Package 'diagmeta'

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Description

R package **diagmeta** implements the method by Steinhauser et al. (2016) for the meta-analysis of diagnostic test accuracy studies with multiple cutoffs.

Details

Main function of R package **diagmeta** is the eponymous diagmeta. Corresponding functions for printing and plotting are available: print.diagmeta, plot.diagmeta

Furthermore, a summary function and corresponding print function are available to provide a briefer output: summary.diagmeta, print.summary.diagmeta

Additional functions provided in **diagmeta** are diagstats to calculate additional statistical measures for the diagnostic test accurary meta-analysis and ipd2diag to transform individual participant data to the data format required by diagmeta.

Type help(package = "diagmeta") for a listing of R functions and datasets available in **diagmeta**.

Type citation("diagmeta") for the preferred citation of R package diagmeta.

To report problems and bugs

- type bug.report(package = "diagmeta") if you do not use RStudio,
- send an email to Guido Schwarzer <sc@imbi.uni-freiburg.de> if you use RStudio.

The development version of diagmeta is available on GitHub https://github.com/guido-s/diagmeta.

Author(s)

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References

Steinhauser S, Schumacher M, Rücker G (2016): Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. *BMC Medical Research Methodology*, **16**, 97

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```
as.data.frame.diagmeta
```

Extract data frame from diagmeta objects

Description

Extract data frame from objects of class diagmeta.

Usage

```
## S3 method for class 'diagmeta'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)
```

Arguments

```
x An object of class diagmeta.
row.names Argument of R function as.data.frame (ignored).
optional Argument of R function as.data.frame (ignored).
... Other arguments.
```

Value

A data frame is returned by the function as.data.frame.

Author(s)

Guido Schwarzer <sc@imbi.uni-freiburg.de>

See Also

```
diagmeta summary.diagmeta
```

Examples

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diagmeta

Meta-analysis of diagnostic test accuracy studies with the multiple cutoffs model

Description

Diagnostic tests may be based on an ordinal or continuous biomarker or an ordinal score together with a cutoff. The decision whether the target condition is present or not (positive or negative test result) depends on whether the observed value is above or below the cutoff. Here we assume that higher values of the biomarker indicate a greater probability for the target condition (e.g., a disease); otherwise, the poling must be changed by multiplying all values of the biomarker by -1. Sensitivity and specificity of the test depend on the chosen cutoff and vary with the cutoff. In meta-analysis of diagnostic accuracy studies, results are often reported for multiple cutoffs within a study, and the cutoffs may differ between studies. The multiple cutoffs model creates a link between the range of cutoffs and the respective pairs of sensitivity and specificity and thus allows identifying cutoffs at which the test is likely to perform best (Steinhauser et al., 2016).

Usage

```
diagmeta(
  TP,
  FP,
  TN,
  FN,
  cutoff,
  studlab,
  data = NULL,
  distr = "logistic",
 model = "CICS",
  equalvar = FALSE,
  lambda = 0.5,
  log.cutoff = FALSE,
 method.weights = "invvar",
  level = 0.95,
  incr = 0.5,
  n.iter.max = 1000,
  tol = 1e-08,
  silent = TRUE,
)
```

Arguments

TP, FP, TN, FN Numeric vectors giving the number of true positives, false positives, true negatives and false negatives

cutoff A number vector indicating the cutoff values

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studlab A numeric or a character vector with study labels An optional data frame containing the study information data distr A character indicating the distribution (see Details) A character indicating the model (see Details) model equalvar A logical indicating whether the variances of the biomarker in both groups are thought equal (see Details) lambda A numeric between 0 and 1 indicating the weight of the sensitivity (such that specificity receives weight 1 - lambda) log.cutoff A logical indicating whether the cutoffs should be log-transformed A character indicating the method for weighting the studies: invvar (default) method.weights means inverse variance weighting, size means weighting by group sample size, equal means that all studies are equally weighted level A numeric indicating the significance level (1 - alpha) for tests (default is 0.95) A numeric between 0 and 1 that is added as a continuity correction incr A numeric indicating the maximal number of fixed point iterations for finding n.iter.max the optimal cutoff tol A numeric indicating the tolerance for convergence of the fixed point iteration

silent

. . .

Details

Each row of the data set provides at least a study label, a cutoff and the numbers of true positives, false positives, true negatives and false negatives. Different studies may contribute a varying number of cutoffs, as well as different sets of cutoffs.

A logical indicating whether iterations should be suppressed

additional arguments

The multiple cutoffs model is a multi-level random effects model. At the study level, for the group of patients without the target condition (in short disease-free), the specificities at all available cutoffs together provide an estimate of the cumulative distribution function (cdf) of the test results within the disease-free individuals. Likewise, for patients with the target condition (in short diseased), via the observed sensitivities at all observed cutoffs we obtain an estimate of the cdf of the test results within the diseased patients. At the meta-analytic level, the model fits the data for both groups and all available cutoffs over all studies. Based on a parametric model, it provides estimates of the two cdfs for the two groups across all studies, accounting for the between-study heterogeneity and correlation between groups.

Users have the choice between the normal (argument distr="normal") and the logistic distribution (argument distr="logistic" which is the default). In addition, it is possible to log-transform the cutoffs (argument log.cutoff, default is FALSE).

The cdf, transformed using the quantile function of the chosen distribution, is modelled by one of eight mixed linear models ("DIDS", "CIDS", "DICS", "CICS", "DS", "CS", "DI", "CI") as described in Steinhauser et al. (2016). The argument equalvar indicates if the variances of the biomarker in both groups are assumed to be equal (equalvar = TRUE) or unequal (equalvar = FALSE).

The pooled sensitivity and specificity values can be obtained at every cutoff; a multiple cutoffs summary ROC (sROC) naturally follows while preserving cutoff information. The optimal cutoff is defined as the cutoff where the maximum of a weighted sum of sensitivity and specificity is

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obtained: lambda * sensitivity + (1 - lambda) * specificity. The 95% confidence intervals of sensitivities, specificities and the optimal cutoff are estimated using the delta method (Steinhauser et al., 2016).

Value

An object of class "diagmeta" with corresponding print, summary, and plot function. The object is a list containing the following components

TP, FP, TN, FN As defined above.

cutoff, studlab

As defined above.

Sens Sensitivity (original data).
Spec Specificity (original data).

distr, model, equalvar, lambda

As defined above.

log.cutoff, method.weights

As defined above.

level, incr As defined above.

k The number of studies in the meta-analysis.

optcut The optimal cutoff.

lower.optcut, upper.optcut

Corresponding lower and upper confidence limits (for normal distribution).

Sens. optcut The sensitivity at the optimal cutoff.

lower.Sens.optcut, upper.Sens.optcut

Corresponding lower and upper confidence limits.

Spec. optcut The specificity at the optimal cutoff.

lower.Spec.optcut, upper.Spec.optcut

Corresponding lower and upper confidence limits.

AUC Area under the curve (AUC)

AUCSens.lower, AUCSens.upper

Corresponding lower and upper confidence limits (based on the confidence region for the sensitivity, given the specificity)

AUCSpec.lower, AUCSpec.upper

Corresponding lower and upper confidence limits (based on the confidence region for the specificity, given the sensitivity)

var.diseased, var.nondiseased

The within-study variance for the diseased and non-diseased group, respectively.

AIC The value of the Akaike information criterion of the Imer object.

BIC The value of the Bayesian information criterion of the Imer object.

data.lmer A list with elements Study (study labels), Group (group labels (0 or 1)), Cutoff,

N (group sizes), Negative (number of negative test results), NN (frequencies of

negative test results).

result.lmer An object of class lmer.

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weights	Normalized weights per study, group, and cutoff such that the sum of weights is twice the number of cutoffs over all studies.
regr	A list with point estimates, variances, and covariances from regression parameters of lmer object.
dist	A list containing estimated means, standard deviations, and variances of distributions from diseased (ending with 1) and non-diseased (ending with 0).
n.iter.max	As defined above.
call	Function call.
version	Version of R package diagmeta used to create object.

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References

Steinhauser S, Schumacher M, Rücker G (2016): Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. *BMC Medical Research Methodology*, **16**, 97

See Also

```
plot.diagmeta, summary.diagmeta
```

Examples

diagstats Calculate statistical measures of test performance for objects of class diagmeta

Description

The user can provide cutoffs, sensitivities, and / or specificities to calculate the respective quantities (with confidence intervals). Furthermore, positive predictive values (PPV), negative predictive values (NPV), and probabilities of disease (PD) are calculated if the prevalence is provided.

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Usage

diagstats(x, cutoff = x\$optcut, sens, spec, prevalence, level = 0.95)

Arguments

x An object of class diagmeta

cutoff A numeric or vector with cutoff value(s)

sens A numeric or vector with sensitivity value(s)

spec A numeric or vector with specificity value(s)

prevalence A numeric or vector with the prevalence(s)

level The level used to calculate confidence intervals

Value

A data frame of class "diagstats" with the following variables:

cutoff Cutoffs provided in argument "cutoff" and / or model-based cutoff values for

given sensitivities / specificities.

Sens Sensitivities provided in argument "sens" and / or model-based estimates of the

sensitivity for given cutoffs / specificities

seSens Standard error of sensitivity

lower.Sens, upper.Sens

Lower and upper confidence limits of the sensitivity

Spec Specificities provided in argument "spec" and / or model-based estimates of the

specificity for given cutoffs / sensitivities

seSpec Standard error of specificity

lower.Spec, upper.Spec

Lower and upper confidence limits of the specificity

prevalence As defined above.

PPV Positive predictive value (based on the cutoff)
NPV Negative predictive value (based on the cutoff)

PD Probability of disease if the given cutoff value was observed as the measurement

for an individual

dens.nondiseased

Value of the model-based density function at the cutoff(s) for non-diseased in-

dividuals

dens.diseased Value of the model-based density function at the cutoff(s) for diseased individ-

uals

Author(s)

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See Also

diagmeta print.diagstats

Examples

ipd2diag

Individual participant data to enter them into diagmeta

Description

Function to transform individual patient data (IPD) to enter them into diagmeta

Usage

```
ipd2diag(studlab, value, status)
```

Arguments

studlab A vector with study labels

value A vector with individual patients' measurements of a discrete or continuous vari-

able

status A vector with information of the individual's status (0 = non-diseased, 1 = dis-

eased)

Value

A data frame with values that can be entered into diagmeta.

Author(s)

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See Also

```
diagmeta, plot. diagmeta, print. diagmeta, summary. diagmeta
```

Examples

```
# Simulate IPD data for three studies, each with 30 patients based
# on normally distributed marker values
set.seed(20)
k <- 3
n <- 60
m < -c(20, 23, 26)
d <- 10
s <- 5
studlab <- c(rep(1, n), rep(2, n), rep(3, n))
status <- rep(c(rep(0, n / 2), rep(1, n / 2)), k)
measurement <- c(rnorm(n / 2, m[1], s), rnorm(n/2, m[1] + d, s),
                 rnorm(n / 2, m[2], s), rnorm(n/2, m[2] + d, s),
                 rnorm(n / 2, m[3], s), rnorm(n/2, m[3] + d, s))
IPDdata <- data.frame(studlab, measurement, status)</pre>
str(IPDdata)
# Transform these data using ipd2diag()
diagdata <- ipd2diag(studlab, value = measurement, status = status)</pre>
str(diagdata)
# Run diagmeta()
diag1 <- diagmeta(TP, FP, TN, FN, cutoff, studlab,</pre>
                  data = diagdata,
                  distr = "normal")
summary(diag1)
plot(diag1)
par(mfrow = c(1, 2))
plot(diag1, which = "ROC", lines = TRUE)
plot(diag1, which = "SROC", ciSens = TRUE,
     ciSpec = TRUE, lines = TRUE, shading = "hatch")
```

plot.diagmeta

Plot for meta-analysis of diagnostic test accuracy studies with the multiple cutoffs model

Description

Provides several plots for meta-analysis of diagnostic test accuracy studies with the multiple cutoffs model

Usage

```
## S3 method for class 'diagmeta'
plot(
 which = c("survival", "youden", "roc", "sroc"),
 xlab = "Threshold",
 main,
  ci = FALSE,
  ciSens = FALSE,
  ciSpec = FALSE,
 mark.optcut = FALSE,
 mark.cutpoints = FALSE,
  points = TRUE,
  lines = FALSE,
  rlines = TRUE,
  line.optcut = TRUE,
  col.points = "rainbow",
  cex = 1,
  pch.points = 16,
  col = "black",
  col.ci = "gray",
  col.optcut = "black",
  cex.marks = 0.7 * cex,
  lwd = 1,
  lwd.ci = lwd,
  lwd.optcut = 2 * lwd,
  lwd.study = lwd,
  shading = "none",
  col.hatching = col.ci,
  lwd.hatching = lwd.ci,
  ellipse = FALSE,
 xlim = NULL,
)
```

Arguments

X	An object of class diagmeta
which	A character vector indicating the type of plot, either "regression" or "cdf" or "survival" or "Youden" or "ROC" or "SROC" or "density" or "sensspec", can be abbreviated
xlab	An x axis label
main	A logical indicating title to the plot

ci A logical indicating whether confidence intervals should be plotted for "regression", "cdf", "survival", "Youden", and "sensspec" ciSens A logical indicating whether confidence intervals should be plotted for sensitivity, given the specificity in "SROC" plot A logical indicating whether confidence intervals should be plotted for speciciSpec ficity, given the sensitivity in "SROC" plot A logical indicating whether the optimal cutoff should be marked on "SROC" mark.optcut mark.cutpoints A logical indicating whether the given cutoffs should be marked on "SROC" plot A logical indicating whether points should be plotted in plots "regression", points "cdf", "survival", "Youden", "ROC", and "sensspec" lines A logical indicating whether polygonal lines connecting points belonging to the same study should be printed in plots "regression", "cdf", "survival", "Youden", and "sensspec" A logical indicating whether regression lines or curves should be plotted for rlines plots "regression", "cdf", "survival", "Youden", and "sensspec" line.optcut A logical indicating whether a vertical line should be plotted at the optimal cutoff line for plots "cdf", "survival", "Youden", and "density" A character string indicating color of points, either "rainbow", "topo", "heat", col.points "terrain", "cm", "grayscale", or any color defined in colours A numeric indicating magnification to be used for plotting text and symbols cex pch.points A numeric indicating plot symbol(s) for points col A character string indicating color of lines col.ci A character string indicating color of confidence lines A character string indicating color of optimal cutoff line col.optcut A numeric indicating magnification(s) to be used for marking cutoffs cex.marks A numeric indicating line width lwd lwd.ci A numeric indicating line width of confidence lines lwd.optcut A numeric indicating line width of optimal cutoff lwd.study A numeric indicating line width of individual studies shading A character indicating shading and hatching confidence region in "SROC" plot, either "none" or "shade" or "hatch" col.hatching A character string indicating color used in hatching of the confidence region lwd.hatching A numeric indicating line width used in hatching of the confidence region ellipse A logical indicating whether a confidence ellipse should be drawn around the optimal cutoff xlim A character or numerical vector indicating the minimum and maximum value for the horizontal axes

Additional graphical arguments

Details

The first argument of the plot function is an object of class "diagmeta".

The second argument which indicates which sort of plot(s) should be shown. For which="regression", a scatter plot of the quantil-transformed proportions of negative test results with two regression lines is shown. Points belonging to the same study are marked with the same colour. For which="cdf", the two cumulative distribution functions are shown, corresponding to the proportions of negative test results. For which="survival", the survival functions are shown, corresponding to the proportions of positive test results. For which="Youden", the (potentially weighted) sum of sensitivity and specificity minus 1 is shown; in case of lambda=0.5 (the default) this is the Youden index. For which="ROC", study-specific ROC curves are shown. For which="SROC", the model-based summary ROC curve is shown. For which="density", the model-based densities of both groups are shown. For which="sensspec", the sensitivity (decreasing with increasing cutoff) and the specificity (increasing with increasing cutoff) are shown. Instead of character strings, a numeric value or vector can be used to specify plots with numbers corresponding to the following order of plots: "regression", "cdf", "survival", "youden", "roc", "sroc", "density", and "sensspec".

Other arguments refer to further plot parameters, such as lines (whether points belonging to the same study should be joined), rlines (whether regression curves should be drawn), ci / ciSens / ciSpec / ellipse (whether confidence regions should be shown), line.optcut / mark.optcut (whether the optimal cutoff should be indicated), and additional plot parameters (see Arguments).

If no further arguments are provided, four standard plots ("survival", "Youden", "ROC", and "SROC") are produced in a 2 x 2 format.

Author(s)

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References

Schneider A, Linde K, Reitsma JB, Steinhauser S, Rücker G (2017): A novel statistical model for analyzing data of a systematic review generates optimal cutoff values for fractional exhaled nitric oxide for asthma diagnosis. *Journal of Clinical Epidemiology*, **92**, 69–78

Steinhauser S, Schumacher M, Rücker G (2016): Modelling multiple thresholds in meta-analysis of diagnostic test accuracy studies. *BMC Medical Research Methodology*, **16**, 97

See Also

diagmeta

Examples

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```
log.cutoff = TRUE)
```

```
# Regression plot with confidence intervals
plot(diag1, which = "regr", lines = FALSE, ci = TRUE)
# Cumulative distribution plot with optimal cutoff line and
# confidence intervals
plot(diag1, which = "cdf", line.optcut = TRUE, ci = TRUE)
# Survival plot with optimal cutoff line and confidence intervals
plot(diag1, which = "survival", line.optcut = TRUE, ci = TRUE)
# Youden plot of optimal cutoff line and confidence intervals
plot(diag1, which = "youden",
     lines = TRUE, line.optcut = TRUE, ci = TRUE)
# ROC plot of lines connecting points belonging to the same study
plot(diag1, which = "ROC", lines = TRUE)
# SROC plot of confidence regions for sensitivity and specificity
# with optimal cutoff mark
plot(diag1, which = "SROC",
    ciSens = TRUE, ciSpec = TRUE, mark.optcut = TRUE,
     shading = "hatch")
# Density plot of densities for both groups with optimal cutoff
# line
plot(diag1, which = "density", line.optcut = TRUE)
```

print.diagmeta

Print method for diagmeta objects

Description

Print method for objects of class diagmeta.

Usage

```
## S3 method for class 'diagmeta'
print(x, digits = 3, ...)
```

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Arguments

x An object of class diagneta.digits Number of significant digits for printing.

... Additional arguments.

Author(s)

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See Also

```
diagmeta summary.diagmeta
```

Examples

print.diagstats

Print method for diagstats objects

Description

Print method for objects of class diagstats.

Usage

```
## S3 method for class 'diagstats'
print(x, sensspec = TRUE, predicted = TRUE, density = FALSE, digits = 3, ...)
```

Arguments

X	An object of class diagmeta.
sensspec	A logical indicating whether sensitivities and specificies should be printed.
predicted	A logical indicating whether predicted values should be printed.
density	A logical indicating whether values of the model-based density functions should be printed.
digits	Number of significant digits for printing.
	Additional arguments.

Author(s)

Guido Schwarzer <sc@imbi.uni-freiburg.de>

See Also

diagstats diagmeta

Examples

print.summary.diagmeta

Print method for summary of diagmeta objects

Description

Print method for objects of class summary.diagmeta.

Usage

```
## S3 method for class 'summary.diagmeta'
print(x, digits = 3, ...)
```

Arguments

x An object of class summary.diagmeta.digits Number of significant digits for printing.Additional arguments.

Author(s)

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See Also

```
diagmeta summary.diagmeta
```

Examples

Schneider2017

Meta-analysis of studies of the diagnostic test accuracy of FENO for diagnosis of asthma

Description

Meta-analysis of studies of the diagnostic test accuracy of fractional exhaled nitric oxide (FENO) for diagnosis of asthma.

The data were collected for a systematic review by Karrasch et al. (2017) and are published as a supplement (Appendix 1) to Schneider et al. (2017). They have been preprocessed for use in R package **diagmeta**.

Format

A data frame with the following columns:

numeric study ID study_id author first author year of publication year information on subgroup group cutpoint cutpoint (FeNO [ppb]) number of true positives tpos fneg number of false negatives fpos number of false positives tneg number of true negatives

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Source

Karrasch S, Linde K, Rücker G, Sommer H, Karsch-Volk M, Kleijnen J, Jörres RA, Schneider A (2017): Accuracy of FENO for diagnosing asthma: a systematic review. *Thorax*, **72**, 109e16

Schneider A, Linde K, Reitsma JB, Steinhauser S, Rücker G (2017): A novel statistical model for analyzing data of a systematic review generates optimal cutoff values for fractional exhaled nitric oxide for asthma diagnosis. *Journal of Clinical Epidemiology*, **92**, 69–78

Examples

summary.diagmeta

Summary method for diagmeta

Description

Summary method for objects of class diagmeta.

Usage

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

Arguments

object An object of class diagmeta.
... Additional arguments.

Value

A list with classes 'summary.diagmeta' and 'diagmeta' is returned. The list elements are identical to a diagmeta object.

Author(s)

Srinath Kolampally <kolampal@imbi.uni-freiburg.de>, Guido Schwarzer <sc@imbi.uni-freiburg.de>

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See Also

diagmeta

Examples

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