

Package ‘remaCor’

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Type Package

Title Random Effects Meta-Analysis for Correlated Test Statistics

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Description Meta-analysis is widely used to summarize estimated effects sizes across multiple statistical tests. Standard fixed and random effect meta-analysis methods assume that the estimated of the effect sizes are statistically independent. Here we relax this assumption and enable meta-analysis when the correlation matrix between effect size estimates is known. Fixed effect meta-analysis uses the method of Lin and Sullivan (2009) <[doi:10.1016/j.ajhg.2009.11.001](https://doi.org/10.1016/j.ajhg.2009.11.001)>, and random effects meta-analysis uses the method of Han, et al. <[doi:10.1093/hmg/ddw049](https://doi.org/10.1093/hmg/ddw049)>.

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URL <https://diseaseneurogenomics.github.io/remaCor/>

BugReports <https://github.com/DiseaseNeurogenomics/remaCor/issues>

Suggests knitr, RUnit, clusterGeneration, metafor

Depends R (>= 3.6.0), ggplot2, methods

Imports mvtnorm, grid, reshape2, compiler, Rcpp, EnvStats, Rdpack, stats

VignetteBuilder knitr

RdMacros Rdpack

Encoding UTF-8

RoxygenNote 7.3.2

LinkingTo Rcpp, RcppArmadillo

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hotelling	<i>Hottelling T^2 test for multivariate regression</i>
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Description

Hottelling T^2 test compares estimated regression coefficients to specified values under the null. This tests a global hypothesis for all specified coefficients. It uses the F-distribution as the null for the test statistic which is exact under finite sample size.

Usage

```
hotelling(beta, Sigma, n, mu_null = rep(0, length(beta)))
```

Arguments

beta	regressioin coefficients
Sigma	covariance matrix of regression coefficients
n	sample size used for estimation
mu_null	the values of the regression coefficients under the null hypothesis. Defaults to all zeros

Details

The Hotelling T^2 test is not defined when $n - p < 1$. Returns data.frame with stat = pvalue = NA.

Examples

```
library(clusterGeneration)
library(mvtnorm)

# sample size
n = 30

# number of response variables
m = 2

# Error covariance
```

```

Sigma = genPositiveDefMat(m)$Sigma

# regression parameters
beta = matrix(.6, 1, m)

# covariates
X = matrix(rnorm(n), ncol=1)

# Simulate response variables
Y = X %*% beta + rmvnorm(n, sigma = Sigma)

# Multivariate regression
fit = lm(Y ~ X)

# extract coefficients and covariance
# corresponding to the x variable
beta = coef(fit)['X',]
S = vcov(fit)[c(2,4), c(2,4)]

# perform Hotelling test
hotelling(beta, S, n)

```

LS

Fixed effect meta-analysis for correlated test statistics

Description

Fixed effect meta-analysis for correlated test statistics using the Lin-Sullivan method.

Usage

```
LS(beta, stders, cor = diag(1, length(beta)))
```

Arguments

beta	regression coefficients from each analysis
stders	standard errors corresponding to betas
cor	correlation matrix between of test statistics. Default considers uncorrelated test statistics

Details

Perform fixed effect meta-analysis for correlated test statistics using method of Lin and Sullivan (2009). By default, correlation is set to identity matrix to for independent test statistics.

This method requires the correlation matrix to be symmetric positive definite (SPD). If this condition is not satisfied, results will be NA. If the matrix is not SPD, there is likely an issue with how it was generated.

However, evaluating the correlation between observations that are not pairwise complete can give correlation matrices that are not SPD. In this case, consider running `Matrix::nearPD(x, corr=TRUE)` to produce the nearest SPD matrix to the input.

Value

beta: effect size

se: effect size standard error

p: p-value

References

Lin D, Sullivan PF (2009). “Meta-analysis of genome-wide association studies with overlapping subjects.” *The American Journal of Human Genetics*, **85**(6), 862–872. <https://doi.org/10.1016/j.ajhg.2009.11.001>.

Examples

```
library(clusterGeneration)
library(mvtnorm)

# sample size
n = 30

# number of response variables
m = 6

# Error covariance
Sigma = genPositiveDefMat(m)$Sigma

# regression parameters
beta = matrix(.6, 1, m)

# covariates
X = matrix(rnorm(n), ncol=1)

# Simulate response variables
Y = X %*% beta + rmvnorm(n, sigma = Sigma)

# Multivariate regression
fit = lm(Y ~ X)

# Correlation between residuals
C = cor(residuals(fit))

# Extract effect sizes and standard errors from model fit
df = lapply(coef(summary(fit)), function(a)
  data.frame(beta = a["X", 1], se = a["X", 2]))
df = do.call(rbind, df)

# Run fixed effects meta-analysis,
```

```
# assume identity correlation
LS( df$beta, df$se)

# Run fixed effects meta-analysis,
# account for correlation
LS( df$beta, df$se, C)
```

LS.empirical

Fixed effect meta-analysis for correlated test statistics

Description

Fixed effect meta-analysis for correlated test statistics using the Lin-Sullivan method using Monte Carlo draws from the null distribution to compute the p-value.

Usage

```
LS.empirical(
  beta,
  stders,
  cor = diag(1, length(beta)),
  nu,
  n.mc.samples = 10000,
  seed = 1,
  useGamma = TRUE
)
```

Arguments

beta	regression coefficients from each analysis
stders	standard errors corresponding to betas
cor	correlation matrix between of test statistics. Default considers uncorrelated test statistics
nu	residual degrees of freedom
n.mc.samples	number of Monte Carlo samples
seed	random seed so results are reproducible
useGamma	if TRUE, use gamma approximation to fit empirical distribution of test statistics and compute p-value. If FALSE, report p-value as $(1 + \sum(\text{obs} > \text{stat})) / (\text{length}(\text{stat}) + 1)$. Using TRUE allows computation of small p-values with fewer Monte Carlo samples.

Details

The theoretical null for the Lin-Sullivan statistic for fixed effects meta-analysis is χ^2 when the regression coefficients are estimated from a large sample size. But for finite sample size, this null distribution is not well characterized. In this case, we are not aware of a closed form cumulative distribution function. Instead we draw covariance matrices from a Wishart distribution, sample coefficients from a multivariate normal with this covariance, and then compute the Lin-Sullivan statistic. A gamma distribution is then fit to these draws from the null distribution and a p-value is computed from the cumulative distribution function of this gamma.

References

Hoffman GE, Roussos P (2025). “Fast, flexible analysis of differences in cellular composition with crumblr.” *bioRxiv*. <https://doi.org/10.1101/2025.01.29.635498>.

See Also

LS()

Examples

```
library(clusterGeneration)
library(mvtnorm)

# sample size
n = 30

# number of response variables
m = 6

# Error covariance
Sigma = genPositiveDefMat(m)$Sigma

# regression parameters
beta = matrix(.6, 1, m)

# covariates
X = matrix(rnorm(n), ncol=1)

# Simulate response variables
Y = X %*% beta + rmvnorm(n, sigma = Sigma)

# Multivariate regression
fit = lm(Y ~ X)

# Correlation between residuals
C = cor(residuals(fit))

# Extract effect sizes and standard errors from model fit
df = lapply(coef(summary(fit)), function(a)
data.frame(beta = a["X", 1], se = a["X", 2]))
df = do.call(rbind, df)
```

```
# Meta-analysis assuming infinite sample size
# but the p-value is anti-conservative
LS(df$beta, df$se, C)

# Meta-analysis explicitly modeling the finite sample size
# Gives properly calibrated p-values
# nu is the residual degrees of freedom from the model fit
LS.empirical(df$beta, df$se, C, nu=n-2)
```

pkg.env	<i>Local environment</i>
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Description

Local environment

Usage

pkg.env

Format

An object of class environment of length 0.

plotCor	<i>Correlation plot</i>
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Description

Correlation plot

Usage

plotCor(cor)

Arguments

cor	correlation matrix between of test statistics. Default considers uncorrelated test statistics
-----	---

Value

Plot of correlation matrix

Examples

```
# Generate effects
library(mvtnorm)
library(clusterGeneration )

n = 4
Sigma = cov2cor(genPositiveDefMat(n)$Sigma)
beta = t(rmvnorm(1, rep(0, n), Sigma))
stders = rep(.1, n)

# set names
rownames(Sigma) = colnames(Sigma) = LETTERS[1:n]
rownames(beta) = names(stders) = LETTERS[1:n]

# Run random effects meta-analysis,
# account for correlation
RE2C( beta, stders, Sigma)

# Make plot
plotCor( Sigma )
```

plotForest	<i>Forest plot of coefficients</i>
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Description

Forest plot of coefficients

Usage

```
plotForest(beta, stders)
```

Arguments

beta	regression coefficients from each analysis
stders	standard errors corresponding to betas

Value

Forest plot of effect sizes and standard errors

Examples

```
# Generate effects
library(mvtnorm)
library(clusterGeneration )

n = 4
```

```

Sigma = cov2cor(genPositiveDefMat(n)$Sigma)
beta = t(rmvnorm(1, rep(0, n), Sigma))
stders = rep(.1, n)

# set names
rownames(Sigma) = colnames(Sigma) = LETTERS[1:n]
rownames(beta) = names(stders) = LETTERS[1:n]

# Run random effects meta-analysis,
# account for correlation
RE2C( beta, stders, Sigma)

# Make plot
plotForest( beta, stders )

```

RE2C

Random effect meta-analysis for correlated test statistics

Description

Random effect meta-analysis for correlated test statistics using RE2C

Usage

```
RE2C(beta, stders, cor = diag(1, length(beta)), twoStep = FALSE)
```

Arguments

beta	regression coefficients from each analysis
stders	standard errors corresponding to betas
cor	correlation matrix between of test statistics. Default considers uncorrelated test statistics
twoStep	Apply two step version of RE2C that is designed to be applied only after the fixed effect model.

Details

Perform random effect meta-analysis for correlated test statistics using RE2 method of Han and Eskin (2011), or RE2 for correlated test statistics from Han et al. (2016). Also uses RE2C method of Lee et al. (2017) to further test for heterogeneity in effect size. By default, correlation is set to identity matrix to for independent test statistics.

This method requires the correlation matrix to be symmetric positive definite (SPD). If this condition is not satisfied, results will be NA. If the matrix is not SPD, there is likely an issue with how it was generated.

For computing Q, QEp, and Isq, the effective number of independent studies is determined by `sum(solve(cor))` (Liu and Liang 1997). When the correlation is diagonal, the studies are independent and this value is simply the number of studies.

Value

stat1: statistic testing effect mean

stat2: statistic testing effect heterogeneity

RE2Cp: RE2 p-value accounting for correlation between tests

RE2Cp.twoStep: two step RE2C test after fixed effect test. Only evaluated if twoStep==TRUE

QE: test statistic for the test of (residual) heterogeneity

QEp: p-value for the test of (residual) heterogeneity

Isq: I^2 statistic

References

Han B, Duong D, Sul JH, de Bakker PI, Eskin E, Raychaudhuri S (2016). “A general framework for meta-analyzing dependent studies with overlapping subjects in association mapping.” *Human Molecular Genetics*, **25**(9), 1857–1866. <https://doi.org/10.1093/hmg/ddw049>.

Han B, Eskin E (2011). “Random-effects model aimed at discovering associations in meta-analysis of genome-wide association studies.” *The American Journal of Human Genetics*, **88**(5), 586–598. <https://doi.org/10.1016/j.ajhg.2011.04.014>.

Lee CH, Eskin E, Han B (2017). “Increasing the power of meta-analysis of genome-wide association studies to detect heterogeneous effects.” *Bioinformatics*, **33**(14), i379–i388. <https://doi.org/10.1093/bioinformatics/btx242>.

Liu G, Liang K (1997). “Sample size calculations for studies with correlated observations.” *Biometrics*, 937–947. <https://doi.org/10.2307/2533554>.

Examples

```
library(clusterGeneration)
library(mvtnorm)

# sample size
n = 30

# number of response variables
m = 6

# Error covariance
Sigma = genPositiveDefMat(m)$Sigma

# regression parameters
beta = matrix(.6, 1, m)

# covariates
X = matrix(rnorm(n), ncol=1)

# Simulate response variables
Y = X %*% beta + rmvnorm(n, sigma = Sigma)
```

```
# Multivariate regression
fit = lm(Y ~ X)

# Correlation between residuals
C = cor(residuals(fit))

# Extract effect sizes and standard errors from model fit
df = lapply(coef(summary(fit)), function(a)
  data.frame(beta = a["X", 1], se = a["X", 2]))
df = do.call(rbind, df)

# Run fixed effects meta-analysis,
# assume identity correlation
LS( df$beta, df$se)

# Run random effects meta-analysis,
# assume identity correlation
RE2C( df$beta, df$se)

# Run fixed effects meta-analysis,
# account for correlation
LS( df$beta, df$se, C)

# Run random effects meta-analysis,
# account for correlation
RE2C( df$beta, df$se, C)
```

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