Package 'nmathresh'

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Type Package

Title Thresholds and Invariant Intervals for Network Meta-Analysis

Version 0.1.6

Description Calculation and presentation of decision-invariant bias adjustment thresholds and intervals for Network Meta-Analysis, as described by Phillippo et al. (2018) <doi:10.1111/rssa.12341>. These describe the smallest changes to the data that would result in a change of decision.

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```
d_ab2i
```

Convert contrast indexing

Description

Functions for converting between d_{ab} indexing of contrasts (useful notationally) and d[i] indexing used by R.

Usage

d_ab2i(a, b, K)

d_i2ab(i, K)

Arguments

а	Vector of treatment codes a .
b	Vector of treatment codes b.
К	Total number of treatments.
i	Vector of indices i.

Value

d_ab2i returns a vector of indices i. d_i2ab returns a data frame of indices a and b.

Functions

- d_ab2i: Convert d[i] type indices to d_{ab} type indices.
- d_i2ab: Convert d_{ab} type indices to d[i] type indices.

Note

By convention, $1 \le a < b \le K$. If this is not the case, an error will be thrown. For a given number of treatments K, the total number of possible contrasts d_{ab} is K(K-1)/2, and hence $i \le K$. Again, if this is not the case, an error will be thrown.

Examples

```
d_ab2i(c(1,1,1, 2,2, 3), c(2,3,4, 3,4, 4), K=4)
d_i2ab(1:6, K=4)
```

get.int

Description

Return the positive and negative thresholds for an observation, given a vector of possible threshold solutions. This function is intended for internal use, and is called by nma_thresh automatically.

Usage

```
get.int(
    x,
    kstar,
    trt.code,
    contrs,
    mcid = FALSE,
    mean.dk = NULL,
    inflmat = NULL,
    opt.max = NULL
)
```

Arguments

х	Column of U matrix, containing all possible threshold solutions for a data point.
kstar	Base-case optimal treatment.
trt.code	Vector of (possibly recoded) treatments. See nma_thresh parameter of the same name.
contrs	Details of contrasts corresponding to rows in x, as rows of the data.frame output by d_i2ab.
mcid	Use MCID decision rule? Default FALSE.
mean.dk	Posterior means of basic treatment parameters, required when mcid is TRUE.
inflmat	Column of influence matrix H for the data point, required when mcid is TRUE.
opt.max	Is the maximum treatment effect optimal? See nma_thresh parameter of same name. Required when mcid is TRUE.

Value

Data frame of thresholds and new optimal treatments with columns lo, lo.newkstar, hi, and hi.newkstar.

nma_thresh

Description

This function calculates decision-invariant bias-adjustment thresholds and intervals for Bayesian network meta-analysis, as described by Phillippo *et al.* (2018). Thresholds are derived from the joint posterior, and reflect the amount of change to a data point before the treatment decision changes. Calculation is achieved using fast matrix operations.

Usage

```
nma_thresh(
  mean.dk,
  lhood,
  post,
  nmatype = "fixed",
  X = NULL,
  mu.design = NULL,
  delta.design = NULL,
  opt.max = TRUE,
  trt.rank = 1,
  trt.code = NULL,
  trt.sub = NULL,
  mcid = 0,
  mcid.type = "decision"
)
```

Arguments

mean.dk	Posterior means of basic treatment parameters d_k .
lhood	Likelihood (data) covariance matrix.
post	Posterior covariance matrix (see details).
nmatype	Character string, giving the type of NMA performed. One of "fixed" (fixed effects, the default) or "random" (random effects). May be abbreviated.
Х	[FE models only] Design matrix for basic treatment parameters.
mu.design	[RE models only] Design matrix for any extra parameters. Defaults to NULL (no extra parameters).
delta.design	[RE models only] Design matrix for delta, defaults to the $N \times N$ identity matrix.
opt.max	Should the optimal decision be the maximal treatment effect (TRUE, default) or the minimum (FALSE).
trt.rank	Rank of the treatment to derive thresholds for. Defaults to 1, thresholds for the optimum treatment.
trt.code	Treatment codings of the reference treatment and in the parameter vector d_k . Use if treatments re-labelled or re-ordered. Default is equivalent to 1:K.

trt.sub	Only look at thresholds in this subset of treatments in trt.code, e.g. if some are excluded from the ranking. Default is equivalent to 1:K.
mcid	Minimal clinically important difference for the decision (when mcid.type = 'decision') or for changing the decision (when mcid.type = 'change'). Defaults to 0, use the maximal efficacy decision rule.
mcid.type	Default 'decision', the decision rule is based on MCID (see details). Otherwise 'change', use the maximum efficacy rule, but only consider changing the decision when the alternative treatment becomes more effective than the base case by mcid or more.

Details

This function provides bias-adjustment threshold analysis for both fixed and random effects NMA models, as described by Phillippo *et al.* (2018). Parameters mean.dk, lhood, and post are always required, however there are differences in the specification of post and other required parameters and between the fixed and random effects cases:

- **FE models** The design matrix X for basic treatment parameters is required. The posterior covariance matrix specified in post should only refer to the basic treatment parameters.
- **RE models** The design matrix mu.design for additional parameters (e.g. covariates) is required, as is the design matrix delta.design for random effects terms. The posterior covariance matrix specified in post should refer to the basic treatment parameters, RE terms, and additional parameters *in that order*; i.e. post should be the posterior covariance matrix of the vector $(d^T, \delta^T, \mu^T)^T$.

Value

An object of class thresh.

Model details

The FE NMA model

The fixed effects NMA model is assumed to be of the form

Prior: $d \sim N(d_0, \Sigma_d)$ Likelihood: $y|d \sim N(\delta, V)$ FE model: $\delta = Xd + M\mu$

The additional parameters μ may be given any sensible prior; they do not affect the threshold analysis in any way.

The RE NMA model

The random effects NMA model is assumed to be of the form

Priors: $d \sim N(d_0, \Sigma_d), \quad \mu \sim N(\mu_0, \Sigma_\mu)$ **Likelihood:** $y|d, \mu, \tau^2 \sim N(L\delta + M\mu, V)$ **RE model:** $\delta \sim N(Xd, \tau^2)$

The between-study heterogeneity parameter τ^2 may be given any sensible prior. In the RE case, the threshold derivations make the approximation that τ^2 is fixed and known.

Decision rules

The default decision rule is maximal efficacy; the optimal treatment is $k^* = \operatorname{argmax}_k E(d_k)$.

When $\epsilon = \text{mcid}$ is greater than zero and mcid.type = 'decision', the decision rule is no longer for a single best treatment, but is based on minimal clinically important difference. A treatment is in the optimal set if $E(d_k) \ge \epsilon$ and $\max_a E(d_a) - E(d_k) \le \epsilon$.

When mcid.type = 'change', the maximal efficacy rule is used, but thresholds are found for when a new treatment is better than the base-case optimal by at least mcid.

See Also

recon_vcov, thresh_forest, thresh-class.

Examples

```
# Please see the vignette "Examples" for worked examples including use of
# this function, including more information on the brief code below.
vignette("Examples", package = "nmathresh")
### Contrast level thresholds for Thrombolytic treatments NMA
K <- 6 # Number of treatments
# Contrast design matrix is
X <- matrix(ncol = K-1, byrow = TRUE,
            c(1, 0, 0, 0, 0,
              0, 1, 0, 0, 0,
              0, 0, 1, 0, 0,
              0, 0, 0, 1, 0,
              0, -1, 1, 0, 0,
              0, -1, 0, 1, 0,
              0, -1, 0, 0, 1))
# Reconstruct hypothetical likelihood covariance matrix using NNLS
lik.cov <- recon_vcov(Thrombo.post.cov, prior.prec = .0001, X = X)</pre>
# Thresholds are then
thresh <- nma_thresh(mean.dk = Thrombo.post.summary$statistics[1:(K-1), "Mean"],</pre>
                     lhood = lik.cov,
                     post = Thrombo.post.cov,
                     nmatype = "fixed",
                     X = X,
                     opt.max = FALSE)
```

recon_vcov

Description

Reconstruct the contrast-level likelihood covariance matrix from prior and posterior covariance matrices. The resulting likelihood covariance matrix can then be used to perform a contrast-level threshold analysis with the function nma_thresh.

Usage

```
recon_vcov(
   post,
   prior.prec = 1e-04,
   prior.vcov = diag(1/prior.prec, dim(post)[1]),
   X = NULL,
   verbose = FALSE
)
```

Arguments

post	Posterior covariance matrix.
prior.prec	Prior precision. Defaults to .0001 which is a common flat prior for NMA. Not used if prior.vcov is specified.
prior.vcov	Prior covariance matrix. Defaults to a diagonal matrix of the same size as post, with elements 1/prior.prec.
Х	Contrast design matrix. If omitted a complete network is assumed.
verbose	Print intermediate matrices? Defaults to FALSE.

Details

Full details of the calculation are given by Phillippo *et al.* (2018). Briefly, the aim is to recover the contrast-level likelihood covariance matrix V that would have led to the posterior covariance matrix Σ being obtained from a fixed effects NMA, with design matrix X and prior covariance matrix Σ_d for a normal prior on the basic treatment parameters. This is possible in this case via the equation (resulting from conjugacy):

$$\Sigma^{-1} = X^T V^{-1} X + \Sigma_d^{-1}.$$

When the treatment network is complete (i.e. fully connected), this equation may be rearranged exactly.

When the treatment network is incomplete (i.e. not all treatments are directly compared), this equation may be solved through the use of non-negative least squares (NNLS).

When NNLS is used, some additional diagnostics are printed (and returned as attributes). Firstly, the residual sum-of-squares (RSS) from the NNLS fit. The RSS is further split into *fixed* RSS, from structural zeros in the reconstructed posterior according to the design matrix (and hence not fitted) that are non-zero in the true posterior, and *fitted* RSS, from the other fitted elements. Secondly, the Kullback-Leibler divergence of the reconstructed posterior from the true posterior. Interpreting the KL divergence as a log Bayes factor, values less than 1 indicate negligible differences between the reconstructed posterior from the true posterior from the true posterior from the true posterior from the true posterior.

A matrix; the reconstructed likelihood covariance matrix. If NNLS is used, the residual sum-ofsquares and Kullback-Leibler divergence diagnostics (as printed to the console) are returned as additional attributes rss.total, rss.fixed, rss.free, kl.divergence.

See Also

nma_thresh.

Examples

```
# Please see the vignette "Examples" for worked examples including use of
# this function, including more information on the brief code below.
vignette("Examples", package = "nmathresh")
### Contrast level thresholds for Thrombolytic treatments NMA
K <- 6 # Number of treatments
# Contrast design matrix is
X <- matrix(ncol = K-1, byrow = TRUE,</pre>
            c(1, 0, 0, 0, 0,
              0, 1, 0, 0, 0,
              0, 0, 1, 0, 0,
              0, 0, 0, 1, 0,
              0, -1, 1, 0, 0,
              0, -1, 0, 1, 0,
              0, -1, 0, 0, 1))
# Reconstruct hypothetical likelihood covariance matrix using NNLS
lik.cov <- recon_vcov(Thrombo.post.cov, prior.prec = .0001, X = X)</pre>
```

SocAnx.post.cov Posterior covariance matrix from Social Anxiety NMA

Description

The posterior covariance matrix of the variables d (basic treatment effect parameters) and delta (shrunken random effects estimates for each study).

Usage

SocAnx.post.cov

Format

An object of class matrix (inherits from array) with 186 rows and 186 columns.

Source

Generated from WinBUGS output, using the WinBUGS code from Mayo-Wilson et al. (2014). See also vignette("Examples", package = "nmathresh").

References

Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry 2014;1:368-76. http://dx.doi.org/10.1016/S2215-0366(14)70329-3

See Also

SocAnx.post.summary

SocAnx.post.summary Posterior summary from Social Anxiety NMA

Description

A summary.mcmc object of the type produced by the coda package, containing the requisite posterior summary information on the variables d (basic treatment effect parameters), delta (shrunken random effects estimates for each study), and diff (contrasts of treatment effect parameters).

Usage

SocAnx.post.summary

Format

A summary.mcmc object. The key components for our use are:

- statistics Matrix containing the posterior summary statistics of the variables d, delta, and diff, with columns for Mean, SD, Naive SE, and Time-series SE (also known as the Monte-Carlo standard error)
- **quantiles** Matrix containing the posterior 2.5%, 25%, 50%, 75%, and 97.5% quantiles of the variables d, delta, and diff

Source

Generated from WinBUGS output, using the WinBUGS code from Mayo-Wilson et al. (2014). See also vignette("Examples", package = "nmathresh").

References

Mayo-Wilson E, Dias S, Mavranezouli I, Kew K, Clark DM, Ades AE, et al. Psychological and pharmacological interventions for social anxiety disorder in adults: a systematic review and network meta-analysis. Lancet Psychiatry 2014;1:368-76. http://dx.doi.org/10.1016/S2215-0366(14)70329-3

See Also

summary.mcmc, SocAnx.post.cov

thresh-class

Description

The function nmathresh returns S3 objects of class thresh.

The thresh class

Details

Objects of class thresh have the following components:

- thresholds A data frame with columns lo and hi for the lower and upper thresholds, and lo.newkstar and hi.newkstar for the new optimal (or rank-trt.rank) treatments at each of the thresholds.
- U The threshold solutions matrix. One column for each data point m, one row for each contrast d_{ab} (in ascending order). The elements $U_{ab,m}$ describe the amount of adjustment to data point y_m required to reverse the relative ranking of treatments a and b. This matrix is particularly useful for deriving thresholds for more complex decisions (e.g. bias-adjustment thresholds for a new treatment entering the top two, for any change in rank of the top three, etc.)
- Ukstar The threshold solutions matrix limited to contrasts involving k^* . In other words, the rows of U corresponding to contrasts of the form d_{ak^*} or d_{k^*a} . Elements $U_{ak^*,m}$ of this matrix describe the amount of adjustment to data point y_m required to make treatment a optimal (or rank-trt.rank) over k^* .
- H The influence matrix of the data on the basic treatment parameters. One column for each data point m, one row for each basic treatment parameter d_k . Elements $H_{k,m}$ describe the influence of data point y_m on parameter d_k . This matrix can be used to derive more complex thresholds (e.g. 2D thresholds for simultaneous adjustments to two data points, or thresholds for common adjustments to a group of data points).
- kstar The base-case optimal (or rank-trt.rank) treatment k^* .
- call A list containing all the arguments defined in the original call to nma_thresh.

See Also

nma_thresh

thresh_2d

Description

This function produces two-dimensional threshold lines and invariant regions, as shown by Phillippo *et al.* (2018).

Usage

```
thresh_2d(
  thresh,
  idx,
  idy,
  xlab = paste("Adjustment to data point", idx),
  ylab = paste("Adjustment to data point", idy),
  xlim = NULL,
  ylim = NULL,
  breaks = waiver(),
  xbreaks = breaks,
  ybreaks = breaks,
  fill = rgb(0.72, 0.8, 0.93, 0.7),
  lwd = 1,
  fontsize = 12
)
```

Arguments

thresh	A thresh object, as produced by nma_thresh.
idx	Integer specifying the index (with respect to thresh\$thresholds) of the first data point to consider adjusting. Will be shown on the x axis.
idy	Integer specifying the index (with respect to thresh\$thresholds) of the second data point to consider adjusting. Will be shown on the y axis.
xlab	Character string giving the label for the x axis.
ylab	Character string giving the label for the y axis.
xlim	Numeric vector of length 2, giving the x axis limits.
ylim	Numeric vector of length 2, giving the y axis limits.
breaks	Numeric vector giving position of tick marks on the x and y axes. Calculated automatically by default.
xbreaks	Numeric vector giving position of tick marks on the x axis. Equal to breaks by default, if set this overrides any value given to breaks.
ybreaks	Numeric vector giving position of tick marks on the y axis. Equal to breaks by default, if set this overrides any value given to breaks.

fill	Fill colour for invariant region. Defaults to a nice shade of blue rgb(.72, .80, .93, .7).
lwd	Line width for threshold lines. Default 1.
fontsize	Font size for labels. Default 12.

Value

A ggplot object containing the 2D threshold plot, which is returned invisibly and plotted (unless assigned).

Examples

```
# Please see the vignette "Examples" for worked examples including use of
# this function, including more information on the brief code below.
vignette("Examples", package = "nmathresh")
### Contrast level thresholds for Thrombolytic treatments NMA
K <- 6 # Number of treatments
# Contrast design matrix is
X <- matrix(ncol = K-1, byrow = TRUE,
            c(1, 0, 0, 0, 0,
              0, 1, 0, 0, 0,
              0, 0, 1, 0, 0,
              0, 0, 0, 1, 0,
              0, -1, 1, 0, 0,
              0, -1, 0, 1, 0,
              0, -1, 0, 0, 1))
# Reconstruct hypothetical likelihood covariance matrix using NNLS
lik.cov <- recon_vcov(Thrombo.post.cov, prior.prec = .0001, X = X)</pre>
# Thresholds are then
thresh <- nma_thresh(mean.dk = Thrombo.post.summary$statistics[1:(K-1), "Mean"],</pre>
                     lhood = lik.cov,
                     post = Thrombo.post.cov,
                     nmatype = "fixed",
                     X = X,
                     opt.max = FALSE)
```

thresh_forest

Description

This function produces threshold forest plots, overlaying the decision-invariant intervals on the data points and their confidence/credible intervals, as shown by Phillippo *et al.* (2018).

Usage

```
thresh_forest(
  thresh,
 у,
 CI.lo,
 CI.hi,
  label,
 orderby = NULL,
  data = NULL,
 CI.title = "95% Confidence Interval",
  label.title = "",
 y.title = "Mean",
  II.title = "Invariant Interval",
 xlab = "",
 xlim = NULL,
  sigfig = 3,
 digits = NULL,
  refline = NULL,
 clinsig = NULL,
  cutoff = NULL,
  II.colw = rgb(0.72, 0.8, 0.93),
  II.cols = rgb(0.93, 0.72, 0.8),
  II.lwd = 8,
 CI.lwd = 1,
  pointsize = 4,
  fontsize = 12,
  xbreaks = NULL,
  add.columns = NULL,
  add.columns.title = NULL,
  add.columns.after = -1,
  add.columns.hjust = 0.5,
  add.columns.uline = TRUE,
  calcdim = display,
  display = TRUE
```

```
)
```

Arguments

thresh

A thresh object, as produced by nma_thresh.

У	Data points. Either a column of data, or a numeric vector.	
CI.lo	Confidence/credible interval lower limits. Either a column of data, or a numeric vector.	
CI.hi	Confidence/credible interval upper limits. Either a column of data, or a numeric vector.	
label	Row labels (for each data point). Either a column of data, or a character vector.	
orderby	Variable(s) to order the table rows by. Either a column or columns of data, or a vector. By default, the rows are not reordered. Further arguments and/or multiple ordering columns may be passed to the function order by instead providing a list containing the arguments to order.	
data	A data frame containing the data points y, confidence/credible intervals (CI.lo, CI.hi), and row labels labels. If data is not provided, the above variables will be searched for in the calling environment.	
CI.title	Title for CI column, default "95% Confidence Interval".	
label.title	Character string giving the heading for the row labels column.	
y.title	Character string giving the heading for the data points column, default "Mean".	
<pre>II.title</pre>	Title for invariant interval column, default "Invariant Interval".	
xlab	Character string giving the label for the <i>x</i> -axis.	
xlim	Numeric vector (length 2) of lower and upper limits for the x -axis. If not set, tries to choose a sensible default.	
sigfig	Number of significant digits to display in the table. Default 3.	
digits	Number of decimal places to display in the table. Overrides sigfig if set.	
refline	x intercept of vertical reference line, if desired.	
clinsig	Set the clinical significance level. Rows are marked with a dagger if they have one or more thresholds less than this value. Not set by default.	
cutoff	A single numeric value or numeric vector pair. Thresholds larger in magnitude than this value, or lying outside this interval, will be cut off and marked as NT (no threshold). Not set by default.	
<pre>II.colw</pre>	Colour for "wide" invariant intervals.	
<pre>II.cols</pre>	Colour for "short" invariant intervals.	
II.lwd	Line width of invariant intervals. Default 8.	
CI.lwd	Line width of confidence/credible intervals. Default 1.	
pointsize	Point size for forest plot means. Default 4.	
fontsize	Base font size. Default 12.	
xbreaks	Position of tick marks on the x-axis as a numeric vector.	
add.columns Data frame (or matrix, vector) of additional columns to add to table. add.columns.title		
odd column C	Optional titles for the additional columns, otherwise use names from provided data.	
add.columns.af	ter Which column to add the new columns after? Default adds the columns to the far right.	

thresh_forest

add.columns.hj	ust
	Vector of horizontal justifications for the new columns, from 0 (left) to 1 (right).
	Default centres every column.
add.columns.uline	
	Underline the header of the new columns? Default TRUE.
calcdim	Logical, calculate suggested output dimensions for saving to pdf? Calculates output size when TRUE; saves time when FALSE.
display	Logical, display the plot? Defaults to TRUE.

Value

Displays the forest plot on the current plot device (if display = TRUE). Also returns invisibly the underlying gtable object, which can be further manipulated.

Examples

```
# Please see the vignette "Examples" for worked examples including use of
# this function, including more information on the brief code below.
vignette("Examples", package = "nmathresh")
### Contrast level thresholds for Thrombolytic treatments NMA
K <- 6 # Number of treatments
# Contrast design matrix is
X <- matrix(ncol = K-1, byrow = TRUE,
            c(1, 0, 0, 0, 0,
              0, 1, 0, 0, 0,
              0, 0, 1, 0, 0,
              0, 0, 0, 1, 0,
              0, -1, 1, 0, 0,
              0, -1, 0, 1, 0,
              0, -1, 0, 0, 1))
# Reconstruct hypothetical likelihood covariance matrix using NNLS
lik.cov <- recon_vcov(Thrombo.post.cov, prior.prec = .0001, X = X)</pre>
# Thresholds are then
thresh <- nma_thresh(mean.dk = Thrombo.post.summary$statistics[1:(K-1), "Mean"],</pre>
                     lhood = lik.cov,
                     post = Thrombo.post.cov,
                     nmatype = "fixed",
                     X = X,
                     opt.max = FALSE)
# Get treatment codes for the contrasts with data
d.a <- d.b <- vector(length = nrow(X))</pre>
for (i in 1:nrow(X)){
  d.a[i] <- ifelse(any(X[i, ] == -1), which(X[i, ] == -1), 0) + 1</pre>
  d.b[i] <- ifelse(any(X[i, ] == 1), which(X[i, ] == 1), 0) + 1
}
```

Thrombo.post.cov Posterior covariance matrix from Thrombolytics NMA

Description

The posterior covariance matrix of the basic treatment effect parameters.

Usage

Thrombo.post.cov

Format

An object of class matrix (inherits from array) with 5 rows and 5 columns.

Source

Generated from WinBUGS output, using the WinBUGS code from Caldwell et al. (2005). See also vignette("Examples", package = "nmathresh").

References

Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. Brit Med J 2005;331:897-900. http://dx.doi.org/10.1136/bmj.331.7521.897

See Also

Thrombo.post.summary

Thrombo.post.summary Posterior summary from Thrombolytics NMA

Description

A summary.mcmc object of the type produced by the coda package, containing the requisite posterior summary information on the variables dd, the contrasts of the treatment effect parameters.

Usage

Thrombo.post.summary

Format

A summary.mcmc object. The key components for our use are:

statistics Matrix containing the posterior summary statistics, with columns for Mean, SD, Naive SE, and Time-series SE (also known as the Monte-Carlo standard error)

quantiles Matrix containing the posterior 2.5%, 25%, 50%, 75%, and 97.5% quantiles

Source

Generated from WinBUGS output, using the WinBUGS code from Caldwell et al. (2005). See also vignette("Examples", package = "nmathresh").

References

Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. Brit Med J 2005;331:897-900. http://dx.doi.org/10.1136/bmj.331.7521.897

See Also

summary.mcmc, Thrombo.post.cov

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