

Package ‘NMAoutlier’

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Title Detecting Outliers in Network Meta-Analysis

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gridExtra (>= 2.3)

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URL <https://github.com/petropouloumaria/NMAoutlier>

Description A set of functions providing the forward search algorithm for detecting outlying studies (i.e., studies with extreme findings) in network meta-analysis:

- provides the length of the initial subset for forward search algorithm;
- iterations of forward search algorithm;
- basic set of studies in each step of forward search algorithm;
- summary estimates and their confidence intervals in each step of forward search algorithm;
- outlying case diagnostics measures;
- ranking measures;
- heterogeneity and inconsistency measures;
- forward plot for summary estimates and their confidence intervals;
- forward plots for monitored measures: outlying case diagnostics measures, ranking measures, heterogeneity, and inconsistency measures.

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NMAoutlier-package	<i>NMAoutlier: Brief overview of methodology for detection of outlying studies in network meta-analysis.</i>
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Description

R package **NMAoutlier** provides diagnostic methods to detect outlying studies in network meta-analysis.

Details

R package **NMAoutlier** implements the forward search (FS) algorithm for the detection of outlying studies (studies with extreme results) in network meta-analysis (NMA) by Petropoulou et al. (2019). The underlying model considered is the frequentist NMA approach based on graph theory by R ucker (2012) which is implemented in R package **netmeta**.

The **NMAoutlier** package implements the following:

- forward search algorithm in network meta-analysis (function `NMAoutlier`) based on Petropoulou et al. (2019);
- forward plots (`fwdplot`) with monitoring statistics in each step of the FS algorithm:
 1. P-scores (R ucker & Schwarzer, 2015),
 2. z-values for difference of direct and indirect evidence with back-calculation method (K onig et al., 2013; Dias et al., 2010),
 3. standardized residuals,
 4. heterogeneity variance estimator,
 5. Cook’s distance,
 6. ratio of variances,
 7. Q statistics (Krahn et al., 2013);
- forward plot (`fwdplotest`) for summary estimates and their confidence intervals for each treatment in each step of the FS algorithm as provided by Petropoulou et al. (2019).

Type `help(package = "NMAoutlier")` for a listing of R functions available in **NMAoutlier**.

Type `citation("NMAoutlier")` on how to cite **NMAoutlier** in publications.

To report problems and bugs, please send an email to Maria Petropoulou <mpetrop@cc.uoi.gr>.

The development version of **NMAoutlier** is available on GitHub <https://github.com/petropouloumaria/NMAoutlier>.

Author(s)

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References

- Dias S, Welton NJ, Caldwell DM, Ades AE (2010): Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine*, **29**, 932–44
- König J, Krahn U, Binder H (2013): Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Statistics in Medicine*, **32**, 5414–29
- Krahn U, Binder H, König J (2013): A graphical tool for locating inconsistency in network meta-analyses. *BMC Medical Research Methodology*, **13**, 35
- Petropoulou M, Salanti G, Rücker G, Schwarzer G, Moustaki I, Mavridis D (2019): A forward search algorithm for detection of extreme study effects in network meta-analysis. *Manuscript*
- Rücker G (2012): Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods*, **3**, 312–24
- Rücker G, Schwarzer G (2015): Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology*, **15**, 58

 fwdplot

Forward plot(s) to monitor selected statistic(s)/method(s)

Description

This function generates forward plot(s) to monitor selected statistic(s) and/or method(s). The function creates a plot of the selected statistic throughout the iterations of the forward search algorithm. Candidate statistics to be monitored can be P-score; z-values by back-calculation method to derive indirect estimates from direct pairwise comparisons and network estimates; standardized residuals; heterogeneity variance estimator; Cook's distance; ratio of variances; Q statistics (Overall heterogeneity / inconsistency Q statistic (Q), overall heterogeneity Q statistic (Q), between-designs Q statistic (Q), based on a random effects design-by-treatment interaction model).

Usage

```
fwdplot(x, stat, select.st = NULL)
```

Arguments

- | | |
|-----------|--|
| x | an object of class NMAoutlier (mandatory). |
| stat | statistical measure to be monitored in forward plot(s) (mandatory), available choice are: "pscore", "nsplit", "estand", "heterog", "cook", "ratio", or "Q" (can be abbreviated). |
| select.st | selected statistic (pscore/nsplit/estand) for selected treatment(s)/comparison(s)/study |

Details

Plot of statistical measures for each iteration of search. Vertical axis provides iterations of search. Horizontal axis provides a monitoring statistical measure.

Author(s)

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Examples

```
data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
                        sm = "OR")

# Forward search algorithm
#
FSresult <- NMAoutlier(p1, P = 1, small.values = "bad", n_cores = 2)

# forward plot for Cook's distance
fwdplot(FSresult, "cook")

## Not run:
data(smokingcessation, package = "netmeta")

# Transform data from arm-based format to contrast-based format
# We use 'sm' argument for odds ratios.
# We use function pairwise from netmeta package

p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data=smokingcessation,
                        sm="OR")

# forward search algorithm
FSresult <- NMAoutlier(p1, small.values = "bad")

FSresult

# forward plot for Cook's distance
fwdplot(FSresult, "cook")

# forward plot for ratio of variances
fwdplot(FSresult, "ratio")

# forward plot for heterogeneity variance estimator
```

```
fwdplot(FSresult, "heterog")

# forward plot for Q statistics
fwdplot(FSresult, "Q")

# forward plot for P-scores
fwdplot(FSresult, "pscore")

# forward plot monitoring P-scores for treatment A
fwdplot(FSresult, "pscore", "A")

# forward plot for z-values of disagreement of direct and indirect evidence
fwdplot(FSresult, "nsplit")

# forward plot for z-values of disagreement of direct and indirect evidence
# monitoring treatment comparison A versus B
fwdplot(FSresult, "nsplit", "A:B")

# forward plot for standardized residuals for study 4
fwdplot(FSresult, "estand", 4)

## End(Not run)
```

fwdplotest

Forward plots of summary estimates

Description

Forward plots of summary estimate with 95 percent confidence interval for each treatment.

Usage

```
fwdplotest(x)
```

Arguments

x object of class NMAoutlier (mandatory).

Details

Plot of summary estimates and their confidence intervals for each iteration of search. Vertical axis provides iterations of search. Horizontal axis provides summary estimate of a treatment.

Author(s)

Maria Petropoulou <mpetrop@cc.uoi.gr>

Examples

```

data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
                        sm = "OR")

# Forward search algorithm
#
FSresult <- NMAoutlier(p1, P = 1, small.values = "bad", n_cores = 2)

# Forward plot for summary estimates for each treatment
# and their confidence intervals
fwdplotest(FSresult)
## Not run:
data(smokingcessation, package = "netmeta")

# Transform data from arm-based format to contrast-based format
# We use 'sm' argument for odds ratios.
# We use function pairwise from netmeta package
#
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data=smokingcessation,
                        sm="OR")

# forward search algorithm
FSresult <- NMAoutlier(p1, small.values = "bad")

# Forward plot for summary estimates for each treatment
# and their confidence intervals
fwdplotest(FSresult)

## End(Not run)

```

Description

Example of network meta-analysis with inconsistency.

Usage

Gupta2013

Format

A data frame in contrast format with the following columns:

<i>logOR</i>	log odds ratio
<i>selogOR</i>	standard error of log odds ratio
<i>id</i>	study ID
<i>t1</i>	first treatment
<i>t2</i>	second treatment

Details

The dataset compares the relative effects of nine interventions:

- placebo / vehicle (including placebo-PDT) (treatment 1),
- diclofenac 3 percent in 2.5 percent hyaluronic acid (DCF/HA) (treatment 2),
- 5-fluorouracil (5-FU) 0.5 percent (treatment 3),
- imiquimod (IMI) 5 percent (treatment 4),
- methyl aminolaevulinate (MAL)-PDT (treatment 5),
- 5-aminolaevulinic acid (ALA)-photodynamic therapy (PDT) (treatment 6),
- 5-fluorouracil (5-FU) 5.0 percent (treatment 7),
- cryotherapy (treatment 8),
- ingenol mebutate (IMB) 0.015–0.05 percent (treatment 9).

The outcome is the number of individuals with participant complete clearance or an equivalent efficacy. These data are in contrast format with effect size odds ratio (OR) and its standard error. Arm-level data used in Gupta and Paquet (2013).

Source

Gupta AK, Paquet M (2013): Network meta-analysis of the outcome ‘participant complete clearance’ in nonimmunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *British Journal of Dermatology*, **169**, 250–9

Examples

```
data(Gupta2013)

# Conduct forward search algorithm for the network of actinic
# keratosis
#
FSresult <- NMAoutlier(logOR, selogOR, t1, t2, id, data = Gupta2013)

# Draw forward plot for z-values from difference of direct and
# indirect evidence
#
fwdplot(FSresult, "nsplit")

# Draw forward plot for Q statistic
```

```
#
fwdplot(FSresult, "Q")
```

NMAoutlier

Forward search algorithm in network meta-analysis

Description

Employs the forward search algorithm for detection of outlying studies (studies with extreme results) fitted in network meta-analysis model from graph-theory. This is a diagnostic tool for detection evidence of outliers. It can also be used to detect studies that are potential sources for heterogeneity and inconsistency.

Monitoring measures during the search are:

- outlying measures (standardized residuals, Cook's distance, ratio of variance);
- ranking measures (P-scores);
- heterogeneity and inconsistency measures (Q statistics for overall heterogeneity / inconsistency, inconsistency by design-by-treatment interaction model, z-values for comparison between direct and indirect evidence by back-calculation method).

A description of the methodology can be found in Petropoulou et al. (2019).

Usage

```
NMAoutlier(TE, seTE, treat1, treat2, studlab, data = NULL, crit1 = "R",
  crit2 = "R", studies = NULL, P = 100, sm, reference = "",
  small.values = "good", n_cores = NULL)
```

Arguments

TE	Estimate of treatment effect, i.e. difference between first and second treatment (e.g. log odds ratio, mean difference, or log hazard ratio).
seTE	Standard error of treatment estimate.
treat1	Label/Number for first treatment.
treat2	Label/Number for second treatment.
studlab	Study labels (important when multi arm studies are included).
data	A data frame containing the study information.
crit1	A character string indicating the criterion to be used for selecting the initial subset, this criterion may be the minimum of median absolute residuals ("R") or the maximum of median absolute likelihood contributions ("L"). Default value is "R".
crit2	A character string indicating the criterion to be used for selecting the study entered from non-basic set to basic set, this criterion may be the minimum of absolute residuals ("R") or the maximum of absolute likelihood contributions ("L"). Default value is "R".

studies	An optional vector specifying the number of the initial subset of studies. The default value is the maximum of the number of treatments and the 20 percent of the total number of studies.
P	An optional vector specifying the number of candidate sample of studies (with length equal to studies) for the choice of the initial subset. Default value is 100.
sm	A character string indicating underlying summary measure, e.g., "RD", "RR", "OR", "ASD", "HR", "MD", "SMD", or "ROM".
reference	Reference treatment group.
small.values	A character string indicating if small values are considered beneficial (option:"good") or harmful (option:"bad") on outcome. This is requirement for p-scores computation. The default value is considered beneficial outcome ("good").
n_cores	The number of cores that the process is running using the parallel (default: NULL, the process is running using all the available cores)

Details

Description of methodology by fitting forward search algorithm in network meta-analysis. Methodology of FS algorithm fitted in NMA model from graph theory is described in Petropoulou et al. 2019.

Let n be the number of treatments in a network and let m be the number of pairwise treatment comparisons. If there are only two-arm studies, m is the number of studies. Let TE and seTE be the vectors of observed effects and their standard errors. Comparisons belonging to multi-arm studies are identified by identical study labels (argument `studLab`). It is therefore important to use identical study labels for all comparisons belonging to the same multi-arm study.

The FS algorithm is a diagnostic iterative procedure. FS algorithm apart from three steps. It starts with a subset of studies and it gradually adds studies until all studies entered. After the search, statistical measures are monitored for sharp changes. FS is a diagnostic method to identify outlying studies.

FS algorithm starts with an initial subset of the dataset that is considered to be outlier-free. Let l the size of the initial subset. Let (argument P) (eg. $P = 100$) a large number of candidate subset of studies with size l . The candidate subset that optimize the criterion (argument `crit1`) is taken as the initial subset (considered outlying-free). Criterion (`crit1`) to be used for selecting the initial subset, may be the minimum of median absolute residuals "R" or the maximum of median absolute likelihood contributions "L". It is conventionally refer this subset as basic set, whereas the remaining studies constitute the non-basic set.

The FS algorithm gradually adds studies from the non-basic to the basic subset based on how close the former studies are to the hypothesized model fit in the basic set. A study from non-basic set entered into the basic set if optimize the criterion (argument `crit2`). Criterion (`crit2`) for selecting the study from non-basic to basic set may be the minimum of absolute residuals "R" or the maximum of absolute likelihood contributions "L". The algorithm order the studies according to their closeness to the basic set by adding the study that optimize the criterion from non-basic set to basic set.

The process is repeated until all studies are entered in the basic set. The number of iterations of algorithm `index` is equal to the total number of studies minus the number of studies entered into the initial subset. When all studies are included in the basic set, parameter estimates (summary

estimates, heterogeneity estimator) and other statistics of interest (outlying measures, heterogeneity and inconsistency measures, ranking measures) are monitored. For each basic set, network meta-analysis model from graph theory (Rücker, 2012) is fitted (`netmeta` function) with R package **netmeta** (Rücker et al., 2018).

Monitoring is helpful to identify outlying studies. Monitoring statistical measures for the basic set in each FS iteration can be:

Outlying case diagnostics measures: Standardized residuals (arithmetic mean in case of multi-arm studies); Cook's statistic; Ratio of determinants of variance-covariance matrix

Ranking measures: P-scores for ranking of treatments (Rücker G & Schwarzer G (2015)) for each basic set with implementation of (`netrank` function) from R package **netmeta**.

Heterogeneity and inconsistency measures: Overall heterogeneity / inconsistency Q statistic (Q). This is the design-based decomposition of Cochran Q as provided by Krahn et al. (2013); Overall heterogeneity Q statistic (Q); Between-designs Q statistic (Q), based on a random effects model with square-root of between-study variance estimated embedded in a full design-by-treatment interaction model. Implementation with (`decomp.design` function) from R package **netmeta**; Z-values for comparison between direct and indirect evidence for each iteration of forward search algorithm. By monitoring difference of direct and indirect evidence, potential sources of consistency can be detected with the implementation of (`netsplit` function) from R package **netmeta** for each basic set of the search. Based on the methodology with back-calculation method to derive indirect estimates from direct pairwise comparisons and network estimates (Dias et al., 2010; König et al., 2013).

Value

An object of class `NMAoutlier`; a list containing the following components:

<code>dat</code>	Matrix containing the data "TE", "seTE", "studlab", "treat1", "treat2" as defined above.
<code>length.initial</code>	The number of studies that constitute the initial (outlying-clean) subset of studies.
<code>index</code>	The number of iterations of forward search algorithm.
<code>basic</code>	Studies entered into the basic set in each iteration of the search. At the first iteration, basic set constitute the studies that are included in the basic-initial subset. The number of studies in the first iteration is equal to <code>length.initial</code> .
<code>taub</code>	Heterogeneity estimator variance for basic set in each iteration of forward search algorithm.
<code>Qb</code>	Overall heterogeneity - inconsistency Q statistic (Q) for the basic set in each iteration of forward search algorithm.
<code>Qhb</code>	Overall heterogeneity Q statistic (Q) for the basic set in each iteration of forward search algorithm.
<code>Qib</code>	Overall inconsistency Q statistic (Q) from design-by-treatment interaction model for the basic set in each iteration of forward search algorithm.
<code>estb</code>	Summary estimates for each treatment for the basic set in each iteration of forward search algorithm.
<code>lb</code>	Lower 95% confidence interval of summary estimates for the basic set in each iteration of forward search algorithm.

ub	Upper 95% confidence interval of summary estimates for the basic set in each iteration of forward search algorithm.
Ratio	Ratio of determinants (COVRATIOj) of variance-covariance matrix of treatment estimates at iteration j to that iteration at (j-1).
cook_d	Cook's statistic (Cj) at iteration j of forward search algorithm.
p.score	P-score for ranking each treatment for the basic set in each iteration of forward search algorithm.
dif	Z-values for comparison between direct and indirect evidence for each iteration of forward search algorithm. Based on back-calculation method to derive indirect estimates from direct pairwise comparisons and network estimates.
estand	Standardized residuals for each study for the basic set in each iteration of forward search algorithm.
call	Function call

Author(s)

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References

- Dias S, Welton NJ, Caldwell DM, Ades AE (2010): Checking consistency in mixed treatment comparison meta-analysis. *Statistics in Medicine*, **29**, 932–44
- König J, Krahn U, Binder H (2013): Visualizing the flow of evidence in network meta-analysis and characterizing mixed treatment comparisons. *Statistics in Medicine*, **32**, 5414–29
- Krahn U, Binder H, König J (2013): A graphical tool for locating inconsistency in network meta-analyses. *BMC Medical Research Methodology*, **13**, 35
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- Rücker G (2012): Network meta-analysis, electrical networks and graph theory. *Research Synthesis Methods*, **3**, 312–24
- Rücker G, Schwarzer G (2015): Ranking treatments in frequentist network meta-analysis works without resampling methods. *BMC Medical Research Methodology*, **15**, 58

Examples

```
data(smokingcessation, package = "netmeta")
smokingcessation$id <- 1:nrow(smokingcessation)

study912 <- subset(smokingcessation, id %in% 9:12)
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = study912,
                        sm = "OR")

# Forward search algorithm
#
```

```

FSresult <- NMAoutlier(p1, P = 1, small.values = "bad", n_cores = 2)

## Not run:
data(smokingcessation, package = "netmeta")

# Transform data from arm-based format to contrast-based format
# We use 'sm' argument for odds ratios.
# We use function pairwise from netmeta package
#
p1 <- netmeta::pairwise(list(treat1, treat2, treat3),
                        list(event1, event2, event3),
                        list(n1, n2, n3),
                        data = smokingcessation,
                        sm = "OR")

# Forward search algorithm
#
FSresult1 <- NMAoutlier(p1, small.values = "bad")

# Basic set for each iteration of forward search algorithm
#
FSresult1$basic

# Forward search algorithm using the criteria (crit1, crit2)
# with the maximum of absolute likelihood contributions ("L")
#
FSresult2 <- NMAoutlier(p1, crit1 = "L", crit2 = "L",
                        small.values = "bad")

FSresult2

## End(Not run)

```

Schoenberg2013

Network meta-analysis comparing the effects after Laparoscopic Heller myotomy

Description

Example of network meta-analysis with inconsistency.

Usage

Schoenberg2013

Format

A data frame in contrast format with the following columns:

logOR log odds ratio

selogOR standard error of log odds ratio
id study ID
t1 first treatment
t2 second treatment

Details

The dataset compares the effects after Laparoscopic Heller myotomy. The outcome is the number of individuals with successful rates at 12 months. These data are in contrast format with effect size odds ratio (OR) and its standard error. Arm-level data can be found in Schoenberg et al. (2013).

Source

Schoenberg MB, Marx S, Kersten JF, Rösch T, Belle S, Kähler G, Vassiliou MC, Lüth S, von Renteln D (2013): Laparoscopic Heller myotomy versus endoscopic balloon dilatation for the treatment of achalasia: a network meta-analysis. *Annals of Surgery*, **258**, 943–52

Examples

```
data(Schoenberg2013)

# Conduct forward search algorithm for the network of Laparoscopic
# Heller myotomy
#
FSresult <- NMAoutlier(logOR, selogOR, t1, t2, id, data = Schoenberg2013)

# Draw forward plot for z-values from difference of direct and
# indirect evidence
#
fwdplot(FSresult, "nsplit")
```

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