Package 'xmeta'

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Type Package

Title A Toolbox for Multivariate Meta-Analysis

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Description A toolbox for meta-analysis. This package includes (1) a robust multivariate meta-analysis of continuous or binary outcomes; (2) a bivariate Egger's test for detecting small study effects; (3) Galaxy Plot: A New Visualization Tool of Bivariate Meta-Analysis Studies; and (4) a bivariate T&F method accounting for publication bias in bivariate meta-analysis, based on symmetry of the galaxy plot.

Depends R (>= 3.5.0)

License GPL (>= 2)

LazyLoad no

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`xmeta-package` *A Tool Box for Multivariate Meta-Analysis*

Description

The package **xmeta** consists of a collection of functions for making inference and detecting publication bias in multivariate meta-analysis (MMA).

Details

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Inference

The aim of the estimation methods is to estimate the coefficients $\boldsymbol{\beta}$ and the components of the between-study (co)variance matrix $\boldsymbol{\Psi}$ for multivariate random-effects meta-analysis. One major challenge in MMA is the standard inference procedures, such as the maximum likelihood or maximum restricted likelihood inference, require the within-study correlations, which are usually unavailable. Different estimators with and without the knowledge of within study correlation are implemented in the package **xmeta**. The estimation methods available in function `mmeta` are:

- **Restricted maximum likelihood for MMA with continuous outcomes**

- **Composite likelihood method for MMA with continuous outcomes**
- **Method of moment for MMA with continuous outocmes**
- **Improved method for Riley model for MMA with continuous outcomes**
- **Marginal bivariate normal model for MMA with binary outcomes**
- **Marginal beta-binomial model for MMA with binary outcomes**
- **Hybrid model for disease prevalence along with sensitivity and specificity for diagnostic test accuracy**
- **Trivariate model for multivariate meta-analysis of diagnostic test accuracy**

Small study effects

Detecting and accounting for small study effects are challenging in MMA setting. The multivariate nature is often not fully accounted for by the existing univariate methods. The score test for detecting small study effects in MMA when the within-study correlations are unknown is implemented in the function `msset`.

Galaxy Plot

A New Visualization Tool of Bivariate Meta-Analysis Studies. This function `galaxy` returns the galaxy plot to visualize bivariate meta-analysis data, which faithfully retains the information in two separate funnel plots, while providing useful insights into outcome correlations, between-study heterogeneity and joint asymmetry. Galaxy plot is the counterpart of the funnel plot in the multivariate setting. The galaxy plot is an intuitive visualization tool that can aid in interpretation of results of multivariate meta-analysis. It preserves all of the information presented by separate funnel plots for each outcome while elucidating more complex features that may only be revealed by examining the joint distribution of the bivariate outcomes.

Publication bias in bivariate meta-analysis

The function `galaxy.trimfill` implements a bivariate T&F method accounting for publication bias in bivariate meta-analysis, based on symmetry of the galaxy plot. The bivariate T&F method assumes studies are suppressed based on a weighted sum of the two outcomes. We use a searching algorithm to find the optimal direction which gives the most trimmed studies. This is based on the observation that the closer a direction is to the truth, the more studies are expected to be trimmed along that direction.

Author(s)

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ca125 *Recurrent ovarian carcinoma study*

Description

A meta-analysis of 52 studies that were reported between January 1995 and November 2007.

Format

The data frame contains the following columns:

n total number of subjects

PiY disease prevalence

SeY true positive

n1 subjects with disease

SpY true negative

n1 health individuals

Note

The dataset ca125 is used to conduct multivariate meta-analysis of diagnostic test accuracy.

References

Chen, Y., Liu, Y., Chu, H., Lee, M. and Schmid, C. (2017) A simple and robust method for multivariate meta-analysis of diagnostic test accuracy, Statistics in Medicine, 36, 105-121.

Gu P, Pan L, Wu S, Sun L, Huang G. CA 125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian carcinoma: a systematic review and meta-analysis. European journal of radiology 2009; 71(1):164-174.

See Also

mmeta, summary.mmeta

Examples

```
data(ca125)
summary(ca125)
```

dat.gen *Generate bivariate meta analysis studies*

Description

Generate bivariate meta analysis studies based on random-effects model, some studies with smallest weighted sum of the two outcomes are suppressed.

Usage

```
dat.gen(
  m.o,
  m.m,
  s.m,
  angle.LC = pi/4,
  mybeta,
  tau.sq,
  rho.w,
  rho.b,
  s.min = 0.01,
  m.m.o = 0,
  s2.dist = 2,
  verbose = F
)
```

Arguments

m.o	number of observed studies
m.m	number of missing / suppressed studies
s.m	vector of the mean of the variances of the two outcomes
angle.LC	direction of suppressing line, default is pi/4, i.e. the studies on the left bottom corner are missing
mybeta	the true center of the effect sizes
tau.sq	between-study variance, the larger it is the more heterogeneity.
rho.w	within-study correlation of the two outcomes
rho.b	between-study correlation of the two outcomes
s.min	minimum of the variances of the outcomes, default is 0.01
m.m.o	number of studies on one side of the suppressing line been observed, i.e. non-deterministic suppressing, default is 0, i.e. deterministic suppressing
s2.dist	options for generating the outcomes' variances. 1=runif, 2=runif^2, 3=runif^4, 4=rnorm
verbose	logical, galaxy plot the studies? Default FALSE

Author(s)

Chongliang Luo, Yong Chen

References

Luo C, Marks-Anglin AK, Duan R, Lin L, Hong C, Chu H, Chen Y. Accounting for small-study effects using a bivariate trim and fill meta-analysis procedure. medRxiv. 2020 Jan 1.

`galaxy` *Galaxy Plot: A New Visualization Tool of Bivariate Meta-Analysis Studies*

Description

A new visualization method that simultaneously presents the effect sizes of bivariate outcomes and their standard errors in a two-dimensional space.

Usage

```
galaxy(data, y1, s1, y2, s2, scale1, scale2, scale.adj,
             corr, group, study.label, annotate, xlab, ylab, main, legend.pos)
```

Arguments

`data`	dataset with at least 4 columns for the effect sizes of the two outcomes and their standard errors
`y1`	column name for outcome 1, default is 'y1'
`s1`	column name for standard error of `y1`, default is 's1'
`y2`	column name for outcome 2, default is 'y2'
`s2`	column name for standard error of `y2`, default is 's2'
`scale1`	parameter for the length of the cross hair: the ellipse width is scale1 / s1 * scale.adj
`scale2`	parameter for the length of the cross hair: the ellipse height is scale2 / s2 * scale.adj
`scale.adj`	a pre-specified parameter to adjust for `scale1` and `scale2`
`corr`	column name for within-study correlation
`group`	column name for study group
`study.label`	column name for study label
`annotate`	logical specifying whether study label should be added to the plot, default is FALSE.
`xlab`	x axis label, default `y1`
`ylab`	y axis label, default `y2`
`main`	main title
`legend.pos`	The position of the legend for study groups if `group` is specified, see `legend`, default is 'bottomright'.

Details

This function returns the galaxy plot to visualize bivariate meta-analysis data, which faithfully retains the information in two separate funnel plots, while providing useful insights into outcome correlations, between-study heterogeneity and joint asymmetry. Galaxy plot: a new visualization tool of bivariate meta-analysis studies. Funnel plots have been widely used to detect small study effects in the results of univariate meta-analyses. However, there is no existing visualization tool that is the counterpart of the funnel plot in the multivariate setting. We propose a new visualization method, the galaxy plot, which can simultaneously present the effect sizes of bivariate outcomes and their standard errors in a two-dimensional space. The galaxy plot is an intuitive visualization tool that can aid in interpretation of results of multivariate meta-analysis. It preserves all of the information presented by separate funnel plots for each outcome while elucidating more complex features that may only be revealed by examining the joint distribution of the bivariate outcomes.

Author(s)

Chuan Hong, Chongliang Luo, Yong Chen

References

Hong, C., Duan, R., Zeng, L., Hubbard, R., Lumley, T., Riley, R., Chu, H., Kimmel, S., and Chen, Y. (2020) Galaxy Plot: A New Visualization Tool of Bivariate Meta-Analysis Studies, American Journal of Epidemiology, https://doi.org/10.1093/aje/kwz286.

Examples

```
data(sim_dat)
galaxy(data=sim_dat, scale.adj = 0.9, corr = 'corr', group = 'subgroup',
        study.label = 'study.id', annotate = TRUE, main = 'galaxy plot')
```

---

galaxy.trimfill *Bivariate trim&fill method*

Description

Bivariate T&F method accounting for small-study effects in bivariate meta-analysis, based on symmetry of the galaxy plot.

Usage

```
galaxy.trimfill(
  y1,
  v1,
  y2,
  v2,
  n.grid = 12,
  angle,
```

```
  estimator,
  side,
  rho = 0,
  method = "mm",
  method.uni = "DL",
  maxiter = 20,
  var.names = c("y1", "y2"),
  scale = 0.02,
  verbose = FALSE
)
```

Arguments

y1	vector of the effect size estimates of the first outcome
v1	estimated variance of y1
y2	vector of the effect size estimates of the second outcome
v2	estimated variance of y2
n.grid	number of grid (equally spaced) candidate directions that the optimal projection direction are searched among, see Details
angle	angles of candidate projection directions not by grid, this will overwrite n.grid
estimator	estimator used for the number of trimmed studies in univariate T&F on the projected studies, one of c('R0', 'L0', 'Q0')
side	either "left" or "right", indicating on which side of the galaxy plot the missing studies should be imputed. If null determined by the univariate T&F
rho	correlation between y1 and y2 when computing the variance of the projected studies. Default is the estimated cor(y1, y2)
method	method to estimate the center for the bivariate outcomes. Default is 'mm', i.e. random-effects model
method.uni	method to estimate the center for the univariate projected studies using a univariate T&F procedure. Default is 'DL', i.e. fixed-effects model
maxiter	max number of iterations used in the univariate T&F. Default is 20.
var.names	names of the two outcomes used in the galaxy plot (if plotted). Default is c('y1', 'y2')
scale	constant scale for plotting the galaxy plot for the bivariate studies, Default is 0.02.
verbose	plot the galaxy plot? Default is FALSE.

Details

The bivariate T&F method assumes studies are suppressed based on a weighted sum of the two outcomes, i.e. the studies with smallest values of z_i = c_1 * y_1i + c_2 * y_2i, i=1,...,N are suppressed. We use a searching algorithm to find the optimal ratio of c_1 and c_2 (i.e. a direction), which gives the most trimmed studies. This is based on the observation that the closer a direction is to the truth, the more studies are expected to be trimmed along that direction. We set a sequence of equally-spaced candidate directions with angle a_m = m*pi/M, and (c_1, c_2) = (cos(a_m), sin(a_m)), m=1,...,M.

Value

List with component:

res a data.frame of 9 columns and n.grid rows. Each row is the result for projection along one candidate grid direction, and the columns are named: 'y1.c', 'y2.c' for projected bivariate center, 'y1.f', 'y2.f' for bivariate center using filled studies, 'k0', 'se.k0' for estimated number of trimmed studies and its standard error, 'se.y1.f', 'se.y2.f' for standard errors of 'y1.f', 'y2.f', 'side.left' for the estimated side

ID.trim list of vectors of ids of studies been trimmed along each of the candidate direction.

Author(s)

Chongliang Luo, Yong Chen

References

Luo C, Marks-Anglin AK, Duan R, Lin L, Hong C, Chu H, Chen Y. Accounting for small-study effects using a bivariate trim and fill meta-analysis procedure. medRxiv. 2020 Jan 1.

Examples

```
## Not run:
require(MASS)
require(mvmeta)
require(metafor)
set.seed(123)
mydata <- dat.gen(m.o=50, m.m=20,       # # observed studies, # missing studies
                  s.m= c(0.5, 0.5),     #  c(mean(s1), mean(s2))
                  angle.LC = pi/4,      # suppress line direction
                  mybeta=c(2,2),        # true effect size
                  tau.sq=c(0.1, 0.1),   # true between-study var
                  rho.w=0.5, rho.b=0.5, # true within-study and between-study corr
                  s.min = 0.1,          # s1i ~ Unif(s.min, 2*s.m[1]-s.min)
                  verbose = TRUE)

y1 <- mydata$mydat.sps$y1
y2 <- mydata$mydat.sps$y2
v1 <- mydata$mydat.sps$s1^2
v2 <- mydata$mydat.sps$s2^2

## unadjusted est
mv_obs <- mvmeta(cbind(y1, y2), cbind(v1, v2), method='mm')
c(mv_obs$coef)
# 2.142687 2.237741

estimator <- 'R0'
## univariate T&F based on y1 or y2
y1.rma <- rma(y1, v1, method='FE')
y2.rma <- rma(y2, v2, method='FE')
y1.tf <- trimfill.rma(y1.rma, estimator = estimator, method.fill = 'DL')
y2.tf <- trimfill.rma(y2.rma, estimator = estimator, method.fill = 'DL')
```

```
c(y1.tf$beta, y2.tf$beta)
# 2.122231 2.181333
c(y1.tf$k0, y2.tf$k0)
# 2 8

## bivariate T&F method (based on galaxy plot)
tf.grid <- galaxy.trimfill(y1, v1, y2, v2, n.grid = 12,
                           estimator=estimator, side='left',
                           method.uni = 'FE',
                           method = 'mm',
                           rho=0.5, maxiter=100, verbose=FALSE)
tf.grid$res
tf.grid$res[which(tf.grid$res$k0==max(tf.grid$res$k0)),3:5]
#     y1.f     y2.f k0
# 2.053306 2.162347 14

## less bias by the proposed bivariate T&F method
rbind(true = c(2,2),
      unadjusted=c(mv_obs$coef),
      tf.uni = c(y1.tf$beta, y2.tf$beta),
      tf.biv = tf.grid$res[which(tf.grid$res$k0==max(tf.grid$res$k0)),3:4])

## unlike the univariate T&Fs, biv T&F obtains one estimate of # missing studies
c(k0.true = 20,
  k0.tf.uni.y1 = y1.tf$k0,
  k0.tf.uni.y2 = y2.tf$k0,
  k0.tf.biv = tf.grid$res[which(tf.grid$res$k0==max(tf.grid$res$k0)),5])
# k0.true k0.tf.uni.y1 k0.tf.uni.y2    k0.tf.biv
# 20            2            8           14

## End(Not run)
```

`mmeta` *Methods for multiviarate random-effects meta-analysis*

Description

Methods for multiviarate random-effects meta-analysis

Usage

```
mmeta(data, rhow, type, k, method)
```

Arguments

`data`	dataset
`rhow`	within-study correlation
`type`	either "continuous" or "binary", indicating the type of outcomes.
`k`	integer indicating the number of outcomes

`method` either "nn.reml", "nn.cl", "nn.mom", "nn.rs", "bb.cl", "bn.cl", "tb.cl" or "tn.cl", indicating the estimation method.

Details

Inference on the multivariate random-effects meta-analysis for both continuous and binary outcomes

The function can be used in meta-analyses with continous outcomes and binary outcomes (e.g., mean differences, diagnostic test results in diagnostic accuracy studies, the exposure status of both cases and controls in case-control studies and so on). Different estimators with and without the knowledge of within-study correlations are implemented in this function. The estimation methods include

- **Restricted maximum likelihood for MMA with continuous outcomes**(nn.reml)
- **Composite likelihood method for MMA with continuous outcomes** (nn.cl)
- **Moment of method for MMA with continuous outocmes** (nn.mom)
- **Improved method for Riley model for MMA with continuous outcomes** (nn.rs)
- **Marginal bivariate normal model for MMA with binary outcomes** (bn.cl)
- **Marginal beta-binomial model for MMA with binary outcomes**(bb.cl)
- **Hybrid model for disease prevalence along with sensitivity and specificity for diagnostic test accuracy** (tb.cl)
- **Trivariate model for multivariate meta-analysis of diagnostic test accuracy**(tn.cl)

Value

An object of class `"mmeta"`. The object is a list containing the following components:

`beta` estimated coefficients of the model.

`beta.cov` covariance matrix of the coefficients.

Multivariate random-effects meta analysis

We consider a meta-analysis with m studies where two outcomes in each study are of interest. For the ith study, denote Y_{ij} and s_{ij} the summary measure for the jth outcome of interest and associated standard error respectively, both assumed known, $i = 1, \ldots, m$, and $j = 1, 2$. Each summary measure Y_{ij} is an estimate of the true effect size θ_{ij}. To account for heterogeneity in effect size across studies, we assume θ_{ij} to be independently drawn from a common distribution with overall effect size β_j and between study variance $\tau_j^2, j = 1, 2$. Under normal distribution assumption for Y_{ij} and θ_{ij}, the general bivariate random-effects meta-analysis can be written as

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix}, \Delta_i\right), \quad \Delta_i = \begin{pmatrix} s_{i1}^2 & s_{i1}s_{i2}\rho_{\mathrm{W}i} \\ s_{i1}s_{i2}\rho_{\mathrm{W}i} & s_{i2}^2 \end{pmatrix},$$

$$\begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \Omega\right), \quad \Omega = \begin{pmatrix} \tau_1^2 & \tau_1\tau_2\rho_{\mathrm{B}} \\ \tau_1\tau_2\rho_{\mathrm{B}} & \tau_2^2 \end{pmatrix},$$

where Δ_i and Ω are the respective within-study and between-study covariance matrices, and $\rho_{\mathrm{W}i}$ and ρ_{B} are the respective within-study and between-study correlations.

Restricted maximum likelihood for MMA

When the within-study correlations are known, inference on the overall effect sizes β_1 and β_2 or their comparative measures (e.g., $\beta_1 - \beta_2$) can be based on the marginal distribution of (Y_{i1}, Y_{i2})

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \end{pmatrix} \sim N\left(\begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \mathbf{V_i}\right), \mathbf{V_i} = \mathbf{\Delta_i}+\mathbf{\Omega} = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & s_{i1}s_{i2}\rho_{wi} + \tau_1\tau_2\rho_{\mathrm{B}} \\ s_{i1}s_{i2}\rho_{wi} + \tau_1\tau_2\rho_{\mathrm{B}} & s_{i2}^2 + \tau_2^2 \end{pmatrix}.$$

For simplicity of notation, denote $\mathbf{Y_i} = (\mathbf{Y_{i1}}, \mathbf{Y_{i2}})^{\mathbf{T}}$, $\beta = (\beta_1, \beta_2)^T$, $\eta_1 = (\beta_1, \tau_1^2)^T$ and $\eta_2 = (\beta_2, \tau_2^2)^T$. The restricted likelihood of $(\eta_1, \eta_2, \rho_{\mathrm{B}})$ can be written as

$$\log L(\eta_1, \eta_2, \rho_{\mathrm{B}}) = -\frac{1}{2}\left[\log\left(\left|\sum_{i=1}^{m} \mathbf{V_i}^{-\mathbf{1}}\right|\right) + \sum_{i=1}^{m}\left\{\log|\mathbf{V_i}| + (\mathbf{Y_i} - \beta)^{\mathbf{T}}\mathbf{V_i}^{-\mathbf{1}}(\mathbf{Y_i} - \beta)\right\}\right].$$

The parameters $(\eta_1, \eta_2, \rho_{\mathrm{B}})$ can be estimated by the restricted maximum likelihood (REML) approach as described in Van Houwelingen et al. (2002). The REML method for MMA is specified via `method` argument (`method="nn.reml"`).

The standard inference procedures, such as the maximum likelihood or maximum restricted likelihood inference, require the within-study correlations, which are usually unavailable. In case within-study correlations are unknown, then one can leave the ρ_w argument unspecified, and specify a method that does not require the within-study correlations via `method` argument.

Composite likelihood method for MMA with continuous outcomes

Chen et al. (2014) proposed a pseudolikelihood method for MMA with unknown within-study correlation. The pseudolikelihood method does not require within-study correlations, and is not prone to singular covariance matrix problem. In addition, it can properly estimate the covariance between pooled estimates for different outcomes, which enables valid inference on functions of pooled estimates, and can be applied to meta-analysis where some studies have outcomes MCAR. This composite likelihood method for MMA is specified via `method` argument (`method="nn.cl"`).

Moment of method for MMA with continuous outocmes

Chen et al. (2015) proposed a simple non-iterative method that can be used for the analysis of multivariate meta-analysis datasets that has no convergence problems and does not require the use of within-study correlations. The strategy is to use standard univariate methods for the marginal effects but also provides valid joint inference for multiple parameters. This method method can directly handle missing outcomes under missing completely at random assumption. This moment of method for MMA is specified via `method` argument (`method="nn.mom"`)

Improved method for Riley model for MMA with continuous outcomes

Riley et al.(2008) proposed a working model and an overall synthesis correlation parameter to account for the marginal correlation between outcomes, where the only data needed are those required for a separate univariate random-effects meta-analysis. As within-study correlations are not required, the Riley method is applicable to a wide variety of evidence synthesis situations. However, the standard variance estimator of the Riley method is not entirely correct under many important settings. As a consequence, the coverage of a function of pooled estimates may not reach the nominal level even when the number of studies in the multivariate meta-analysis is large. Hong et al.

(2015) improved the Riley method by proposing a robust variance estimator, which is asymptotically correct even when the model is misspecified (i.e., when the likelihood function is incorrect). The improved method for Riley model MMA is specified via `method` argument (`method="nn.rs"`)

Marginal bivariate normal model for MMA with binary outcomes

Diagnostic systematic review is a vital step in the evaluation of diagnostic technologies. In many applications, it invovles pooling paris of sensitivity and specificity of a dichotomized diagnostic test from multiple studies. Chen et al. (2014) proposed a composite likelihood method for bivariate meta-analysis in diagnostic systematic reviews. The idea of marginal bivariate normal model for MMA with binary outcomes is to construct a composite likelihood (CL) funciton by using an independent working assumption between sensitivity and specificity. There are three immediate advantages of using this CL method. First, the non-convergence or non positive definite covariance matrix problem is resolved since there is no correlation parameter involved in the CL. Secondly, because the two-dimensional integration involved in the standard likelihood is substituted by one-dimensional integrals, the approximation errors are substantially reduced. Thirdly, the inference based on the CL only relies on the marginal normality of logit sensitivity and specificity. Hence the proposed method can be more robust than the standard likelihood inference to mis-specifications of the joint distribution assumption. This method is specified via `method` argument (`method="bn.cl"`)

Marginal beta-binomial model for MMA with binary outcomes

When conducting a meta-analysis of studies with bivariate binary outcomes, challenges arise when the within-study correlation and between-study heterogeneity should be taken into account. Chen et al. (2015) proposed a marginal beta-binomial model for the meta-analysis of studies with binary outcomes. This model is based on the composite likelihood approach, and has several attractive features compared to the existing models such as bivariate generalized linear mixed model (Chu and Cole, 2006) and Sarmanov beta-binomial model (Chen et al., 2012). The advantages of the proposed marginal model include modeling the probabilities in the original scale, not requiring any transformation of probabilities or any link function, having closed-form expression of likelihood function, and no constraints on the correlation parameter. More importantly, since the marginal beta-binomial model is only based on the marginal distributions, it does not suffer from potential misspecification of the joint distribution of bivariate study-specific probabilities. Such misspecification is difficult to detect and can lead to biased inference using currents methods. This method is specified via `method` argument (`method="bb.cl"`)

Hybrid model for disease prevalence along with sensitivity and specificity for diagnostic test accuracy

Meta-analysis of diagnostic test accuracy often involves mixture of case-control and cohort studies. The existing bivariate random effects models, which jointly model bivariate accuracy indices (e.g., sensitivity and specificity), do not differentiate cohort studies from case-control studies, and thus do not utilize the prevalence information contained in the cohort studies. The trivariate generalized linear mixed models are only applicable to cohort studies, and more importantly, they assume the common correlation structure across studies, and the trivariate normality on disease prevalence, test sensitivity and specificity after transformation by some pre-specified link functions. In practice, very few studies provide justifications of these assumptions, and sometimes these assumptions are violated. Chen et al. (2015) evaluated the performance of the commonly used random effects

model under violations of these assumptions and propose a simple and robust method to fully utilize the information contained in case-control and cohort studies. The proposed method avoids making the aforementioned assumptions and can provide valid joint inferences for any functions of overall summary measures of diagnostic accuracy. This method is specified via `method` argument (`method="tb.cl"`)

Trivariate model for multivariate meta-analysis of diagnostic test accuracy

The standard methods for evaluating diagnostic accuracy only focus on sensitivity and specificity and ignore the information on disease prevalence contained in cohort studies. Consequently, such methods cannot provide estimates of measures related to disease prevalence, such as population averaged or overall positive and negative predictive values, which reflect the clinical utility of a diagnostic test. Chen et al. (2014) proposed a hybrid approach that jointly models the disease prevalence along with the diagnostic test sensitivity and specificity in cohort studies, and the sensitivity and specificity in case-control studies. In order to overcome the potential computational difficulties in the standard full likelihood inference of the proposed hybrid model, an alternative inference procedure was proposed based on the composite likelihood. Such composite likelihood based inference does not suffer computational problems and maintains high relative efficiency. In addition, it is more robust to model mis-specifications compared to the standard full likelihood inference. This method is specified via `method` argument (`method="tn.cl"`)

Author(s)

Yong Chen, Yulun Liu

References

Chen, Y., Hong, C. and Riley, R. D. (2015). An alternative pseudolikelihood method for multivariate random-effects meta-analysis. Statistics in medicine, 34(3), 361-380.

Chen, Y., Hong, C., Ning, Y. and Su, X. (2015). Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach, Statistics in Medicine (in press).

Hong, C., Riley, R. D. and Chen, Y. (2015). An improved method for multivariate random-effects meta-analysis (in preparation).

Chen, Y., Liu, Y., Ning, J., Nie, L., Zhu, H. and Chu, H. (2014). A composite likelihood method for bivariate meta-analysis in diagnostic systematic reviews. Statistical methods in medical research (in press).

Chen, Y., Cai, Y., Hong, C. and Jackson, D. (2015). Inference for correlated effect sizes using multiple univariate meta-analyses, Statistics in Medicine (provisional acceptance).

Chen, Y., Liu, Y., Ning, J., Cormier J. and Chu H. (2014). A hybrid model for combining case-control and cohort studies in systematic reviews of diagnostic tests, Journal of the Royal Statistical Society: Series C (Applied Statistics) 64.3 (2015): 469-489.

Chen, Y., Liu, Y., Chu, H., Lee, M. and Schmid, C. (2017) A simple and robust method for multivariate meta-analysis of diagnostic test accuracy, Statistics in Medicine, 36, 105-121.

Examples

```
data(prostate)
fit.nn=mmeta(data=prostate, type="continuous", k=2, method="nn.cl")
```

```
summary(fit.nn)

rhow=runif(dim(prostate)[1], -0.2, 0.8)
fit.reml=mmeta(data=prostate, rhow=rhow, type="continuous", k=2, method="nn.reml")
print(fit.reml)

data(nat2)
fit.bb=mmeta(data=nat2, type="binary", k=2, method="bb.cl")
summary(fit.bb)

data(ca125)
fit.tb=mmeta(data=ca125, type="binary", k=2, method="tb.cl")
summary(fit.tb)
```

`msset` *Testing and correcting for small study effects of multivariate meta-analysis*

Description

Testing and correcting for small study effects of multivariate meta-analysis

Usage

```
msset(data, nm.y1, nm.s1, nm.y2, nm.s2, method, type, k)
```

Arguments

`data`	dataset
`nm.y1`	column name for outcome 1
`nm.s1`	column name for standard error of outcome 1
`nm.y2`	column name for outcome 2
`nm.s2`	column name for standard error of outcome 2
`method`	"nn.cl" indicating the score test for detecting small study effects of MMA
`type`	either "continuous" or "binary" indicating the type of outcomes
`k`	integer indicating the number of outcomes

Details

This function returns the test statistics for testing small study effects of multivariate meta-analysis using regression method.

Value

`msset.TS` returns the test statistic and p value of the score test.

A score test for detecting small study effects in multivariate meta-analysis

Small study effects occur when smaller studies show different, often larger, treatment effects than large ones, which may threaten the validity of systematic reviews and meta-analyses. Detecting small study effects in a multivariate meta-analysis setting remains an untouched research area. Hong et al. (2019) propose a pseudolikelihood-based score test for detecting small study effects in multivariate random-effects meta-analysis. This is the first test for detecting small study effects in multivariate meta-analysis setting.

Author(s)

Chuan Hong

References

Hong, C., Salanti, G., Morton, S., Riley, R., Chu, H., Kimmel, S.E. and Chen Y. (2019). Testing small study effects in multivariate meta-analysis (Biometrics).

Examples

```
data(prostate)
fit.msset=msset(data=prostate, nm.y1="y1", nm.s1="s1", nm.y2="y2", nm.s2="s2",
method = "nn.cl", type = "continuous", k=2)
summary(fit.msset)
```

---

nat2 — *A meta-analysis of the association between N-acetyltransterase 2 acetylation status and colorectal cancer*

Description

A meta-analysis of 20 published case-control studies from January 1985 to October 2001

Format

The data frame contains the following columns:

y1 acetylator status (exposed) in control group

n1 total number of subjects in control group

y2 acetylator status (exposed) in case group

n2 total number of subjects in case group

Note

The dataset `nat2` is used to conduct marginal bivariate normal model for MMA with binary outcomes

References

Chen, Y., Hong, C., Ning, Y. and Su, X. (2015). Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach, Statistics in Medicine (in press).

Ye Z, Parry JM. Meta-analysis of 20 case-control studies on the n-acetyltransferase 2 acetylation status and colorectal cancer risk. Medical Science Review 2002; 8(8):CR558-CR565.

See Also

`mmeta`, `summary.mmeta`

Examples

```
data(nat2)
summary(nat2)
```

`prostate` *Comparison between overall survival and disease-free survival for prostate cancer*

Description

Results from five randomized clinical trials published between 1988 and 2011

Format

The data frame contains the following columns:

y1 log-hazard ratio estimates comparing combined therapy using Goserelin acetate with radiotherapy with respect to overall survival

s1 within-study standard error for outcome 1

y2 log-hazard ratio estimates comparing combined therapy using Goserelin acetate with radiotherapy with respect to disease-free survival

s2 within-study stamdard error for outcome 2

Note

The dataset `prostate` is used to conduct bivariate random-effects meta-analysis when the within-study correlations are unknown.

References

Chen, Y., Hong, C. and Riley, R. D. (2015). An alternative pseudolikelihood method for multivariate random-effects meta-analysis. Statistics in medicine, 34(3), 361-380.

Sasse A, Sasse E, Carvalho A, Macedo L. Androgenic suppression combined with radiotherapy for the treatment of prostate adenocarcinoma: a systematic review. BMC cancer 2012; 12(1):54. 30.

See Also

mmeta, summary.mmeta

Examples

```
data(prostate)
summary(prostate)
```

---

sim_dat *Simulated data*

Description

A simulated dataset for galaxy function

Format

The data frame contains the following columns:

study.id study id

y1 effect size for the first outcome

s1 within-study standard error for the first outcome

y2 effect size for the second outcome

s2 within-study stamdard error for the second outcome

corr within-study correlation

subgroup subgroup of the studies

Note

The dataset sim_dat is used to illustrate the galaxy plot.

See Also

galaxy

Examples

```
data(sim_dat)
summary(sim_dat)
```

summary.mmeta *Summarize the objects* mmeta

Description

Summarize a model of class mmeta fitted by mmeta.

Usage

```
      ## S3 method for class 'mmeta'
summary(object,...)
```

Arguments

object	an object inheriting from class mmeta.
...	additional arguments; currently none is used.

Value

A list with the following components: coefficients, covariance matrix.

References

Chen, Y., Hong, C. and Riley, R. D. (2015). An alternative pseudolikelihood method for multivariate random-effects meta-analysis. Statistics in medicine, 34(3), 361-380.

Chen, Y., Hong, C., Ning, Y. and Su, X. (2015). Meta-analysis of studies with bivariate binary outcomes: a marginal beta-binomial model approach, Statistics in Medicine (in press).

Hong, C., Riley, R. D. and Chen, Y. (2015). An improved method for multivariate random-effects meta-analysis (in preparation).

Chen, Y., Liu, Y., Ning, J., Nie, L., Zhu, H. and Chu, H. (2014). A composite likelihood method for bivariate meta-analysis in diagnostic systematic reviews. Statistical methods in medical research (in press).

Chen, Y., Cai, Y., Hong, C. and Jackson, D. (2015). Inference for correlated effect sizes using multiple univariate meta-analyses, Statistics in Medicine (provisional acceptance).

Chen, Y., Liu, Y., Ning, J., Cormier J. and Chu H. (2014). A hybrid model for combining case-control and cohort studies in systematic reviews of diagnostic tests, Journal of the Royal Statistical Society: Series C (Applied Statistics) 64.3 (2015): 469-489.

Chen, Y., Liu, Y., Chu, H., Lee, M. and Schmid, C. (2017) A simple and robust method for multivariate meta-analysis of diagnostic test accuracy, Statistics in Medicine, 36, 105-121.

See Also

mmeta

Examples

```
data(prostate)
fit.nn=mmeta(data=prostate, type="continuous", k=2, method="nn.cl")
summary(fit.nn)
```

`summary.msset` *Summarize the objects* `msset`

Description

Summarize a model of class `msset` fitted by `msset`.

Usage

```
      ## S3 method for class 'msset'
summary(object,...)
```

Arguments

`object`	an object inheriting from class `msset`.
`...`	additional arguments; currently none is used.

Value

A list with the following components: test statistics (msset) and p-value.

References

Hong, C., Salanti, G., Morton, S., Riley, R., Chu, H., Kimmel, S.E. and Chen Y. (2019). Testing small study effects in multivariate meta-analysis (Biometrics).

See Also

`msset`

Examples

```
data(prostate)
fit.msset=msset(data=prostate, nm.y1="y1", nm.s1="s1", nm.y2="y2", nm.s2="s2",
method = "nn.cl", type = "continuous", k=2)
summary(fit.msset)
```

`trimfill.rma` *Trim&fill method for univariate meta analysis*

Description

Modified metafor::trimfill.rma.uni to avoid the invalid sqrt in k0 calculation when estimator == "Q0"

Usage

```
## S3 method for class 'rma'
trimfill(
  x,
  side,
  estimator = "L0",
  maxiter = 100,
  method.trim = NULL,
  method.fill = NULL,
  verbose = FALSE,
  ilim
)
```

Arguments

`x`	an object of class "rma.uni".
`side`	the same as in metafor::trimfill
`estimator`	the same as in metafor::trimfill
`maxiter`	the same as in metafor::trimfill
`method.trim`	the model used in rma.uni() for estimating the center when trimming studies, default is x$method
`method.fill`	the model used in rma.uni() for estimating the center after filling studies, default is x$method
`verbose`	the same as in metafor::trimfill
`ilim`	limits for the imputed values as in metafor::trimfill. If unspecified, no limits are used.

Details

It is recommend using fixed-effects for method.trim and random-effects for method.fill when heterogeneity exists.

Value

the same as in metafor::trimfill

Author(s)

Chongliang Luo, Yong Chen

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