates
- vcov: covariance matrix of pooled estimates
- se: standard errors
- z: z statistics
- pval: p values
- ci: 95% confidence intervals
- X2, df, p: heterogeneity test
- logLik: model log-likelihood
- k: number of studies
- p_outcomes: number of pooled outcomes

Author(s)

Jing Hua Zhao

References

Hartung J, Knapp G, Sinha BK (2008). *Statistical Meta-analysis with Applications*. Wiley. ISBN 978-0-470-29089-7.

See Also

metareg

Examples

```
## Not run:
# Example 11.3 from Hartung et al.
b <- matrix(c(
0.808, 1.308, 1.379, NA, NA,
NA, 1.266, 1.828, 1.962, NA,
NA, 1.835, NA, 2.568, NA,
NA, 1.272, NA, NA, 2.038,
1.171, 2.024, 2.423, 3.159, NA,
0.681, NA, NA, NA, NA), ncol=5, byrow=TRUE)

psi1 <- psi2 <- psi3 <- psi4 <- psi5 <- psi6 <- matrix(0,5,5)
psi1[1,1] <- 0.0985; psi1[1,2] <- 0.0611; psi1[1,3] <- 0.0623
psi1[2,2] <- 0.1142; psi1[2,3] <- 0.0761; psi1[3,3] <- 0.1215

psi2[2,2] <- 0.0713; psi2[2,3] <- 0.0539; psi2[2,4] <- 0.0561
psi2[3,3] <- 0.0938; psi2[3,4] <- 0.0698; psi2[4,4] <- 0.0981

psi3[2,2] <- 0.1228; psi3[2,4] <- 0.1119; psi3[4,4] <- 0.1790
psi4[2,2] <- 0.0562; psi4[2,5] <- 0.0459; psi4[5,5] <- 0.0815

psi5[1,1] <- 0.0895; psi5[1,2] <- 0.0729; psi5[1,3] <- 0.0806
psi5[1,4] <- 0.0950; psi5[2,2] <- 0.1350; psi5[2,3] <- 0.1151
psi5[2,4] <- 0.1394; psi5[3,3] <- 0.1669; psi5[3,4] <- 0.1609
psi5[4,4] <- 0.2381

psi6[1,1] <- 0.0223

V <- rbind(psi1[upper.tri(psi1,diag=TRUE)],
           psi2[upper.tri(psi2,diag=TRUE)],
           psi3[upper.tri(psi3,diag=TRUE)],
           psi4[upper.tri(psi4,diag=TRUE)],
           psi5[upper.tri(psi5,diag=TRUE)],
           psi6[upper.tri(psi6,diag=TRUE)])

fit <- mvmeta(b, V)
summary(fit)
logLik(fit)
AIC(fit)
BIC(fit)

## End(Not run)
```

pbsize *Power for population-based association design*

Description

Power for population-based association design

Usage

```
pbsize(kp, gamma = 4.5, p = 0.15, alpha = 5e-08, beta = 0.2)
```

Arguments

kp	population disease prevalence.
gamma	genotype relative risk assuming multiplicative model.
p	frequency of disease allele.
alpha	type I error rate.
beta	type II error rate.

Details

This function implements Scott et al. (1997) statistics for population-based association design. This is based on a contingency table test and accurate level of significance can be obtained by Fisher's exact test.

Value

The returned value is scaler containing the required sample size.

Author(s)

Jing Hua Zhao extracted from rm.c.

References

Scott WK, Pericak-Vance MA, Haines JL (1997). "Genetic analysis of complex diseases." *Science*, **275**(5304), 1327; author reply 1329-30.Rosner B (2000). *Fundamentals of biostatistics*, 5 edition. Duxbury, Pacific Grove, CA. ISBN 9780534370688.Armitage P, Colton T (eds.) (2005). *Encyclopedia of biostatistics*, 2 edition. John Wiley, Chichester, West Sussex, England ; Hoboken, NJ. ISBN 9780470849071.

See Also

fbsize

Examples

```
kp <- c(0.01,0.05,0.10,0.2)
models <- matrix(c(
    4.0, 0.01,
    4.0, 0.10,
    4.0, 0.50,
    4.0, 0.80,
    2.0, 0.01,
    2.0, 0.10,
    2.0, 0.50,
    2.0, 0.80,
    1.5, 0.01,
    1.5, 0.10,
    1.5, 0.50,
    1.5, 0.80), ncol=2, byrow=TRUE)
outfile <- "pbsize.txt"
cat("gamma","p","p1","p5","p10","p20\n",sep="\t",file=outfile)
for(i in 1:dim(models)[1])
{
  g <- models[i,1]
  p <- models[i,2]
  n <- vector()
  for(k in kp) n <- c(n,ceiling(pbsize(k,g,p)))
  cat(models[i,1:2],n,sep="\t",file=outfile,append=TRUE)
  cat("\n",file=outfile,append=TRUE)
}
table5 <- read.table(outfile,header=TRUE,sep="\t")
unlink(outfile)

# Alzheimer's disease
g <- 4.5
p <- 0.15
alpha <- 5e-8
beta <- 0.2
z1alpha <- qnorm(1-alpha/2)   # 5.45
z1beta <- qnorm(1-beta)
q <- 1-p
pi <- 0.065                   # 0.07 and zbeta generate 163
k <- pi*(g*p+q)^2
s <- (1-pi*g^2)*p^2+(1-pi*g)*2*p*q+(1-pi)*q^2
# LGL formula
lambda <- pi*(g^2*p+q-(g*p+q)^2)/(1-pi*(g*p+q)^2)
# mine
lambda <- pi*p*q*(g-1)^2/(1-k)
n <- (z1alpha+z1beta)^2/lambda
cat("\nPopulation-based result: Kp =",k, "Kq =",s, "n =",ceiling(n),"\n")
```

---

pbsize2 *Power for case-control association design*

Description

Power for case-control association design

Usage

```
pbsize2(
  N,
  fc = 0.5,
  alpha = 0.05,
  gamma = 4.5,
  p = 0.15,
  kp = 0.1,
  model = "additive"
)
```

Arguments

`N`	The sample size.
`fc`	The proportion of cases in the sample.
`alpha`	Type I error rate.
`gamma`	The genotype relative risk (GRR).
`p`	Frequency of the risk allele.
`kp`	The prevalence of disease in the population.
`model`	Disease model, i.e., "multiplicative","additive","dominant","recessive","overdominant".

Details

This extends `pbsize` from a multiplicative model for a case-control design under a range of disease models. Essentially, for given sample sizes(s), a proportion of which (fc) being cases, the function calculates power estimate for a given type I error (alpha), genotype relative risk (gamma), frequency of the risk allele (p), the prevalence of disease in the population (kp) and optionally a disease model (model). A major difference would be the consideration of case/control ascertainment in `pbsize`.

Internally, the function obtains a baseline risk to make the disease model consistent with Kp as in `tscc` and should produce accurate power estimate. It provides power estimates for given sample size(s) only.

Value

The returned value is the power for the specified design.

See Also

The design follows that of `pbsize`.

Examples

```
## Not run:
# single calculation
m <- c("multiplicative","recessive","dominant","additive","overdominant")
for(i in 1:5) print(pbsize2(N=50,alpha=5e-2,gamma=1.1,p=0.1,kp=0.1, model=m[i]))

# a range of sample sizes
pbsize2(p=0.1, N=c(25,50,100,200,500), gamma=1.2, kp=.1, alpha=5e-2, model='r')

# a power table
m <- sapply(seq(0.1,0.9, by=0.1),
            function(x) pbsize2(p=x, N=seq(100,1000,by=100),
                        gamma=1.2, kp=.1, alpha=5e-2, model='recessive'))
colnames(m) <- seq(0.1,0.9, by=0.1)
rownames(m) <- seq(100,1000,by=100)
print(round(m,2))

## End(Not run)
```

`pedtodot` *Converting pedigree(s) to dot file(s)*

Description

Converting pedigree(s) to dot file(s)

Usage

```
pedtodot(
  pedfile,
  makeped = FALSE,
  sink = TRUE,
  page = "B5",
  url = "https://jinghuazhao.github.io/",
  height = 0.5,
  width = 0.75,
  rotate = 0,
  dir = "none"
)
```

Arguments

`pedfile`	a pedigree file in GAS or LINKAGE format, note if individual's ID is character then it is necessary to specify as.is=T in the read.table command.
`makeped`	a logical variable indicating if the pedigree file is post-makeped.
`sink`	a logical variable indicating if .dot file(s) are created.

page	a string indicating the page size, e.g, A4, A5, B5, Legal, Letter, Executive, "x,y", where x, y is the customized page size.
url	Unified Resource Locator (URL) associated with the diagram(s).
height	the height of node(s).
width	the width of node(s).
rotate	if set to 90, the diagram is in landscape.
dir	direction of edges, i.e., "none", "forward","back","both". This will be useful if the diagram is viewed by lneato.

Details

This function converts GAS or LINKAGE formatted pedigree(s) into .dot file for each pedigree to be used by dot in graphviz, which is a flexible package for graphics freely available.

Note that a single PostScript (PDF) file can be obtainaed by `dot`, `fdp`, or `neato`.

```
dot -Tps <dot file> -o <ps file>
```

or

```
fdp -Tps <dot file> -o <ps file>
```

or

```
neato -Tps <dot file> -o <ps file>
```

See relevant documentations for other formats.

To preserve the original order of pedigree(s) in the data, you can examine the examples at the end of this document.

Under Cygwin/Linux/Unix, the PostScript file can be converted to Portable Document Format (PDF) default to Acrobat.

```
ps2pdf <ps file>
```

Use `ps2pdf12`, `ps2pdf13`, or `ps2pdf14` for appropriate versions of Acrobat according to information given on the headline of `<ps file>`.

Under Linux, you can also visualize the .dot file directly via command,

```
dotty <dot file> &
```

We can extract the code below (or within `pedtodot.Rd`) to pedtodot and then use command:

```
sh pedtodot <pedigree file>
```

Value

For each pedigree, the function generates a .dot file to be used by dot. The collection of all pedigrees (*.dot) can also be put together.

Note

This is based on the gawk script program pedtodot by David Duffy with minor changes.

Author(s)

David Duffy, Jing Hua Zhao

See Also

package sem in CRAN and Rgraphviz in BioConductor https://www.bioconductor.org/.

Examples

```
## Not run:
# example as in R News and Bioinformatics (see also plot.pedigree in package kinship)
# it works from screen paste only
p1 <- scan(nlines=16,what=list(0,0,0,0,0,"",""))
 1   2   3  2  2  7/7  7/10
 2   0   0  1  1  -/-  -/-
 3   0   0  2  2  7/9  3/10
 4   2   3  2  2  7/9  3/7
 5   2   3  2  1  7/7  7/10
 6   2   3  1  1  7/7  7/10
 7   2   3  2  1  7/7  7/10
 8   0   0  1  1  -/-  -/-
 9   8   4  1  1  7/9  3/10
10   0   0  2  1  -/-  -/-
11   2  10  2  1  7/7  7/7
12   2  10  2  2  6/7  7/7
13   0   0  1  1  -/-  -/-
14  13  11  1  1  7/8  7/8
15   0   0  1  1  -/-  -/-
16  15  12  2  1  6/6  7/7

p2 <- as.data.frame(p1)
names(p2) <-c("id","fid","mid","sex","aff","GABRB1","D4S1645")
p3 <- data.frame(pid=10081,p2)
attach(p3)
pedtodot(p3)
#
# Three examples of pedigree-drawing
# assuming pre-MakePed LINKAGE file in which IDs are characters
pre<-read.table("pheno.pre",as.is=TRUE)[,1:6]
pedtodot(pre)
dir()
# for post-MakePed LINKAGE file in which IDs are integers
ped <-read.table("pheno.ped")[,1:10]
```

```
pedtodot(ped,makeped=TRUE)
dir()
# for a single file with a list of pedigrees ordered data
sink("gaw14.dot")
pedtodot(ped,sink=FALSE)
sink()
file.show("gaw14.dot")
# more details
pedtodot(ped,sink=FALSE,page="B5",url="https://jinghuazhao.github.io/")

# An example from Richard Mott and in the demo
filespec <- system.file("tests/ped.1.3.pre")
pre <- read.table(filespec,as.is=TRUE)
pre
pedtodot(pre,dir="forward")

## End(Not run)
```

`pedtodot_verbatim` *Pedigree-drawing with graphviz*

Description

Pedigree-drawing with graphviz

Usage

```
pedtodot_verbatim(f, run = FALSE)
```

Arguments

`f`	A data.frame containing pedigrees, each with pedigree id, individual id, father id, mother id, sex and affection status.
`run`	A flag to run dot/neato on the generated .dot file(s).

Details

Read a GAS or LINKAGE format pedigree, return a digraph in the dot language and optionally call dot/neato to make pedigree drawing.

This is a verbatim translation of the original pedtodot implemneted in Bash/awk in contrast to `pedtodot` which was largely a mirror. To check independently, try `xsel -i < <(cat pedtodot_verbatim.R)` or `cat pedtodot_verbatim.R | xsel -i` and paste into an R session.

Value

No value is returned but outputs in .dot, .pdf, and .svg.

Note

Adapted from Bash/awk script by David Duffy

Examples

```
## Not run:
# pedigree p3 in pedtodot / toDOT=TRUE
  pedtodot_verbatim(p3,run=TRUE)

## End(Not run)
```

---

pfc   *Probability of familial clustering of disease*

Description

Probability of familial clustering of disease

Usage

```
pfc(famdata, enum = 0)
```

Arguments

famdata	collective information of sib size, number of affected sibs and their frequencies.
enum	a switch taking value 1 if all possible tables are to be enumerated.

Details

To calculate exact probability of familial clustering of disease

Value

The returned value is a list containing (tailp,sump,nenum are only available if enum=1:

- p the probabitly of familial clustering.
- stat the deviances, chi-squares based on binomial and hypergeometric distributions, the degrees of freedom should take into account the number of marginals used.
- tailp the exact statistical significance.
- sump sum of the probabilities used for error checking.
- nenum the total number of tables enumerated.

Note

Adapted from family.for by Dani Zelterman, 25/7/03

Author(s)

Dani Zelterman, Jing Hua Zhao

References

Yu C, Zelterman D (2001). "Exact inference for family disease clusters." *Communications in Statistics - Theory and Methods*, **30**(11), 2293-2305. doi:10.1081/STA100107686.

Yu C, Zelterman D (2002). "Statistical inference for familial disease clusters." *Biometrics*, **58**(3), 481-91. doi:10.1111/j.0006341x.2002.00481.x.

See Also

kin.morgan

Examples

```
## Not run:
# IPF among 203 siblings of 100 COPD patients from Liang KY, SL Zeger,
# Qaquish B. Multivariate regression analyses for categorical data
# (with discussion). J Roy Stat Soc B 1992, 54:3-40

# the degrees of freedom is 15
famtest<-c(
1, 0, 36,
1, 1, 12,
2, 0, 15,
2, 1,  7,
2, 2,  1,
3, 0,  5,
3, 1,  7,
3, 2,  3,
3, 3,  2,
4, 0,  3,
4, 1,  3,
4, 2,  1,
6, 0,  1,
6, 2,  1,
6, 3,  1,
6, 4,  1,
6, 6,  1)
test<-t(matrix(famtest,nrow=3))
famp<-pfc(test)

## End(Not run)
```

`pfc.sim` *Probability of familial clustering of disease*

Description

Probability of familial clustering of disease

Usage

```
pfc.sim(famdata, n.sim = 1e+06, n.loop = 1)
```

Arguments

`famdata`	collective information of sib size, number of affected sibs and their frequencies.
`n.sim`	number of simulations in a single Monte Carlo run.
`n.loop`	total number of Monte Carlo runs.

Details

To calculate probability of familial clustering of disease using Monte Carlo simulation.

Value

The returned value is a list containing:

- n.sim a copy of the number of simulations in a single Monte Carlo run.
- n.loop the total number of Monte Carlo runs.
- p the observed p value.
- tailpl accumulated probabilities at the lower tails.
- tailpu simulated p values.

Note

Adapted from runi.for from Change Yu, 5/6/4

Author(s)

Chang Yu, Dani Zelterman

References

Yu C, Zelterman D (2001). "Exact inference for family disease clusters." *Communications in Statistics - Theory and Methods*, **30**(11), 2293-2305. doi:10.1081/STA100107686.

See Also

`pfc`

Examples

```
## Not run:
# Li FP, Fraumeni JF Jr, Mulvihill JJ, Blattner WA, Dreyfus MG, Tucker MA,
# Miller RW. A cancer family syndrome in twenty-four kindreds.
# Cancer Res 1988, 48(18):5358-62.

# family_size  #_of_affected frequency

famtest<-c(
1, 0, 2,
1, 1, 0,
2, 0, 1,
2, 1, 4,
2, 2, 3,
3, 0, 0,
3, 1, 2,
3, 2, 1,
3, 3, 1,
4, 0, 0,
4, 1, 2,
5, 0, 0,
5, 1, 1,
6, 0, 0,
6, 1, 1,
7, 0, 0,
7, 1, 1,
8, 0, 0,
8, 1, 1,
8, 2, 1,
8, 3, 1,
9, 3, 1)

test<-matrix(famtest,byrow=T,ncol=3)

famp<-pfc.sim(test)

## End(Not run)
```

---

pgc *Preparing weight for GENECOUNTING*

Description

Preparing weight for GENECOUNTING

Usage

```
pgc(data, handle.miss = 1, is.genotype = 0, with.id = 0)
```

Arguments

`data`	the multilocus genotype data for a set of individuals.
`handle.miss`	a flag to indicate if missing data is kept, 0 = no, 1 = yes.
`is.genotype`	a flag to indicate if the data is already in the form of genotype identifiers.
`with.id`	a flag to indicate if the unique multilocus genotype identifier is generated.

Details

This function is a R port of the GENECOUNTING/PREPARE program which takes an array of genotyep data and collapses individuals with the same multilocus genotype. This function can also be used to prepare for the genotype table in testing Hardy-Weinberg equilibrium.

Value

The returned value is a list containing:

- cdata the collapsed genotype data.
- wt the frequency weight.
- obscom the observed number of combinations or genotypes.
- idsave optional, available only if with.id = 1.

Note

Built on pgc.c.

Author(s)

Jing Hua Zhao

References

Zhao JH, Sham PC (2003). "Generic number systems and haplotype analysis." *Comput Methods Programs Biomed*, **70**(1), 1-9. doi:10.1016/s01692607(01)001936.

See Also

`genecounting`, `hwe.hardy`

Examples

```
## Not run:
require(gap.datasets)
data(hla)
x <- hla[,3:8]

# do not handle missing data
y<-pgc(x,handle.miss=0,with.id=1)
hla.gc<-genecounting(y$cdata,y$wt)
```

```
# handle missing but with multilocus genotype identifier
pgc(x,handle.miss=1,with.id=1)

# handle missing data with no identifier
pgc(x,handle.miss=1,with.id=0)

## End(Not run)
```

`plot.hap.score` *Plot haplotype frequencies versus haplotype score statistics*

Description

Method function to plot a class of type hap.score

Usage

```
## S3 method for class 'hap.score'
plot(x, ...)
```

Arguments

`x`	The object returned from hap.score (which has class hap.score).
`...`	Optional arguments.

Value

Nothing is returned.

This is a plot method function used to plot haplotype frequencies on the x-axis and haplotype-specific scores on the y-axis. Because hap.score is a class, the generic plot function can be used, which in turn calls this plot.hap.score function.

References

Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA (2002) Score tests for association of traits with haplotypes when linkage phase is ambiguous. Amer J Hum Genet 70:425-34

See Also

`hap.score`

Examples

```
## Not run:
save <- hap.score(y, geno, trait.type = "gaussian")

# Example illustrating generic plot function:
plot(save)

# Example illustrating specific method plot function:
plot.hap.score(save)

## End(Not run)
```

`print.hap.score` *Print a hap.score object*

Description

Method function to print a class of type hap.score

Usage

```
## S3 method for class 'hap.score'
print(x, ...)
```

Arguments

`x`	The object returned from hap.score (which has class hap.score).
`...`	Optional argunents.

Value

Nothing is returned.

This is a print method function used to print information from hap.score class, with haplotype-specific information given in a table. Because hap.score is a class, the generic print function can be used, which in turn calls this print.hap.score function.

References

Schaid DJ, Rowland CM, Tines DE, Jacobson RM, Poland GA (2002) Score tests for association of traits with haplotypes when linkage phase is ambiguous. Amer J Hum Genet 70:425-34

See Also

`hap.score`

Examples

```
## Not run:
save <- hap.score(y, geno, trait.type = "gaussian")

# Example illustrating generic print function:
print(save)

# Example illustrating specific method print function:
print.hap.score(save)

## End(Not run)
```

---

pvalue — *P value for a normal deviate*

Description

P value for a normal deviate

Usage

```
pvalue(z, decimals = 2)
```

Arguments

z	normal deviate.
decimals	number of decimal places.

Value

P value as a string variable.

Examples

```
pvalue(-1.96)
```

qqfun *Quantile-comparison plots*

Description

Quantile-comparison plots

Usage

```
qqfun(
  x,
  distribution = "norm",
  ylab = deparse(substitute(x)),
  xlab = paste(distribution, "quantiles"),
  main = NULL,
  las = par("las"),
  envelope = 0.95,
  labels = FALSE,
  col = palette()[4],
  lcol = palette()[2],
  xlim = NULL,
  ylim = NULL,
  lwd = 1,
  pch = 1,
  bg = palette()[4],
  cex = 0.4,
  line = c("quartiles", "robust", "none"),
  ...
)
```

Arguments

`x`	vector of numeric values.
`distribution`	root name of comparison distribution – e.g., `norm` for the normal distribution; `t` for the t-distribution.
`ylab`	label for vertical (empirical quantiles) axis.
`xlab`	label for horizontal (comparison quantiles) axis.
`main`	label for plot.
`las`	if `0`, ticks labels are drawn parallel to the axis; set to `1` for horizontal labels (see `graphics::par`).
`envelope`	confidence level for point-wise confidence envelope, or `FALSE` for no envelope.
`labels`	vector of point labels for interactive point identification, or `FALSE` for no labels.
`col`	color for points; the default is the *fourth* entry in the current color palette (see `grDevices::palette` and `graphics::par`).

`lcol`	color for lines; the default is the *second* entry as above.
`xlim`	the x limits (x1, x2) of the plot. Note that x1 > x2 is allowed and leads to a reversed axis.
`ylim`	the y limits of the plot.
`lwd`	line width; default is `1` (see `graphics::par`). Confidence envelopes are drawn at half this line width.
`pch`	plotting character for points; default is `1` (a circle, see `graphics::par`).
`bg`	background color of points.
`cex`	factor for expanding the size of plotted symbols; the default is `.4`.
`line`	`"quartiles"` to pass a line through the quartile-pairs, or `"robust"` for a robust-regression line; the latter uses the `rlm` function in the `MASS` package. Specifying `line = "none"` suppresses the line.
`...`	arguments such as `df` to be passed to the appropriate quantile function.

Details

Plots empirical quantiles of a variable against theoretical quantiles of a comparison distribution.

Draws theoretical quantile-comparison plots for variables and for studentized residuals from a linear model. A comparison line is drawn on the plot either through the quartiles of the two distributions, or by robust regression.

Any distribution for which quantile and density functions exist in R (with prefixes `q` and `d`, respectively) may be used. Studentized residuals are plotted against the appropriate t-distribution.

This is adapted from `car::qq.plot` with different values for points and lines, more options, more transparent code and examples in the current setting. Another similar but sophisticated function is `lattice::qqmath`.

Value

These functions are used only for their side effect (to make a graph).

Author(s)

John Fox, Jing Hua Zhao

References

Davison AC (2003). *Statistical Models (Cambridge Series in Statistical and Probabilistic Mathematics)*. Cambridge University Press (2003-08-04). doi:10.1017/CBO9780511815850. Leemis LM, McQueston JT (2008). "Univariate Distribution Relationships." *The American Statistician*, **62**(1), 45-53. doi:10.1198/000313008X270448.

See Also

`stats::qqnorm`, `qqunif`, `gcontrol2`

Examples

```
## Not run:
p <- runif(100)
alpha <- 1/log(10)

qqfun(p,distribution="unif")
qqfun(-log10(p),distribution="exp",rate=alpha,pch=21)

library(car)
qq.plot(p,dist="unif")
qq.plot(-log10(p),dist="exp",rate=alpha)

library(lattice)
qqmath(~ -log10(p), distribution=function(p) qexp(p,rate=alpha))

## End(Not run)
```

---

qqunif — *Q-Q plot for uniformly distributed random variables*

Description

Q-Q plot for uniformly distributed random variables

Usage

```
qqunif(
  u,
  type = "unif",
  logscale = TRUE,
  base = 10,
  col = palette()[4],
  lcol = palette()[2],
  ci = FALSE,
  alpha = 0.05,
  ...
)
```

Arguments

`u`	A vector of uniformly distributed random variables.
`type`	Distribution type: `"unif"` for uniform order statistics or `"exp"` for exponential order statistics.
`logscale`	Logical; use log scale.
`base`	Base of the logarithm.
`col`	Color for points.

lcol	Color for the diagonal reference line.
ci	Logical; show confidence intervals.
alpha	Significance level for confidence intervals.
...	Additional graphical arguments passed to qqplot().

Details

This function produces a Q-Q plot for a random variable following a uniform distribution, optionally on a logarithmic scale.

For type = "exp", the plot is based on exponential order statistics, which is generally more appropriate than directly log-transforming the expected uniform order statistics.

Value

Invisibly returns the list produced by qqplot() with components:

x Expected quantiles.

y Observed quantiles.

Author(s)

Jing Hua Zhao

References

Balakrishnan N, Nevzorov VB (2003). *A Primer on Statistical Distributions*. Wiley, Hoboken, N.J. ISBN 9780471427988. doi:10.1002/0471722227. Casella G, Berger RL (2002). *Statistical Inference*, 2 edition. Duxbury. ISBN 978-0-534-24312-8. Davison AC (2003). *Statistical Models (Cambridge Series in Statistical and Probabilistic Mathematics)*. Cambridge University Press (2003-08-04). doi:10.1017/CBO9780511815850.

See Also

qqfun

Examples

```
## Not run:
u_obs <- runif(1000)
r <- qqunif(u_obs,pch=21,bg="blue",bty="n")
u_exp <- r$y
hits <- u_exp >= 2.30103
points(r$x[hits],u_exp[hits],pch=21,bg="green")
legend("topleft",sprintf("GC.lambda = %.4f",gc.lambda(u_obs)))

## End(Not run)
```

qtl2dplot *2D QTL plot*

Description

2D QTL plot

Usage

```
qtl2dplot(
  d,
  chrlen = gap::hg19,
  snp_name = "SNP",
  snp_chr = "Chr",
  snp_pos = "bp",
  gene_chr = "p.chr",
  gene_start = "p.start",
  gene_end = "p.end",
  trait = "p.target.short",
  gene = "p.gene",
  TSS = FALSE,
  cis = "cis",
  value = "log10p",
  plot = TRUE,
  cex.labels = 0.6,
  cex.points = 0.6,
  xlab = "QTL position",
  ylab = "Gene position"
)
```

Arguments

d	Data to be used.
chrlen	lengths of chromosomes for specific build: hg18, hg19, hg38.
snp_name	variant name.
snp_chr	variant chromosome.
snp_pos	variant position.
gene_chr	gene chromosome.
gene_start	gene start position.
gene_end	gene end position.
trait	trait name.
gene	gene name.
TSS	to use TSS when TRUE.
cis	cis variant when TRUE.

value	A specific value to show.
plot	to plot when TRUE.
cex.labels	Axis label extension factor.
cex.points	Data point extension factor.
xlab	X-axis title.
ylab	Y-axis title.

Details

This function is both used as its own for a 2d plot and/or generate data for a plotly counterpart.

Value

positional information.

Examples

```
## Not run:
INF <- Sys.getenv("INF")
d <- read.csv(file.path(INF,"work","INF1.merge.cis.vs.trans"),as.is=TRUE)
r <- qtl2dplot(d)
# A qtlClaaifier/qtl2dplot coupling example:
ucsc_modified <- bind_rows(ucsc,APOC,AMY,C4B,HIST,HBA)
pqtls <- select(merged,prot,SNP,log.P.) %>%
         mutate(log10p=-log.P.) %>%
         left_join(caprion_modified) %>%
         select(Gene,SNP,prot,log10p)
posSNP <- select(merged,SNP,Chr,bp)
cis.vs.trans <- qtlClassifier(pqtls,posSNP,ucsc_modified,1e6) %>%
                mutate(geneChrom=as.integer(geneChrom),
                       cis=if_else(Type=="cis",TRUE,FALSE))
head(cis.vs.trans)
    Gene            SNP  prot log10p geneChrom geneStart  geneEnd SNPChrom    SNPPos  cis
   YWHAB 8:111907280_A_T 1433B   7.38        20  43530174 43535076        8 111907280 FALSE
     A2M 14:34808001_A_T  A2MG   7.51        12   9220421  9268445       14  34808001 FALSE
    APEH  1:12881809_A_G  ACPH   7.83         3  49711834 49720772        1  12881809 FALSE
     PGD 2:121896327_A_G  6PGD   7.79         1  10459174 10479803        2 121896327 FALSE
SERPINF2  17:1618262_C_T  A2AP  12.59        17   1648289  1657825       17   1618262  TRUE
    PGLS 19:54327869_G_T  6PGL   9.87        19  17622481 17631887       19  54327869 FALSE
qtl2dplot(cis.vs.trans,chrlen=gap::hg19,
          snp_name="SNP",snp_chr="SNPChrom",snp_pos="SNPPos",
          gene_chr="geneChrom",gene_start="geneStart",gene_end="geneEnd",
          trait="prot",gene="Gene",
          TSS=TRUE,cis="cis",plot=TRUE,cex.labels=0.6,cex.points=0.6,
          xlab="pQTL position",ylab="Gene position")

## End(Not run)
```

qtl2dplotly *2D QTL plotly*

Description

2D QTL plotly

Usage

```
qtl2dplotly(
  d,
  chrlen = gap::hg19,
  qtl.id = "SNPid:",
  qtl.prefix = "QTL:",
  qtl.gene = "Gene:",
  target.type = "Protein",
  TSS = FALSE,
  xlab = "QTL position",
  ylab = "Gene position",
  ...
)
```

Arguments

`d`	Data in qtl2dplot() format.
`chrlen`	Lengths of chromosomes for specific build: hg18, hg19, hg38.
`qtl.id`	QTL id.
`qtl.prefix`	QTL prefix.
`qtl.gene`	QTL gene.
`target.type`	Type of target, e.g., protein.
`TSS`	to use TSS when TRUE.
`xlab`	X-axis title.
`ylab`	Y-axis title.
`...`	Additional arguments, e.g., target, log10p, to qtl2dplot.

Value

A plotly figure.

Examples

```
## Not run:
INF <- Sys.getenv("INF")
d <- read.csv(file.path(INF,"work","INF1.merge.cis.vs.trans"),as.is=TRUE)
r <- qtl2dplotly(d)
htmlwidgets::saveWidget(r,file=file.path(INF,"INF1.qtl2dplotly.html"))
r

## End(Not run)
```

`qtl3dplotly` *3D QTL plot*

Description

3D QTL plot

Usage

```
qtl3dplotly(
  d,
  chrlen = gap::hg19,
  zmax = 300,
  qtl.id = "SNPid:",
  qtl.prefix = "QTL:",
  qtl.gene = "Gene:",
  target.type = "Protein",
  TSS = FALSE,
  xlab = "QTL position",
  ylab = "Gene position",
  ...
)
```

Arguments

`d`	Data in qtl2d() format.
`chrlen`	Lengths of chromosomes for specific build: hg18, hg19, hg38.
`zmax`	Maximum value (e.g., -log10p) to truncate, above which they would be set to this value.
`qtl.id`	QTL id.
`qtl.prefix`	QTL prefix.
`qtl.gene`	QTL target gene.
`target.type`	Type of target, e.g., protein.
`TSS`	to use TSS when TRUE.
`xlab`	X-axis title.
`ylab`	Y-axis title.
`...`	Additional arguments, e.g., to qtl2dplot().

Value

A plotly figure.

Examples

```
## Not run:
suppressMessages(library(dplyr))
INF <- Sys.getenv("INF")
d <- read.csv(file.path(INF,"work","INF1.merge.cis.vs.trans"),as.is=TRUE) %>%
     mutate(log10p=-log10p)
r <- qtl3dplotly(d,zmax=300)
htmlwidgets::saveWidget(r,file=file.path(INF,"INF1.qtl3dplotly.html"))
r

## End(Not run)
```

`qtlClassifier` *A QTL cis/trans classifier*

Description

A QTL cis/trans classifier

Usage

```
qtlClassifier(geneSNP, SNPPos, genePos, radius)
```

Arguments

`geneSNP`	data.frame with columns on gene, SNP and biomarker (e.g., expression, protein).
`SNPPos`	data.frame containing SNP, chromosome and position.
`genePos`	data.frame containing gene, chromosome, start and end positions.
`radius`	flanking distance.

Details

The function obtains QTL (simply called SNP here) cis/trans classification based on gene positions.

Value

It returns a geneSNP-prefixed data.frame with the following columns:

- geneChrom gene chromosome.
- geneStart gene start.
- geneEnd gene end.
- SNPChrom pQTL chromosome.
- SNPPos pQTL position.
- Type cis/trans labels.

Note

This is adapted from iBMQ/eqtlClassifier as an xQTL (x=e, p, me, ...) classifier.

See Also

cis.vs.trans.classification

Examples

```
## Not run:
  merged <- read.delim("INF1.merge",as.is=TRUE)
  hits <- merge(merged[c("CHR","POS","MarkerName","prot","log10p")],
                inf1[c("prot","uniprot")],by="prot")
  names(hits) <- c("prot","Chr","bp","SNP","log10p","uniprot")

  options(width=200)
  geneSNP <- merge(hits[c("prot","SNP","log10p")],
                   inf1[c("prot","gene")],by="prot")[c("gene","SNP","prot","log10p")]
  SNPPos <- hits[c("SNP","Chr","bp")]
  genePos <- inf1[c("gene","chr","start","end")]
  cvt <- qtlClassifier(geneSNP,SNPPos,genePos,1e6)
  cvt
  cistrans <- cis.vs.trans.classification(hits,inf1,"uniprot")
  cis.vs.trans <- with(cistrans,data)
 cistrans.check <- merge(cvt[c("gene","SNP","Type")],cis.vs.trans[c("p.gene","SNP","cis.trans")],
                         by.x=c("gene","SNP"),by.y=c("p.gene","SNP"))
  with(cistrans.check,table(Type,cis.trans))

## End(Not run)
```

---

qtlFinder *Distance-based signal identification*

Description

Distance-based signal identification

Usage

```
qtlFinder(
  d,
  Chromosome = "Chromosome",
  Position = "Position",
  MarkerName = "MarkerName",
  Allele1 = "Allele1",
  Allele2 = "Allele2",
  EAF = "Freq1",
  Effect = "Effect",
```

```
  StdErr = "StdErr",
  log10P = "log10P",
  N = "N",
  radius = 1e+06,
  collapse.hla = TRUE,
  build = "hg19"
)
```

Arguments

d	input data.
Chromosome	chromosome.
Position	position.
MarkerName	RSid or SNPid.
Allele1	effect allele.
Allele2	other allele.
EAF	effect allele frequency.
Effect	b.
StdErr	SE.
log10P	-log(P).
N	sample size.
radius	a flanking distance.
collapse.hla	a flag to collapse signals in the HLA region.
build	genome build to define the HLA region.

Details

This function implements an iterative merging algorithm to identify signals. The setup follows output from METAL. When collapse.hla=TRUE, a single most significant signal in the HLA region is chosen. The Immunogenomics paper gives hg19/GRCh37: chr6:28477797-33448354 (6p22.1-21.3), hg38/GRCh38: chr6:28510020-33480577.

Value

The function lists QTLs and meta-information.

Examples

```
## Not run:
  f <- "ZPI_dr.p.gz"
  varlist=c("Chromosome","Position","MarkerName","Allele1","Allele2",
            "Freq1","FreqSE","MinFreq","MaxFreq",
            "Effect","StdErr","log10P","Direction",
            "HetISq","HetChiSq","HetDf","logHetP","N")
  d <- read.table(f,col.names=varlist,check.names=FALSE)
  qtlFinder(d)

## End(Not run)
```

read.ms.output *A utility function to read ms output*

Description

A utility function to read ms output

Usage

```
read.ms.output(
  msout,
  is.file = TRUE,
  xpose = TRUE,
  verbose = TRUE,
  outfile = NULL,
  outfileonly = FALSE
)
```

Arguments

`msout`	an ms output.
`is.file`	a flag indicating ms output as a system file or an R object.
`xpose`	a flag to obtain the tranposed format as it is (when TRUE).
`verbose`	when TRUE, display on screen every 1000 for large nsam.
`outfile`	to save the haplotypes in a tab-delimited ASCII file.
`outfileonly`	to reset gametes to NA when nsam/nreps is very large and is useful with outfile.

Details

This function reads in the output of the program ms, a program to generate samples under a variety of neutral models.

The argument indicates either a file name or a vector of character strings, one string for each line of the output of ms. As with the second case, it is appropriate with system(,intern=TRUE), see example below.

Value

The returned value is a list storing the results:

- call system call to ms.
- seed random number seed to ms.
- nsam number of copies of the locus in each sample.
- nreps the number of independent samples to generate.
- segsites a vector of the numbers of segregating sites.

- times vectors of time to most recent ancester (TMRCA) and total tree lengths.
- positions positions of polymorphic sites on a scale of (0,1).
- gametes a list of haplotype arrays.
- probs the probability of the specified number of segregating sites given the genealogical history of the sample and the value to -t option.

Author(s)

D Davison, RR Hudson, JH Zhao

References

Hudson RR (2002). "Generating samples under a Wright-Fisher neutral model of genetic variation." *Bioinformatics*, **18**(2), 337-8. doi:10.1093/bioinformatics/18.2.337.

Press WH, SA Teukolsky, WT Vetterling, BP Flannery (1992). Numerical Recipes in C. Cambridge University Press, Cambridge.

Examples

```
## Not run:
# Assuming ms is on the path

system("ms 5 4 -s 5 > ms.out")
msout1 <- read.ms.output("ms.out")

system("ms 50 4 -s 5 > ms.out")
msout2 <- read.ms.output("ms.out",outfile="out",outfileonly=TRUE)

msout <- system("ms 5 4 -s 5 -L", intern=TRUE)
msout3 <- read.ms.output(msout,FALSE)

## End(Not run)
```

ReadGRM *A function to read GRM file*

Description

A function to read GRM file

Usage

```
ReadGRM(prefix = 51)
```

Arguments

prefix file root.

ReadGRMBin *A function to read GRM binary files*

Description

A function to read GRM binary files

Usage

```
ReadGRMBin(prefix, AllN = FALSE, size = 4)
```

Arguments

prefix	file root.
AllN	a logical variable.
size	size.

Details

Modified from GCTA documentation

revStrand *Allele on the reverse strand*

Description

Allele on the reverse strand

Usage

```
revStrand(allele)
```

Arguments

allele	Allele to reverse.

Details

The function obtains allele on the reverse strand.

Value

Allele on the reverse strand.

Examples

```
## Not run:
  alleles <- c("a","c","G","t")
  reverse_strand(alleles)

## End(Not run)
```

`runshinygap` *Start shinygap*

Description

Start shinygap

Usage

```
runshinygap(...)
```

Arguments

`...`	Additional arguments passed to the 'runApp' function from the 'shiny' package.

Details

This function starts the interactive 'shinygap' shiny web application that allows for flexible model specification.

The 'shiny' based web application allows for flexible model specification for the implemented study designs.

Value

These are design specific.

`s2k` *Statistics for 2 by K table*

Description

Statistics for 2 by K table

Usage

```
s2k(y1, y2)
```

Arguments

y1	a vector containing the first row of a 2 by K contingency table.
y2	a vector containing the second row of a 2 by K contingency table.

Details

This function calculates one-to-others and maximum accumulated chi-squared statistics for a 2 by K contingency table.

Value

The returned value is a list containing:

- x2a the one-to-other chisquare.
- x2b the maximum accumulated chisquare.
- col1 the column index for x2a.
- col2 the column index for x2b.
- p the corresponding p value.

Note

The lengths of y1 and y2 should be the same.

Author(s)

Chihiro Hirotsu, Jing Hua Zhao

References

Hirotsu C, Aoki S, Inada T, Kitao Y (2001). "An exact test for the association between the disease and alleles at highly polymorphic loci with particular interest in the haplotype analysis." *Biometrics*, **57**, 769-778.

Examples

```
## Not run:
# an example from Mike Neale
# termed 'ugly' contingency table by Patrick Sullivan
y1 <- c(2,15,16,35,132,30,25,7,12,24,10,10,0)
y2 <- c(0, 6,31,49,120,27,15,8,14,25, 3, 9,3)

result <- s2k(y1,y2)

## End(Not run)
```

`sentinels` *Sentinel identification from GWAS summary statistics*

Description

Sentinel identification from GWAS summary statistics

Usage

```
sentinels(
  p,
  pid,
  st,
  debug = FALSE,
  flanking = 1e+06,
  chr = "Chrom",
  pos = "End",
  b = "Effect",
  se = "StdErr",
  log_p = NULL,
  snp = "MarkerName",
  sep = ","
)
```

Arguments

`p`	an object containing GWAS summary statistics.
`pid`	a phenotype (e.g., protein) name in pGWAS.
`st`	row number as in p.
`debug`	a flag to show the actual data.
`flanking`	the width of flanking region.
`chr`	Chromosome name.
`pos`	Position.
`b`	Effect size.
`se`	Standard error.
`log_p`	log(P).
`snp`	Marker name.
`sep`	field delimitor.

Details

This function accepts an object containing GWAS summary statistics for signal identification as defined by flanking regions. As the associate P value could be extremely small, the effect size and its standard error are used.

A distance-based approach was consequently used and reframed as an algorithm here. It takes as input signals multiple correlated variants in particular region(s) which reach genomewide significance and output three types of sentinels in a region-based manner. For a given protein and a chromosome, the algorithm proceeds as follows:

Algorithm sentinels

Step 1. for a particular collection of genomewide significant variants on a chromosome, the width of the region is calculated according to the start and end chromosomal positions and if it is smaller than the flanking distance, the variant with the smallest P value is taken as sentinel (I) otherwise goes to step 2.

Step 2. The variant at step 1 is only a candidate and a flanking region is generated. If such a region contains no variant the candidate is recorded as sentinel (II) and a new iteration starts from the variant next to the flanking region.

Step 3. When the flanking is possible at step 2 but the P value is still larger than the candidate at step 2, the candidate is again recorded as sentinel (III) but next iteration starts from the variant just after the variant at the end position; otherwise the variant is updated as a new candidate where the next iteration starts.

Note Type I signals are often seen from variants in strong LD at a cis region, type II results seen when a chromosome contains two trans signals, type III results seen if there are multiple trans signals.

Typically, input to the function are variants reaching certain level of significance and the functtion identifies minimum p value at the flanking interval; in the case of another variant in the flanking window has smaller p value it will be used instead.

For now key variables in p are "MarkerName", "End", "Effect", "StdErr", "P.value", where "End" is as in a bed file indicating marker position, and the function is set up such that row names are numbered as 1:nrow(p); see example below. When log_p is specified, log(P) is used instead, which is appropriate with output from METAL with LOGPVALUE ON. In this case, the column named log(P) in the output is actually log10(P).

Value

The function give screen output.

Examples

```
## Not run:
 ## OPG as a positive control in our pGWAS
 require(gap.datasets)
 data(OPG)
 p <- reshape::rename(OPGtbl, c(Chromosome="Chrom", Position="End"))
 chrs <- with(p, unique(Chrom))
 for(chr in chrs)
 {
   ps <- subset(p[c("Chrom","End","MarkerName","Effect","StdErr")], Chrom==chr)
```

```
    row.names(ps) <- 1:nrow(ps)
    sentinels(ps, "OPG", 1)
  }
  subset(OPGrsid,MarkerName=="chr8:120081031_C_T")
  subset(OPGrsid,MarkerName=="chr17:26694861_A_G")
  ## log(P)
  p <- within(p, {logp <- log(P.value)})
  for(chr in chrs)
  {
    ps <- subset(p[c("Chrom","End","MarkerName","logp")], Chrom==chr)
    row.names(ps) <- 1:nrow(ps)
    sentinels(ps, "OPG", 1, log_p="logp")
  }
  ## to obtain variance explained
  tbl <- within(OPGtbl, chi2n <- (Effect/StdErr)^2/N)
  s <- with(tbl, aggregate(chi2n,list(prot),sum))
  names(s) <- c("prot", "h2")
  sd <- with(tbl, aggregate(chi2n,list(prot),sd))
  names(sd) <- c("p1","sd")
  m <- with(tbl, aggregate(chi2n,list(prot),length))
  names(m) <- c("p2","m")
  h2 <- cbind(s,sd,m)
  ord <- with(h2, order(h2))
  sink("h2.dat")
  print(h2[ord, c("prot","h2","sd","m")], row.names=FALSE)
  sink()
  png("h2.png", res=300, units="in", width=12, height=8)
  np <- nrow(h2)
  with(h2[ord,], {
      plot(h2, cex=0.4, pch=16, xaxt="n", xlab="protein", ylab=expression(h^2))
      xtick <- seq(1, np, by=1)
      axis(side=1, at=xtick, labels = FALSE)
      text(x=xtick, par("usr")[3],labels = prot, srt = 75, pos = 1, xpd = TRUE, cex=0.5)
  })
  dev.off()
  write.csv(tbl,file="INF1.csv",quote=FALSE,row.names=FALSE)

## End(Not run)
```

snpHWE *Functions for single nucleotide polymorphisms*

Description

These are a set of functions specifically for single nucleotide polymorphisms (SNPs), which are biallelic markers. This is particularly relevant to the genomewide association studies (GWAS) using GeneChips and in line with the classic generalised single-locus model. snpHWE is from Abecasis's website and yet to be adapted for chromosome X.

Usage

```
snpHWE(g)

PARn(p, RRlist)

snpPVE(beta, se, N)

snpPAR(RR, MAF, unit = 2)
```

Arguments

g	Observed genotype vector.
p	genotype frequencies.
RRlist	A list of RRs.
beta	Regression coefficient.
se	Standard error for beta.
N	Sample size.
RR	Relative risk.
MAF	Minar allele frequency.
unit	Unit to exponentiate for homozygote.

Details

snpHWE gives an exact Hardy-Weinberg Equilibrium (HWE) test and it return -1 in the case of misspecification of genotype counts.

snpPAR calculates the the population attributable risk (PAR) for a particular SNP. Internally, it calls for an internal function PARn, given a set of frequencies and associate relative risks (RR). Other 2x2 table statistics familiar to epidemiologists can be added when necessary.

snpPVE provides proportion of variance explained (PVE) estimate based on the linear regression coefficient and standard error. For logistic regression, we can have similar idea for log(OR) and log(SE(OR)).

Author(s)

Jing Hua Zhao, Shengxu Li

---

snptest_sample *A utility to generate SNPTEST sample file*

Description

A utility to generate SNPTEST sample file

Usage

```
snptest_sample(
  data,
  sample_file = "snptest.sample",
  ID_1 = "ID_1",
  ID_2 = "ID_2",
  missing = "missing",
  C = NULL,
  D = NULL,
  P = NULL
)
```

Arguments

data	Data to be used.
sample_file	Output filename.
ID_1	ID_1 as in the sample file.
ID_2	ID_2 as in the sample file.
missing	Missing data column.
C	Continuous variables.
D	Discrete variables.
P	Phenotypic variables.

Value

Output file in SNPTEST's sample format.

Examples

```
## Not run:
d <- data.frame(ID_1=1,ID_2=1,missing=0,PC1=1,PC2=2,D1=1,P1=10)
snptest_sample(d,C=paste0("PC",1:2),D=paste0("D",1:1),P=paste0("P",1:1))

## End(Not run)
```

---

tscc *Power calculation for two-stage case-control design*

Description

Power calculation for two-stage case-control design

Usage

```
tscc(model, GRR, p1, n1, n2, M, alpha.genome, pi.samples, pi.markers, K)
```

Arguments

`model`	any in c("multiplicative","additive","dominant","recessive").
`GRR`	genotype relative risk.
`p1`	the estimated risk allele frequency in cases.
`n1`	total number of cases.
`n2`	total number of controls.
`M`	total number of markers.
`alpha.genome`	false positive rate at genome level.
`pi.samples`	sample% to be genotyped at stage 1.
`pi.markers`	markers% to be selected (also used as the false positive rate at stage 1).
`K`	the population prevalence.

Details

This function gives power estimates for two-stage case-control design for genetic association.

The false positive rates are calculated as follows,

$$P(|z1| > C1)P(|z2| > C2, sign(z1) = sign(z2))$$

and

$$P(|z1| > C1)P(|zj| > Cj||z1| > C1)$$

for replication-based and joint analyses, respectively; where C1, C2, and Cj are threshoulds at stages 1, 2 replication and joint analysis,

$$z1 = z(p1, p2, n1, n2, pi.samples)$$

$$z2 = z(p1, p2, n1, n2, 1 - pi.samples)$$

$$zj = sqrt(pi.samples) * z1 + sqrt(1 - pi.samples) * z2$$

Value

The returned value is a list containing a copy of the input plus output as follows,

- model any in c("multiplicative","additive","dominant","recessive").
- GRR genotype relative risk.
- p1 the estimated risk allele frequency in cases.
- pprime expected risk allele frequency in cases.
- p expected risk allele frequency in controls.
- n1 total number of cases.
- n2 total number of controls.
- M total number of markers.
- alpha.genome false positive rate at genome level.

- pi.samples sample% to be genotyped at stage 1.
- pi.markers markers% to be selected (also used as the false positive rate at stage 1).
- K the population prevalence.
- C threshoulds for no stage, stage 1, stage 2, joint analysis.
- power power corresponding to C.

Note

`solve.skol` is adapted from CaTS.

Author(s)

Jing Hua Zhao

References

Skol AD, Scott LJ, Abecasis GR, Boehnke M (2006). "Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies." *Nat Genet*, **38**(2), 209-13. doi:10.1038/ng1706.

Examples

```
## Not run:
K <- 0.1
p1 <- 0.4
n1 <- 1000
n2 <- 1000
M <- 300000
alpha.genome <- 0.05
GRR <- 1.4
p1 <- 0.4
pi.samples <- 0.2
pi.markers <- 0.1

options(echo=FALSE)
cat("sample%,marker%,GRR,(thresholds x 4)(power estimates x 4)","\n")
for(GRR in c(1.3,1.35,1.40))
{
   cat("\n")
   for(pi.samples in c(1.0,0.5,0.4,0.3,0.2))
   {
      if(pi.samples==1.0) s <- 1.0
      else s <- c(0.1,0.05,0.01)
      for(pi.markers in s)
      {
        x <- tscc("multiplicative",GRR,p1,n1,n2,M,alpha.genome,
                  pi.samples,pi.markers,K)
        l <- c(pi.samples,pi.markers,GRR,x$C,x$power)
        l <- sprintf("%.2f %.2f %.2f, %.2f %.2f %.2f %.2f, %.2f %.2f %.2f %.2f",
                     l[1],l[2],l[3],l[4],l[5],l[6],l[7],l[8],l[9],l[10],l[11])
        cat(l,"\n")
```

```
        }
        cat("\n")
    }
}
options(echo=TRUE)

## End(Not run)
```

`whscore` *Whittemore-Halpern scores for allele-sharing*

Description

Whittemore-Halpern scores for allele-sharing

Usage

```
whscore(allele, type)
```

Arguments

`allele`	a matrix of alleles of affected pedigree members.
`type`	0 = pairs, 1 = all.

Details

Allele sharing score statistics.

Value

The returned value is the value of score statistic.

Note

adapted from GENEHUNTER.

Author(s)

Leonid Kruglyak, Jing Hua Zhao

References

Kruglyak L, Daly MJ, Reeve-Daly MP, Lander ES (1996). “Parametric and nonparametric linkage analysis: a unified multipoint approach.” *Am J Hum Genet*, **58**(6), 1347-63.

Whittemore AS, Halpern J (1994). “A class of tests for linkage using affected pedigree members.” *Biometrics*, **50**(1), 118-27.

Whittemore AS, Halpern J (1994). “Probability of gene identity by descent: computation and applications.” *Biometrics*, **50**(1), 109-17.

Examples

```
## Not run:
c<-matrix(c(1,1,1,2,2,2),ncol=2)
whscore(c,type=1)
whscore(c,type=2)

## End(Not run)
```

WriteGRM — *A function to write GRM file*

Description

A function to write GRM file

Usage

```
WriteGRM(prefix = 51, id, N, GRM)
```

Arguments

prefix	file root.
id	id.
N	sample size.
GRM	a GRM.

WriteGRMBin — *A function to write GRM binary file*

Description

A function to write GRM binary file

Usage

```
WriteGRMBin(prefix, grm, N, id, size = 4)
```

Arguments

prefix	file root.
grm	a GRM.
N	Sample size.
id	id.
size	size.

xy — *Conversion of chromosome names to strings*

Description

Conversion of chromosome names to strings

Usage

```
xy(x)
```

Arguments

`x`	(alpha)numeric value indicating chromosome.

Details

This function converts x=1:24 to 1:22, X, Y

Value

As indicated.

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