Package ‘bimetallic’

February 19, 2015

Type Package

Title Power for SNP analyses using silver standard cases

Version 1.0

Date 2011-08-03

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Description A power calculator for Genome-wide association studies (GWAs) with combined gold (error-free) and silver (erroneous) phenotyping per McDavid A, Crane PK, Newton KM, Crosslin DR, et al. (2011)

License GPL-2

LazyLoad yes

Repository CRAN

Date/Publication 2012-10-29 08:58:17

NeedsCompilation no

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Description

A power calculator for Genome-wide association studies (GWAs) with combined gold (error-free) and silver (erroneous) phenotyping per McDavid A, Crane PK, Newton KM, Crosslin DR, et al. (2011)

Details

Package: bimetallic
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Version: 1.0
Date: 2011-08-03
License: GPL-2
LazyLoad: yes

chisq.sim.factory, chisq.lytic.func and dlambda, is.legal all use common parameters. chisq.sim.factory returns a function that repeatedly calculates chi-square statistics (X^2) and point estimates of allelic odds ratios (allelicOR) for a study specified by the simulation parameters. chisq.lytic.func returns lambda, the non-centrality parameter of the asymptotic sampling distribution of (X^2), which happens to be non-central chi-square with two degrees of freedom. dlambda returns the derivative of lambda with respect to gam_ca or gam_co. If this is positive then power is increasing with the addition of a silver-standard subject. is.legal determines if the parameters provided are ‘legal’ in the sense of inducing valid probabilities in affected and unaffected populations in the simulation

Author(s)

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References

See McDavid A, Crane PK, Newton KM, Crosslin DR, et al. (2011) for a full description of the model and parameters.

Examples

```r
# Make a chisq simulator under a study scenario
sim = chisq.sim.factory(R = 4, gam_ca = 3, gam_co = 0,
                        ppv = .8, npv = 1, homRR = 2.2, N_co = 1000,
                        maf = .1, prev = .01, model = "mult")
```
### allelicOR

Run one realization of the simulation

sim()

---

| allelicOR | Calculate an odds ratio from a 2x3 contingency table of genotype X phenotype |

#### Description

Find the odds ratio, per allele, in biallelic marker in a diploid individual. The locus must be under Hardy-Weinburg at the margin, ie, alleles are independent, for this calculation to hold.

#### Usage

```r
allelicOR(xtable)
```

#### Arguments

- `xtable` A 2x3 contingency table of frequencies or counts of individuals.

#### Details

The OR is calculated as 

\[
\frac{(2\times AA.\text{Case} + Aa.\text{Case}) \times (2\times AA.\text{Control} + Aa.\text{Control})}{(2\times aa.\text{Case} + Aa.\text{Case}) \times (2\times aa.\text{Control} + Aa.\text{Control})}
\]

#### Value

The odds ratio, floating point.

#### Author(s)

Andrew McDavid

#### See Also

- `chisq.sim.factory`

#### Examples

```r
cont.table = matrix(c(5, 4, 1, 4, 3, 4), nrow=2, ncol=3, byrow=TRUE)
allelicOR(cont.table)
```

---

| bimetallic=internal | bimetallic internal functions |

#### Description

Internal functions in package
Power of Chi-square tests

Description

Produce a function that returns a simulator of chi-square statistics and odds ratios, determine if a set of parameters is legal, return the non-centrality parameter, lambda, of the chi-square distribution under a set of parameters, take a derivative of lambda with respect to number of silver-standard samples under a set of parameters.

Usage

chisq.sim.factory(rL, gam_caL, gam_coL, ppvL, npvL, homRR, N_coL, mafL, prevL, modelL)
is.legal(rL, gam_caL, gam_coL, ppvL, npvL, homRR, N_coL, mafL, prevL, modelL)
chisq.lytic.func(rL, gam_caL, gam_coL, ppvL, npvL, homRR, N_coL, mafL, prevL, modelL)
dlambdas(rL, gam_caL, gam_coL, ppvL, npvL, homRR, N_coL, mafL, prevL, modelL, diff="gam_ca")

Arguments

- **R**
  Ratio of gold standard controls to gold standard cases
- **gam_ca**
  Ratio of silver standard cases to gold standard cases
- **gam_co**
  Ratio of silver standard controls to gold standard controls
- **ppv**
  The positive predictive value of the criteria used to identify silver standard cases, ie, \(P(\text{Affected} \mid \text{Case})\)
- **npv**
  The negative predictive value of the criteria used to identify silver standard controls, ie, \(P(\text{Unaffected} \mid \text{Control})\)
- **homRR**
  The relative risk of a homozygous genotype, ie, \(P(\text{Affected} \mid \text{geno}=\text{AA}) / P(\text{Affected} \mid \text{geno}=\text{aa})\)
- **N_co**
  The number of gold-standard controls
- **maf**
  The minor allele frequency of the risk locus
- **prev**
  Disease prevalence, ie, \(P(\text{Affected})\)
- **model**
  Disease risk model, either one of ‘dominant’, ‘recessive’, ‘multiplicative’ or number giving the heterozygous relative risk.
- **diff**
  Take the derivative of lambda with respect to ‘gam_ca’ (default) or ‘gam_co’
Details

This function simulates the behavior of chi-square tests for independence in a genome-wide association study consisting of two cohorts. The first cohort, the gold standard cohort, is assumed to have been classified into affected and unaffected without error. The second cohort, the silver standard cohort, is assumed to have errors in disease classification subject to the npv and ppv arguments. A distinction is drawn between affected, unaffected and case and control. Affected and unaffected are the true disease status, which is observed in the gold standard cohort. In the silver standard cohort the case/control criteria are observed instead, while the affected/unaffected status is latent.

The numbers of gold and silver standard cases and controls are set by N_co and the ratios R, gam_co and gam_ca. The genotype frequencies in the gold standard cohort are governed by a genotypic disease risk model and the parameters homRR, maf, prev and model. The model argument may be a character vector of length one, either ‘dominant’, ‘recessive’, ‘multiplicative’ (or an unambiguous abbreviation thereof), which links the heterozygous relative risk \( P(\text{Affected} | Aa) / P(\text{Affected} | aa) \) to homRR, or it may be a floating point value directly specifying the heterozygous relative risk.

These functions offer a way to simulate power as well as calculate it asymptotically. The distribution of chi-square statistics under the disease risk model, ppv, npv and case/control ratios is asymptotically distributed non-central chi-square. chisq.lytic.func returns the non-centrality parameter associated with the model. dLambda returns the first derivative of lambda. Since power is increasing in lambda, if dLambda is positive, then an additional silver standard case (if diff="gam_ca") increases power.

Value

chisq.sim.factory returns a argument-less function that may be repeatedly called to sample from the simulated distribution. This function returns a vector of length 2, consisting of the chi-square statistic and the point estimate of the allelic odds ratio. Parameters are not checked for legality.

is.legal returns a boolean value indicating if the disease risk model parameters are legal, ie, induce genotype probabilities on \([0,1]\), conditional on affected/unaffected status.

chisq.lytic.func returns \( \lambda \), the non-centrality parameter of the asymptotic sampling distribution of the chi-square test under the model.

dLambda returns the first derivative of lambda with respect to gam_ca or gam_co

Author(s)

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References


See Also

dLambda
Examples

```r
## Make a chisq simulator under a study scenario
sim = chisq.sim.factory(R = 4, gam_ca = 3, gam_co = 0,
                         ppv = 0.8, npv = 1, homRR = 2.2, N_co = 1000,
                         maf = 0.1, prev = 0.01, model = "mult")

## Run one realization of the simulation
sim()

## Run 100 realizations of the simulation
times = 100
chisq_or = as.data.frame(t(replicate(times, sim())))

## Find the number of times chisq_or$stat exceeded 0.01 significance
sig = 0.01
critval = qchisq(1-sig, 2)
sucess = sum(chisq_or$stat > critval)

## Find the power
nsucess/times

## Compare to asymptotic
lambda = chisq.lytic.func(R = 4, gam_ca = 3, gam_co = 0,
                           ppv = 0.8, npv = 1, homRR = 2.2, N_co = 1000,
                           maf = 0.1, prev = 0.01, model = "mult")
1-pchisq(qchisq(1-sig, 2), 2, ncp=lambda)

## Generate a multifactorial design
paramset = list(R = c(0.5, 1, 2, 4), gam_ca = c(0, 1), gam_co = 0,
                ppv = c(0.4, 0.6, 0.8), npv = 0.8, homRR = c(1.4, 3, 9), N_co = 1000,
                maf = 0.1, prev = 0.01, model = "mult")
paramgrid = do.call(expand.grid, c(paramset, stringsAsFactors=FALSE))

## Call chisq.lytic and dlambda for each experiment
lambda = vector()
dl = vector()
for( i in 1:nrow(paramgrid)){
  lambda[i] = do.call(chisq.lytic.func, paramgrid[i,])
  dl[i] = do.call(dlambda, paramgrid[i,])
}

## Bind it to the parameter data.frame
## Calculate the difference in lambda for gam_ca=0 vs gam_ca=1
paramgrid = cbind(paramgrid, lambda, dl)
param0 = subset(paramgrid, gam_ca==0)
param1 = subset(paramgrid, gam_ca==1)
all(paste(param0[,c(1, 3:10)])==paste(param1[,c(1, 3:10)]))
param0 = cbind(param0, finite_diff_dl = param1$lambda - param0$lambda)

## Do they agree?
with(param0, cor(dl, finite_diff_dl))
```
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