Package 'multinma'

March 2, 2022

Title Bayesian Network Meta-Analysis of Individual and Aggregate Data

Version 0.4.2

Description Network meta-analysis and network meta-regression models for aggregate data, individual patient data, and mixtures of both individual and aggregate data using multilevel network meta-regression as described by Phillippo et al. (2020) <doi:10.1111/rssa.12579>. Models are estimated in a Bayesian framework using 'Stan'.

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Encoding UTF-8

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Biarch true

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- **Imports** methods, stats, graphics, Rcpp (>= 0.12.0), RcppParallel (>= 5.0.1), rstan (>= 2.19.2), rstantools (>= 2.0.0), Rdpack (>= 0.7), tibble (>= 2.1.3), dplyr (>= 0.8.3), rlang, purrr, forcats, glue, randtoolbox, copula, tidyr (>= 1.0.0), stringr, Matrix, igraph, ggraph, ggplot2, ggdist (>= 2.1.1), truncdist, bayesplot
- LinkingTo BH (>= 1.66.0), Rcpp (>= 0.12.0), RcppEigen (>= 0.3.3.3.0), RcppParallel (>= 5.0.1), rstan (>= 2.18.1), StanHeaders (>= 2.18.0)

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RdMacros Rdpack

URL https://dmphillippo.github.io/multinma/,

https://github.com/dmphillippo/multinma

BugReports https://github.com/dmphillippo/multinma/issues

VignetteBuilder knitr, R.rsp NeedsCompilation yes Author David M. Phillippo [aut, cre] (<https://orcid.org/0000-0003-2672-7841>) Maintainer David M. Phillippo <david.phillippo@bristol.ac.uk> Repository CRAN Date/Publication 2022-03-02 14:20:13 UTC

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multinma-package

multinma: A Package for Network Meta-Analysis of Individual and Aggregate Data in Stan

Description

An R package for performing network meta-analysis and network meta-regression with aggregate data, individual patient data, or mixtures of both.

Details

Network meta-analysis (NMA) combines (aggregate) data from multiple studies on multiple treatments in order to produce consistent estimates of relative treatment effects between each pair of treatments in the network (Dias et al. 2011).

Network meta-regression (NMR) extends NMA to include covariates, allowing adjustment for differences in effect-modifying variables between studies (Dias et al. 2011). NMR is typically performed using aggregate data (AgD), which lacks power and is prone to ecological bias. NMR with individual patient data (IPD) is the gold standard, if data are available.

Multilevel network meta-regression (ML-NMR) allows IPD and AgD to be incorporated together in a network meta-regression (Phillippo et al. 2020; Phillippo 2019). As in IPD NMR, an individual-level regression model is defined. AgD studies are then fitted by integrating the individual-level model over the respective covariate distributions. This correctly links the two levels of the model (instead of "plugging in" mean covariate values), avoiding aggregation bias. Population-adjusted treatment effects (Phillippo et al. 2016) can be produced for any study population in the network, or for an external target population.

Models are estimated in a Bayesian framework using Stan (Carpenter et al. 2017). Quasi-Monte Carlo numerical integration based on Sobol' sequences is used for the integration in ML-NMR models, with a Gaussian copula to account for correlations between covariates (Phillippo et al. 2020; Phillippo 2019).

Getting Started

A good place to start is with the package vignettes which walk through example analyses, see vignette("vignette_overview") for an overview. The series of NICE Technical Support Documents on evidence synthesis gives a detailed introduction to network meta-analysis:

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Reken S, Ades AE (2011). "NICE DSU Technical Support Documents 1-7: Evidence Synthesis for Decision Making." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Multilevel network meta-regression is set out in the following methods paper:

Phillippo DM, Dias S, Ades AE, Belger M, Brnabic A, Schacht A, Saure D, Kadziola Z, Welton NJ (2020). "Multilevel Network Meta-Regression for population-adjusted treatment comparisons." *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, **183**(3), 1189–1210. doi: 10.1111/rssa.12579.

References

Carpenter B, Gelman A, Hoffman MD, Lee D, Goodrich B, Betancourt M, Brubaker M, Guo J, Li P, Riddell A (2017). "Stan: A Probabilistic Programming Language." *Journal of Statistical Software*, **76**(1). doi: 10.18637/jss.v076.i01.

Dias S, Sutton AJ, Welton NJ, Ades AE (2011). "NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised

.default

controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites. sheffield.ac.uk.

Phillippo DM (2019). Calibration of Treatment Effects in Network Meta-Analysis using Individual Patient Data. Ph.D. thesis, University of Bristol. Available from https://research-information.bris.ac.uk/.

Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ (2016). "NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submission to NICE." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield. ac.uk.

Phillippo DM, Dias S, Ades AE, Belger M, Brnabic A, Schacht A, Saure D, Kadziola Z, Welton NJ (2020). "Multilevel Network Meta-Regression for population-adjusted treatment comparisons." *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, **183**(3), 1189–1210. doi: 10.1111/rssa.12579.

.default

Set default values

Description

The .default() function is used internally to mark certain values as default, so that the user may be notified when default values are being used. For example, choosing a default reference treatment for a network, or using default prior distributions. The function .is_default() checks whether an argument/object is set to a default value. Neither of these functions are intended to be called by the user.

Usage

.default(x = list())
.is_default(x)

Arguments

x An object

Value

For .default(), an identical object with additional attribute .default. For .is_default(), a logical value (TRUE or FALSE).

```
adapt_delta
```

Description

The Stan control argument adapt_delta sets the target average acceptance probability for the No-U-Turn Sampler (NUTS) used by Stan.

Details

The default value of adapt_delta used by nma() is 0.8 for fixed effect models, and 0.95 for random effects models.

You should not need to change adapt_delta unless you see a warning message about divergent transitions. Increasing adapt_delta from the default to a value closer to 1 means that Stan will use a smaller step size, making sampling slower but more robust, and resulting in fewer divergent transitions.

For more details see the Stan documentation available from https://mc-stan.org/users/documentation/.

add_integration Add nu

Add numerical integration points to aggregate data

Description

The add_integration() generic creates numerical integration points using a Gaussian copula approach, as described in Phillippo et al. (2020). Methods are available for networks stored in nma_data objects, and for data frames. The function unnest_integration() unnests integration points stored in a data frame, to aid plotting or other exploration.

Usage

```
add_integration(x, ...)
## Default S3 method:
add_integration(x, ...)
## S3 method for class 'data.frame'
add_integration(
    x,
    ...,
    cor = NULL,
    cor_adjust = NULL,
    n_int = 1000L,
    int_args = list()
)
```

```
## S3 method for class 'nma_data'
add_integration(
    x,
    ...,
    cor = NULL,
    cor_adjust = NULL,
    n_int = 1000L,
    int_args = list()
)
```

unnest_integration(data)

Arguments

x	An nma_data object, as created by the set_*() functions or combine_network(), or data frame
	Distributions for covariates, see "Details"
cor	Correlation matrix to use for generating the integration points. By default, this takes a weighted correlation matrix from all IPD studies. Rows and columns should match the order of covariates specified in
cor_adjust	Adjustment to apply to the correlation matrix given by cor (or computed from the IPD if cor = NULL) to obtain the Gaussian copula correlations, either "spearman", "pearson", or "none", see "Details". The default when cor = NULL is "spearman", otherwise the default is "pearson".
n_int	Number of integration points to generate, default 1000
int_args	A named list of arguments to pass to sobol()
data	Data frame with nested integration points, stored in list columns as .int_ <variable name=""></variable>

Details

The arguments passed to ... specify distributions for the covariates. Argument names specify the name of the covariate, which should match a covariate name in the IPD (if IPD are present). The required marginal distribution is then specified using the function distr().

The argument cor_adjust specifies how the correlation matrix given by cor (or computed from the IPD if cor = NULL) is adjusted to obtain the correlation matrix for the Gaussian copula, using the formulae in Xiao and Zhou (2018).

- cor_adjust = "spearman" should be used when the correlations cor have been computed using Spearman's rank correlation. Correlations between continuous covariates will be reproduced exactly by the integration points. Correlations between discrete covariates will be reproduced approximately. This is the default when cor = NULL and correlations are calculated from the IPD studies.
- cor_adjust = "pearson" should be used when the correlations cor have been computed using Pearson's product-moment correlation. Correlations between Normal covariates will be reproduced exactly by the integration points, all others will be reproduced approximately. Correlations between discrete covariates will be reproduced approximately (and identically to

cor_adjust = "spearman"). This is the default when cor is provided by the user, since cor()
defaults to method = "pearson" and Pearson correlations are most likely reported in published
data. However, we recommend providing Spearman correlations (e.g. from cor(.,method =
"spearman")) and using cor_adjust = "spearman" where possible.

- cor_adjust = "none" allows the user to specify the correlation matrix for the Gaussian copula directly; no adjustment is applied.
- cor_adjust = "legacy" is also available, which reproduces exactly the behaviour from version 0.3.0 and earlier. This is similar to cor_adjust = "none", but unadjusted Spearman correlations are used if cor = NULL.

When adding integration points to a network object the correlation matrix used is stored in \$int_cor, and the copula correlation matrix and adjustment used are stored as attributes of \$int_cor. If this correlation matrix is passed again to add_integration() (e.g. to reuse the correlations for an external target population) this will be detected, and the correct setting for cor_adjust will automatically be applied.

Value

For the nma_data method, an object of class nma_data. For the data.frame method, the input data frame is returned (as a tibble) with an added column for each covariate (prefixed with ".int_"), containing the numerical integration points nested as length-n_int vectors within each row. For unnest_integration(), a data frame with integration points unnested.

References

Phillippo DM, Dias S, Ades AE, Belger M, Brnabic A, Schacht A, Saure D, Kadziola Z, Welton NJ (2020). "Multilevel Network Meta-Regression for population-adjusted treatment comparisons." *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, **183**(3), 1189–1210. doi: 10.1111/rssa.12579.

Xiao Q, Zhou S (2018). "Matching a correlation coefficient by a Gaussian copula." *Communications in Statistics - Theory and Methods*, **48**(7), 1728–1747. doi: 10.1080/03610926.2018.1439962.

Examples

```
prevsys = as.numeric(prevsys),
   psa = as.numeric(psa),
   weight = weight / 10,
   durnpso = durnpso / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                         trtn == 4 ~ "TNFa blocker"),
    # Check complete cases for covariates of interest
   complete = complete.cases(durnpso, prevsys, bsa, weight, psa)
 )
pso_agd <- pso_agd %>%
 mutate(
    # Variable transformations
   bsa_mean = bsa_mean / 100,
   bsa_sd = bsa_sd / 100,
   prevsys = prevsys / 100,
   psa = psa / 100,
   weight_mean = weight_mean / 10,
   weight_sd = weight_sd / 10,
   durnpso_mean = durnpso_mean / 10,
   durnpso_sd = durnpso_sd / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                         trtn == 4 ~ "TNFa blocker")
 )
# Exclude small number of individuals with missing covariates
pso_ipd <- filter(pso_ipd, complete)</pre>
pso_net <- combine_network(</pre>
 set_ipd(pso_ipd,
          study = studyc,
          trt = trtc,
          r = pasi75,
          trt_class = trtclass),
 set_agd_arm(pso_agd,
              study = studyc,
              trt = trtc,
              r = pasi75_r,
              n = pasi75_n,
              trt_class = trtclass)
)
# Print network details
pso_net
# Add integration points to the network
pso_net <- add_integration(pso_net,</pre>
 durnpso = distr(qgamma, mean = durnpso_mean, sd = durnpso_sd),
 prevsys = distr(qbern, prob = prevsys),
```

```
bsa = distr(qlogitnorm, mean = bsa_mean, sd = bsa_sd),
 weight = distr(qgamma, mean = weight_mean, sd = weight_sd),
 psa = distr(qbern, prob = psa),
 n_{int} = 1000)
## Adding integration points to a data frame, e.g. for prediction
# Define a data frame of covariate summaries
new_agd_int <- data.frame(</pre>
 bsa_mean = 0.6,
 bsa_sd = 0.3,
 prevsys = 0.1,
 psa = 0.2,
 weight_mean = 10,
 weight_sd = 1,
 durnpso_mean = 3,
 durnpso_sd = 1)
# Adding integration points, using the weighted average correlation matrix
# computed for the plaque psoriasis network
new_agd_int <- add_integration(new_agd_int,</pre>
 durnpso = distr(qgamma, mean = durnpso_mean, sd = durnpso_sd),
 prevsys = distr(qbern, prob = prevsys),
 bsa = distr(qlogitnorm, mean = bsa_mean, sd = bsa_sd),
 weight = distr(qgamma, mean = weight_mean, sd = weight_sd),
 psa = distr(qbern, prob = psa),
 cor = pso_net$int_cor,
 n_{int} = 1000)
# Here, since we reused the correlation matrix pso_net$int_cor from the
# network, the correct setting of cor_adjust = "spearman" is automatically
# applied
new_agd_int
```

as.array.stan_nma Convert samples into arrays, matrices, or data frames

Description

Samples (post warm-up) from a stan_nma model object can be coerced into an array, matrix, or data frame.

Usage

S3 method for class 'stan_nma'
as.array(x, ..., pars, include = TRUE)
S3 method for class 'stan_nma'

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as.igraph.nma_data

as.data.frame(x, ..., pars, include = TRUE)
S3 method for class 'stan_nma'
as.matrix(x, ..., pars, include = TRUE)

Arguments

x	A stan_nma object
	Additional arguments passed to as.array.stanfit()
pars	Optional character vector of parameter names to include in output. If not specified, all parameters are used.
include	Logical, are parameters in pars to be included (TRUE, default) or excluded (FALSE)?

Value

The as.array() method produces a 3D array [Iteration, Chain, Parameter] containing posterior samples of each parameter (as class mcmc_array). This has the side effect of enabling bayesplot functions to seamlessly work on stan_nma objects.

The as.data.frame() method produces a data frame containing posterior samples of each parameter, combined over all chains.

The as.matrix() method produces a matrix containing posterior samples of each parameter, combined over all chains.

as.igraph.nma_data Convert networks to graph objects

Description

The method as.igraph() converts nma_data objects into the form used by the igraph package. The method as_tbl_graph() converts nma_data objects into the form used by the ggraph and tidygraph packages.

Usage

```
## S3 method for class 'nma_data'
as.igraph(x, ..., collapse = TRUE)
## S3 method for class 'nma_data'
as_tbl_graph(x, ...)
```

as.stanfit

Arguments

х	An nma_data object to convert
	Additional arguments
collapse	Logical, collapse edges over studies? Default TRUE, only one edge is produced for each comparison (by IPD or AgD study type) with a .nstudy attribute giving the number of studies making that comparison. If FALSE, repeated edges are added for each study making the comparison.

Value

An igraph object for as.igraph(), a tbl_graph object for as_tbl_graph().

Examples

```
# Set up network of smoking cessation data
head(smoking)
smk_net <- set_agd_arm(smoking,</pre>
                       study = studyn,
                       trt = trtc,
                       r = r,
                       n = n,
                       trt_ref = "No intervention")
# Print details
smk_net
# Convert to igraph object
igraph::as.igraph(smk_net) # Edges combined by default
igraph::as.igraph(smk_net, collapse = FALSE) # Without combining edges
# Convert to tbl_graph object
tidygraph::as_tbl_graph(smk_net) # Edges combined by default
tidygraph::as_tbl_graph(smk_net, collapse = FALSE) # Without combining edges
```

as.stanfit as.stanfit

Description

Attempt to turn an object into a stanfit object.

Usage

```
as.stanfit(x, ...)
## S3 method for class 'stan_nma'
as.stanfit(x, ...)
```

Default S3 method:
as.stanfit(x, ...)

Arguments

х	an object
	additional arguments

Value

A stanfit object.

atrial_fibrillation Stroke prevention in atrial fibrillation patients

Description

Data frame containing the results of 26 trials comparing 17 treatments in 4 classes for the prevention of stroke in patients with atrial fibrillation (Cooper et al. 2009). The data are the corrected versions given by van Valkenhoef and Kuiper (2016).

Usage

atrial_fibrillation

Format

A data frame with 63 rows and 11 variables:

studyc study name

studyn numeric study ID

trtc treatment name

trtn numeric treatment code

trt_class treatment class

 \mathbf{r} number of events

n sample size

E person-years at risk

stroke proportion of individuals with prior stroke

year year of study publication

followup mean length of follow-up (years)

References

Cooper NJ, Sutton AJ, Morris D, Ades AE, Welton NJ (2009). "Addressing between-study heterogeneity and inconsistency in mixed treatment comparisons: Application to stroke prevention treatments in individuals with non-rheumatic atrial fibrillation." *Statistics in Medicine*, **28**(14), 1861–1881. doi: 10.1002/sim.3594.

van Valkenhoef G, Kuiper J (2016). *gemtc: Network Meta-Analysis Using Bayesian Methods*. R package version 0.8-2, https://CRAN.R-project.org/package=gemtc.

bcg_vaccine

BCG vaccination

Description

Data frame containing the results of 13 trials comparing BCG vaccination to no vaccination for preventing tuberculosis (TB) (Dias et al. 2011; Berkey et al. 1995). The numbers of individuals diagnosed with TB in each arm during the study follow-up period are recorded. The absolute degrees latitude at which the study was conducted are also recorded.

Usage

bcg_vaccine

Format

A data frame with 26 rows and 6 variables:

studyn numeric study ID

trtn numeric treatment code

trtc treatment name

latitude absolute degrees latitude

- r number diagnosed with TB
- n sample size

References

Berkey CS, Hoaglin DC, Mosteller F, Colditz GA (1995). "A random-effects regression model for meta-analysis." *Statistics in Medicine*, **14**(4), 395–411. doi: 10.1002/sim.4780140406.

Dias S, Sutton AJ, Welton NJ, Ades AE (2011). "NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk. blocker

Description

Data frame containing the number of deaths in 22 trials comparing beta blockers vs. control for preventing mortality after myocardial infarction (Carlin 1992; Dias et al. 2011).

Usage

blocker

Format

A data frame with 44 rows and 5 variables:

studyn numeric study ID

trtn numeric treatment code

trtc treatment name

- r total number of events
- **n** total number of individuals

References

Carlin JB (1992). "Meta-analysis for 2 x 2 tables: A bayesian approach." *Statistics in Medicine*, **11**(2), 141–158. doi: 10.1002/sim.4780110202.

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

combine_network Combine multiple data sources into one network

Description

Multiple data sources created using set_ipd(), set_agd_arm(), or set_agd_contrast() can be combined into a single network for analysis.

Usage

```
combine_network(..., trt_ref)
```

Arguments

	multiple data sources, as defined using the set_* functions
trt_ref	reference treatment for the entire network, as a string (or coerced as such) refer-
	ring to the levels of the treatment factor variable

Value

An object of class nma_data

See Also

set_ipd(), set_agd_arm(), and set_agd_contrast() for defining different data sources.

print.nma_data() for the print method displaying details of the network, and plot.nma_data()
for network plots.

Examples

```
## Parkinson's - combining contrast- and arm-based data
studies <- parkinsons$studyn</pre>
(parkinsons_arm <- parkinsons[studies %in% 1:3, ])</pre>
(parkinsons_contr <- parkinsons[studies %in% 4:7, ])</pre>
park_arm_net <- set_agd_arm(parkinsons_arm,</pre>
                              study = studyn,
                              trt = trtn,
                              y = y,
                              se = se,
                              sample_size = n)
park_contr_net <- set_agd_contrast(parkinsons_contr,</pre>
                                     study = studyn,
                                     trt = trtn,
                                     y = diff,
                                     se = se_diff,
                                     sample_size = n)
park_net <- combine_network(park_arm_net, park_contr_net)</pre>
# Print network details
park_net
# Plot network
plot(park_net, weight_edges = TRUE, weight_nodes = TRUE)
## Plaque Psoriasis - combining IPD and AgD in a network
# Set up plaque psoriasis network combining IPD and AgD
library(dplyr)
pso_ipd <- filter(plaque_psoriasis_ipd,</pre>
                   studyc %in% c("UNCOVER-1", "UNCOVER-2", "UNCOVER-3"))
```

pso_agd <- filter(plaque_psoriasis_agd,</pre>

```
studyc == "FIXTURE")
head(pso_ipd)
head(pso_agd)
pso_ipd <- pso_ipd %>%
  mutate(# Variable transformations
   bsa = bsa / 100,
   prevsys = as.numeric(prevsys),
   psa = as.numeric(psa),
   weight = weight / 10,
   durnpso = durnpso / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                         trtn == 4 ~ "TNFa blocker"),
    # Check complete cases for covariates of interest
    complete = complete.cases(durnpso, prevsys, bsa, weight, psa)
  )
pso_agd <- pso_agd %>%
  mutate(
    # Variable transformations
    bsa_mean = bsa_mean / 100,
   bsa_sd = bsa_sd / 100,
   prevsys = prevsys / 100,
    psa = psa / 100,
    weight_mean = weight_mean / 10,
    weight_sd = weight_sd / 10,
    durnpso_mean = durnpso_mean / 10,
    durnpso_sd = durnpso_sd / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                          trtn == 4 ~ "TNFa blocker")
  )
# Exclude small number of individuals with missing covariates
pso_ipd <- filter(pso_ipd, complete)</pre>
pso_net <- combine_network(</pre>
  set_ipd(pso_ipd,
          study = studyc,
          trt = trtc,
          r = pasi75,
          trt_class = trtclass),
  set_agd_arm(pso_agd,
              study = studyc,
              trt = trtc,
              r = pasi75_r,
              n = pasi75_n,
              trt_class = trtclass)
)
```

```
# Print network details
pso_net
# Plot network
plot(pso_net, weight_nodes = TRUE, weight_edges = TRUE, show_trt_class = TRUE)
```

dgent

Generalised Student's t distribution (with location and scale)

Description

Density, distribution, and quantile function for the generalised t distribution with degrees of freedom df, shifted by location and scaled by scale.

Usage

dgent(x, df, location = 0, scale = 1)
pgent(q, df, location = 0, scale = 1)
qgent(p, df, location = 0, scale = 1)

Arguments

x,q	Vector of quantiles
df	Degrees of freedom, greater than zero
location	Location parameter
scale	Scale parameter, greater than zero
р	Vector of probabilities

Value

dgent() gives the density, pgent() gives the distribution function, qgent() gives the quantile function.

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diabetes

Description

Data frame containing the number of new cases of diabetes in 22 trials of 6 antihypertensive drugs (Elliott and Meyer 2007; Dias et al. 2011). The trial duration (in years) is also recorded.

Usage

diabetes

Format

A data frame with 48 rows and 7 variables:

studyn numeric study ID

studyc study name

trtn numeric treatment code

trtc treatment name

r total number of events

n total number of individuals

time trial follow-up (years)

References

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Elliott WJ, Meyer PM (2007). "Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis." *The Lancet*, **369**(9557), 201–207. doi: 10.1016/s01406736(07)601081, https://doi.org/10.1016/s0140-6736(07)60108-1.

dic

Deviance Information Criterion (DIC)

Description

Calculate the DIC for a model fitted using the nma() function.

Usage

dic(x, ...)

Arguments

х	A fitted model object, inheriting class stan_nma
	Other arguments (not used)

Value

A nma_dic object.

See Also

print.nma_dic() for printing details, plot.nma_dic() for producing plots of residual deviance contributions.

Examples

```
## Smoking cessation
```

```
# Run smoking FE NMA example if not already available
if (!exists("smk_fit_FE")) example("example_smk_fe", run.donttest = TRUE)
```

```
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
```

```
# Compare DIC of FE and RE models
(smk_dic_FE <- dic(smk_fit_FE))
(smk_dic_RE <- dic(smk_fit_RE))  # substantially better fit</pre>
```

```
# Plot residual deviance contributions under RE model
plot(smk_dic_RE)
```

Check for inconsistency using UME model

```
# Run smoking UME NMA example if not already available
if (!exists("smk_fit_RE_UME")) example("example_smk_ume", run.donttest = TRUE)
```

```
# Compare DIC
smk_dic_RE
(smk_dic_RE_UME <- dic(smk_fit_RE_UME)) # no difference in fit</pre>
```

```
# Compare residual deviance contributions
plot(smk_dic_RE, smk_dic_RE_UME, show_uncertainty = FALSE)
```

dietary_fat

Description

Data frame containing the number of deaths and person-years at risk in 10 trials comparing reduced fat diets vs. control (non-reduced fat diet) for preventing mortality (Hooper et al. 2000; Dias et al. 2011).

Usage

dietary_fat

Format

A data frame with 21 rows and 7 variables:

studyn numeric study ID

studyc study name

trtn numeric treatment code

trtc treatment name

r number of events

n number randomised

E person-years at risk

References

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Hooper L, Summerbell CD, Higgins JPT, Thompson RL, Clements G, Capps N, Davey Smith G, Riemersma R, Ebrahim S (2000). "Reduced or modified dietary fat for preventing cardio-vascular disease." *Cochrane Database of Systematic Reviews*. ISSN 1465-1858, doi: 10.1002/14651858.CD002137.

Description

distr() is used within the function add_integration() to specify marginal distributions for the covariates, via a corresponding inverse CDF. It is also used in predict.stan_nma() to specify a distribution for the baseline response (intercept) when predicting absolute outcomes.

Usage

distr(qfun, ...)

Arguments

qfun	an inverse CDF, either as a function name or a string
	parameters of the distribution as arguments to qfun, these will be quoted and evaluated later in the context of the aggregate data sources

Details

The function qfun should have a formal argument called p. This restriction serves as a crude check for inverse CDFs (e.g. an error will be given if dnorm is used instead of qnorm). If a user-written CDF is supplied, it must have an argument p which takes a vector of probabilities.

Value

An object of class distr.

See Also

add_integration() where distr() is used to specify marginal distributions for covariates to integrate over, and predict.stan_nma() where distr() is used to specify a distribution on the baseline response.

Examples

Specifying marginal distributions for integration

df <- data.frame(x1_mean = 2, x1_sd = 0.5, x2 = 0.8)

Distribution parameters are evaluated in the context of the data frame add_integration(df,

> x1 = distr(qnorm, mean = x1_mean, sd = x1_sd), x2 = distr(qbern, prob = x2), cor = diag(2))

distr

example_pso_mlnmr Example plaque psoriasis ML-NMR

Description

Calling example("example_pso_mlnmr") will run a ML-NMR model with the plaque psoriasis IPD and AgD, using the code in the Examples section below. The resulting stan_nma object pso_fit will then be available in the global environment.

Details

Plaque psoriasis ML-NMR for use in examples.

Examples

```
# Set up plaque psoriasis network combining IPD and AgD
library(dplyr)
pso_ipd <- filter(plaque_psoriasis_ipd,</pre>
                  studyc %in% c("UNCOVER-1", "UNCOVER-2", "UNCOVER-3"))
pso_agd <- filter(plaque_psoriasis_agd,</pre>
                  studyc == "FIXTURE")
head(pso_ipd)
head(pso_agd)
pso_ipd <- pso_ipd %>%
  mutate(# Variable transformations
   bsa = bsa / 100,
   prevsys = as.numeric(prevsys),
   psa = as.numeric(psa),
   weight = weight / 10,
    durnpso = durnpso / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                         trtn == 4 ~ "TNFa blocker"),
    # Check complete cases for covariates of interest
    complete = complete.cases(durnpso, prevsys, bsa, weight, psa)
  )
pso_agd <- pso_agd %>%
  mutate(
    # Variable transformations
   bsa_mean = bsa_mean / 100,
   bsa_sd = bsa_sd / 100,
   prevsys = prevsys / 100,
   psa = psa / 100,
   weight_mean = weight_mean / 10,
   weight_sd = weight_sd / 10,
```

```
durnpso_mean = durnpso_mean / 10,
    durnpso_sd = durnpso_sd / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                         trtn == 4 ~ "TNFa blocker")
 )
# Exclude small number of individuals with missing covariates
pso_ipd <- filter(pso_ipd, complete)</pre>
pso_net <- combine_network(</pre>
 set_ipd(pso_ipd,
          study = studyc,
          trt = trtc,
          r = pasi75,
          trt_class = trtclass),
 set_agd_arm(pso_agd,
              study = studyc,
              trt = trtc,
              r = pasi75_r,
              n = pasi75_n,
              trt_class = trtclass)
)
# Print network details
pso_net
# Add integration points to the network
pso_net <- add_integration(pso_net,</pre>
 durnpso = distr(qgamma, mean = durnpso_mean, sd = durnpso_sd),
 prevsys = distr(qbern, prob = prevsys),
 bsa = distr(qlogitnorm, mean = bsa_mean, sd = bsa_sd),
 weight = distr(qgamma, mean = weight_mean, sd = weight_sd),
 psa = distr(qbern, prob = psa),
 n_{int} = 1000)
# Fitting a ML-NMR model.
# Specify a regression model to include effect modifier interactions for five
# covariates, along with main (prognostic) effects. We use a probit link and
# specify that the two-parameter Binomial approximation for the aggregate-level
# likelihood should be used. We set treatment-covariate interactions to be equal
# within each class. We narrow the possible range for random initial values with
# init_r = 0.1, since probit models in particular are often hard to initialise.
# Using the QR decomposition greatly improves sampling efficiency here, as is
# often the case for regression models.
pso_fit <- nma(pso_net,</pre>
               trt_effects = "fixed",
               link = "probit",
               likelihood = "bernoulli2",
               regression = ~(durnpso + prevsys + bsa + weight + psa)*.trt,
               class_interactions = "common",
```

pso_fit

```
prior_intercept = normal(scale = 10),
prior_trt = normal(scale = 10),
prior_reg = normal(scale = 10),
init_r = 0.1,
QR = TRUE)
```

example_smk_fe Example smoking FE NMA

Description

Calling example("example_smk_fe") will run a fixed effects NMA model with the smoking cessation data, using the code in the Examples section below. The resulting stan_nma object smk_fit_FE will then be available in the global environment.

Details

Smoking FE NMA for use in examples.

Examples

smk_fit_FE

example_smk_nodesplit Example smoking node-splitting

Description

Calling example("example_smk_nodesplit") will run node-splitting models with the smoking cessation data, using the code in the Examples section below. The resulting nma_nodesplit_df object smk_fit_RE_nodesplit will then be available in the global environment.

Details

Smoking node-splitting for use in examples.

Examples

```
# Set up network of smoking cessation data
head(smoking)
smk_net <- set_agd_arm(smoking,</pre>
                        study = studyn,
                        trt = trtc,
                        r = r,
                        n = n,
                        trt_ref = "No intervention")
# Print details
smk_net
# Fitting all possible node-splitting models
smk_fit_RE_nodesplit <- nma(smk_net,</pre>
                             consistency = "nodesplit",
                             trt_effects = "random",
                             prior_intercept = normal(scale = 100),
                             prior_trt = normal(scale = 100),
                             prior_het = normal(scale = 5))
```

example_smk_re Exa

Example smoking RE NMA

Description

Calling example("example_smk_re") will run a random effects NMA model with the smoking cessation data, using the code in the Examples section below. The resulting stan_nma object smk_fit_RE will then be available in the global environment.

example_smk_ume

Details

Smoking RE NMA for use in examples.

Examples

```
# Set up network of smoking cessation data
head(smoking)
smk_net <- set_agd_arm(smoking,</pre>
                        study = studyn,
                        trt = trtc,
                        r = r,
                        n = n,
                        trt_ref = "No intervention")
# Print details
smk_net
# Fitting a random effects model
smk_fit_RE <- nma(smk_net,</pre>
                  trt_effects = "random",
                   prior_intercept = normal(scale = 100),
                   prior_trt = normal(scale = 100),
                   prior_het = normal(scale = 5))
```

smk_fit_RE

example_smk_ume Example smoking UME NMA

Description

Calling example("example_smk_ume") will run an unrelated mean effects (inconsistency) NMA model with the smoking cessation data, using the code in the Examples section below. The resulting stan_nma object smk_fit_RE_UME will then be available in the global environment.

Details

Smoking UME NMA for use in examples.

Examples

Set up network of smoking cessation data head(smoking)

```
smk_net <- set_agd_arm(smoking,</pre>
                        study = studyn,
                        trt = trtc,
                        r = r,
                        n = n,
                        trt_ref = "No intervention")
# Print details
smk_net
# Fitting an unrelated mean effects (inconsistency) model
smk_fit_RE_UME <- nma(smk_net,</pre>
                      consistency = "ume",
                       trt_effects = "random",
                      prior_intercept = normal(scale = 100),
                      prior_trt = normal(scale = 100),
                      prior_het = normal(scale = 5))
smk_fit_RE_UME
```

get_nodesplits Direct and indirect evidence

Description

Determine whether two treatments in a network are connected by direct and/or indirect evidence, and generate a list of comparisons with both direct and indirect evidence (i.e. potential inconsistency) for node-splitting.

Usage

```
get_nodesplits(network, include_consistency = FALSE)
```

has_direct(network, trt1, trt2)

has_indirect(network, trt1, trt2)

Arguments

network	An nma_data object, as created by the functions set_*() or combine_network().	
include_consistency		
	Logical, whether to include a row of NAs to indicate that a consistency model (i.e. a model with no node-splitting) should also be fitted by the nma() function. Default is FALSE when calling get_nodesplits() by hand, and nma() sets this to TRUE by default.	
trt1, trt2	Treatments, each as a single integer, string, or factor	

get_nodesplits

Details

The list of comparisons for node-splitting is generated following the algorithm of van Valkenhoef et al. (2016). A comparison between two treatments has the potential for inconsistency, and is thus considered for node-splitting, if the comparison has both direct evidence and *independent* indirect evidence.

The notion of independent indirect evidence is necessary when multi-arm trials are present, since by design these trials are internally consistent. A comparison between two treatments has independent indirect evidence if, after removing all studies comparing the two treatments from the network, the two treatments are still connected by a path of evidence. This is the criterion considered by the has_indirect() function.

Value

For has_direct() and has_indirect(), a single logical value. For get_nodesplits(), a data frame with two columns giving the comparisons for node-splitting.

References

van Valkenhoef G, Dias S, Ades AE, Welton NJ (2016). "Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis." *Research Synthesis Methods*, 7(1), 80–93. doi: 10.1002/jrsm.1167.

Examples

```
# Parkinsons example
park_net <- set_agd_arm(parkinsons,</pre>
                        study = studyn,
                        trt = trtn,
                        y = y,
                        se = se,
                        trt_ref = 1)
# View the network plot
plot(park_net)
# The 4 vs. 5 comparison is a spur on the network
has_direct(park_net, 4, 5)
has_indirect(park_net, 4, 5)
# 1 and 5 are not directly connected
has_direct(park_net, 1, 5)
has_indirect(park_net, 1, 5)
# The 1 vs. 2 comparison does not have independent indirect evidence, since
# the 1-2-4 loop is a multi-arm study
has_indirect(park_net, 1, 2)
# Get a list of comparisons with potential inconsistency for node-splitting
get_nodesplits(park_net)
```

See van Valkenhoef (2016) for a discussion of this example

hta_psoriasis

Description

Data frame containing the results of 16 trials comparing 8 treatments for moderate-to-severe plaque psoriasis from an HTA report (Woolacott et al. 2006), analysed in TSD2 (Dias et al. 2011). Outcomes are success/failure to achieve 50%, 75%, or 90% reduction in symptoms on the Psoriasis Area and Severity Index (PASI) scale. Some studies report all three ordered outcomes, others only one or two. The latter are coded as missing values (see details).

Usage

hta_psoriasis

Format

A data frame with 36 rows and 9 variables:

studyn numeric study ID

studyc study name

year year of publication

trtn numeric treatment code

trtc treatment name

sample_size sample size in each arm

PASI50, PASI75, PASI90 ordered multinomial outcome counts (exclusive, see details)

Details

Outcome counts are "exclusive"; that is, for a study reporting all outcomes, the counts represent the categories 50 < PASI < 75, 75 < PASI < 90, and 90 < PASI < 100, and are named by the lower end of the interval. (As opposed to "inclusive" counts, which would represent the overlapping categories PASI > 50, PASI > 70, and PASI > 90.) The count for the fourth category (the lowest), 0 < PASI < 50, is equal to sample_size -PASI50 -PASI75 -PASI90.

Missing values are used where studies only report a subset of the outcomes. For a study reporting only two outcomes, say 50 and 75, the counts represent 50 < PASI < 75 and 75 < PASI < 100. For a study reporting only one outcome, say PASI 75, the count represents 75 < PASI < 100.

References

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, Misso K, Light K, Chalmers R, Sculpher M, Riemsma R (2006). "Etanercept and efalizumab for the treatment of psoriasis: a systematic review." *Health Technology Assessment*, **10**(46). doi: 10.3310/hta10460.

is_network_connected Check network connectedness

Description

Check whether a network is connected - whether there is a path of study evidence linking every pair of treatments in the network.

Usage

is_network_connected(network)

Arguments

network

An nma_data object, as created by the functions set_*() or combine_network().

Details

Models will still run with disconnected networks. However, estimated relative effects between treatments across disconnected parts of the network will be entirely based on the prior distribution (typically very uncertain), as there is no information to update the prior distribution. Relative effects within each connected sub-network will be estimated as if each sub-network had been analysed separately.

Value

Logical TRUE or FALSE

Examples

```
## Smoking cessation
# Set up network of smoking cessation data
head(smoking)
```

```
trt = trtc,
r = r,
n = n,
trt_ref = "No intervention")
```

```
# Print details
smk_net
```

is_network_connected(smk_net) # TRUE, network is connected

loo.stan_nma Model comparison using the loo package

Description

The loo() and waic() functions from the loo package may be called directly on stan_nma and stan_mlnmr objects.

Usage

```
## S3 method for class 'stan_nma'
loo(x, ...)
## S3 method for class 'stan_nma'
waic(x, ...)
```

Arguments

х	An object of class stan_nma or stan_mlnmr
	Further arguments to loo() or waic()

mcmc_array-class Working with 3D MCMC arrays

Description

3D MCMC arrays (Iterations, Chains, Parameters) are produced by as.array() methods applied to stan_nma or nma_summary objects.

mcmc_array-class

Usage

```
## S3 method for class 'mcmc_array'
summary(object, ..., probs = c(0.025, 0.25, 0.5, 0.75, 0.975))
## S3 method for class 'mcmc_array'
print(x, ...)
## S3 method for class 'mcmc_array'
names(x)
## S3 replacement method for class 'mcmc_array'
names(x) <- value</pre>
```

Arguments

•••	Further arguments passed to other methods
probs	Numeric vector of quantiles of interest
x,object	A 3D MCMC array of class mcmc_array
value	Character vector of replacement parameter names

Value

The summary() method returns a nma_summary object, the print() method returns x invisibly. The names() method returns a character vector of parameter names, and names()<- returns the object with updated parameter names.

Examples

```
## Smoking cessation
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
# Working with arrays of posterior draws (as mcmc_array objects) is
# convenient when transforming parameters
# Transforming log odds ratios to odds ratios
LOR_array <- as.array(relative_effects(smk_fit_RE))
OR_array <- exp(LOR_array)
# mcmc_array objects can be summarised to produce a nma_summary object
smk_OR_RE <- summary(OR_array)
# This can then be printed or plotted
smk_OR_RE
plot(smk_OR_RE, ref_line = 1)</pre>
```

Transforming heterogeneity SD to variance

```
tau_array <- as.array(smk_fit_RE, pars = "tau")
tausq_array <- tau_array^2
# Correct parameter names
names(tausq_array) <- "tausq"
# Summarise
summary(tausq_array)</pre>
```

multi

Multinomial outcome data

Description

This function aids the specification of multinomial outcome data when setting up a network with set_agd_arm() or set_ipd(). It takes a set of columns (or, more generally, numeric vectors of the same length) of outcome counts in each category, and binds these together to produce a matrix.

Usage

multi(..., inclusive = FALSE, type = c("ordered", "competing"))

Arguments

	Two or more numeric columns (or vectors) of category counts. Argument names (optional) will be used to label the categories.
inclusive	Logical, are ordered category counts inclusive (TRUE) or exclusive (FALSE)? De- fault FALSE. Only used when ordered = TRUE. See details.
type	String, indicating whether categories are "ordered" or "competing". Currently only ordered categorical outcomes are supported by the modelling functions in this package.

Details

When specifying ordered categorical counts, these can either be given as *exclusive* counts (inclusive = FALSE, the default) where individuals are only counted in the highest category they achieve, or *inclusive* counts (inclusive = TRUE) where individuals are counted in every category up to and including the highest category achieved. (Competing outcomes, by nature, are always specified as exclusive counts.)

NA values can be used to indicate categories/cutpoints that were not measured.

Value

A matrix of (exclusive) category counts

34

multi

Examples

```
# These two data sets specify the same ordered categorical data for outcomes
\# r0 < r1 < r2, but the first uses the "inclusive" format and the second the
# "exclusive" format.
df_inclusive <- tibble::tribble(~r0, ~r1, ~r2,</pre>
                                 1, 1, 1,
                                 5, 4, 1,
                                 5, 2, 2,
                                 10, 5, 0,
                                 5, 5, 0,
                                 7, NA, 6,
                                             # Achieved r2 or not (no r1)
                                 10, 4, NA) # Achieved r1 or not (no r2)
df_exclusive <- tibble::tribble(~r0, ~r1, ~r2,</pre>
                                 0, 0, 1,
                                 1, 3, 1,
                                 3, 0, 2,
                                 5, 5, 0,
                                 0, 5, 0,
                                             # Achieved r2 or not (no r1)
                                 1, NA, 6,
                                 6, 4, NA) # Achieved r1 or not (no r2)
(r_inclusive <- with(df_inclusive, multi(r0, r1, r2, inclusive = TRUE)))</pre>
(r_exclusive <- with(df_exclusive, multi(r0, r1, r2, inclusive = FALSE)))</pre>
# Counts are always stored in exclusive format
stopifnot(isTRUE(all.equal(r_inclusive, r_exclusive)))
## HTA Plaque Psoriasis
library(dplyr)
# Ordered outcomes here are given as "exclusive" counts
head(hta_psoriasis)
# Calculate lowest category count (failure to achieve PASI 50)
pso_dat <- hta_psoriasis %>%
  mutate(`PASI<50` = sample_size - rowSums(cbind(PASI50, PASI75, PASI90), na.rm = TRUE))</pre>
# Set up network
pso_net <- set_agd_arm(pso_dat,</pre>
                        study = paste(studyc, year),
                        trt = trtc,
                        r = multi(`PASI<50`, PASI50, PASI75, PASI90,</pre>
                                  inclusive = FALSE,
                                  type = "ordered"))
```

pso_net

Description

The nma function fits network meta-analysis and (multilevel) network meta-regression models in Stan.

Usage

```
nma(
  network,
  consistency = c("consistency", "ume", "nodesplit"),
  trt_effects = c("fixed", "random"),
  regression = NULL,
  class_interactions = c("common", "exchangeable", "independent"),
  likelihood = NULL,
  link = NULL,
  ...,
  nodesplit = get_nodesplits(network, include_consistency = TRUE),
  prior_intercept = .default(normal(scale = 100)),
  prior_trt = .default(normal(scale = 10)),
  prior_het = .default(half_normal(scale = 5)),
  prior_het_type = c("sd", "var", "prec"),
  prior_reg = .default(normal(scale = 10)),
  prior_aux = .default(),
  QR = FALSE,
  center = TRUE,
  adapt_delta = NULL,
  int_thin = max(network$n_int%/%10, 1)
)
```

Arguments

network	An nma_data object, as created by the functions set_*(), combine_network(), or add_integration()	
consistency	Character string specifying the type of (in)consistency model to fit, either "consistency", "ume", or "nodesplit"	
trt_effects	Character string specifying either "fixed" or "random" effects	
regression	A one-sided model formula, specifying the prognostic and effect-modifying terms for a regression model. Any references to treatment should use the .trt special variable, for example specifying effect modifier interactions as variable:.trt (see details).	
class_interactions		
	Character string specifying whether effect modifier interactions are specified as "common", "exchangeable", or "independent".	

nma

nma

likelihood	Character string specifying a likelihood, if unspecified will be inferred from the data (see details)
link	Character string specifying a link function, if unspecified will default to the canonical link (see details)
	Further arguments passed to sampling(), such as iter, chains, cores, etc.
nodesplit	For consistency = "nodesplit", the comparison(s) to split in the node-splitting model(s). Either a length 2 vector giving the treatments in a single comparison, or a 2 column data frame listing multiple treatment comparisons to split in turn. By default, all possible comparisons will be chosen (see get_nodesplits()).
prior_intercept	
	Specification of prior distribution for the intercept
prior_trt	Specification of prior distribution for the treatment effects
prior_het	$Specification \ of \ prior \ distribution \ for \ the \ heterogeneity \ (if \ trt_effects = "random")$
prior_het_type	Character string specifying whether the prior distribution prior_het is placed on the heterogeneity standard deviation τ ("sd", the default), variance τ^2 ("var"), or precision $1/\tau^2$ ("prec").
prior_reg	Specification of prior distribution for the regression coefficients (if regression formula specified)
prior_aux	Specification of prior distribution for the auxiliary parameter, if applicable (see details)
QR	Logical scalar (default FALSE), whether to apply a QR decomposition to the model design matrix
center	Logical scalar (default TRUE), whether to center the (numeric) regression terms about the overall means
adapt_delta	See adapt_delta for details
int_thin	A single integer value, the thinning factor for returning cumulative estimates of integration error

Details

When specifying a model formula in the regression argument, the usual formula syntax is available (as interpreted by model.matrix()). The only additional requirement here is that the special variable .trt should be used to refer to treatment. For example, effect modifier interactions should be specified as variable:.trt. Prognostic (main) effects and interactions can be included together compactly as variable*.trt, which expands to variable + variable:.trt (plus .trt, which is already in the NMA model).

For the advanced user, the additional specials .study and .trtclass are also available, and refer to studies and (if specified) treatment classes respectively. When node-splitting models are fitted (consistency = "nodesplit") the special .omega is available, indicating the arms to which the node-splitting inconsistency factor is added.

See ?priors for details on prior specification. Default prior distributions are available, but may not be appropriate for the particular setting and will raise a warning if used. No attempt is made to tailor these defaults to the data provided. Please consider appropriate prior distributions for the particular setting, accounting for the scales of outcomes and covariates, etc. The function plot_prior_posterior() may be useful in examining the influence of the chosen prior distributions on the posterior distributions, and the summary() method for nma_prior objects prints prior intervals.

Value

nma() returns a stan_nma object, except when consistency = "nodesplit" when a nma_nodesplit
or nma_nodesplit_df object is returned. nma.fit() returns a stanfit object.

Likelihoods and link functions

Currently, the following likelihoods and link functions are supported for each data type:

Data type	Likelihood	Link function
Binary	bernoulli, bernoulli2	logit, probit, cloglog
Count	binomial, binomial2	logit, probit, cloglog
Rate	poisson	log
Continuous	normal	identity,log
Ordered	ordered	<pre>logit, probit, cloglog</pre>

The bernoulli2 and binomial2 likelihoods correspond to a two-parameter Binomial likelihood for arm-based AgD, which more closely matches the underlying Poisson Binomial distribution for the summarised aggregate outcomes in a ML-NMR model than the typical (one parameter) Binomial distribution (see Phillippo et al. 2020).

When a cloglog link is used, including an offset for log follow-up time (i.e. regression = ~offset(log(time))) results in a model on the log hazard (see Dias et al. 2011).

Further details on each likelihood and link function are given by Dias et al. (2011).

Auxiliary parameters

Auxiliary parameters are only present in the following models.

Normal likelihood with IPD:

When a Normal likelihood is fitted to IPD, the auxiliary parameters are the arm-level standard deviations σ_{jk} on treatment k in study j.

Ordered multinomial likelihood:

When fitting a model to M ordered outcomes, the auxiliary parameters are the latent cutoffs between each category, $c_0 < c_1 < \ldots < c_M$. Only c_2 to c_{M-1} are estimated; we fix $c_0 = -\infty$, $c_1 = 0$, and $c_M = \infty$. When specifying priors for these latent cutoffs, we choose to specify priors on the *differences* $c_{m+1} - c_m$. Stan automatically truncates any priors so that the ordering constraints are satisfied.

References

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.

nma

sheffield.ac.uk.

Phillippo DM, Dias S, Ades AE, Belger M, Brnabic A, Schacht A, Saure D, Kadziola Z, Welton NJ (2020). "Multilevel Network Meta-Regression for population-adjusted treatment comparisons." *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, **183**(3), 1189–1210. doi: 10.1111/rssa.12579.

Examples

```
## Smoking cessation NMA
# Set up network of smoking cessation data
head(smoking)
smk_net <- set_agd_arm(smoking,</pre>
                        study = studyn,
                        trt = trtc,
                        r = r,
                        n = n,
                        trt_ref = "No intervention")
# Print details
smk_net
# Fitting a fixed effect model
smk_fit_FE <- nma(smk_net,</pre>
                  trt_effects = "fixed",
                   prior_intercept = normal(scale = 100),
                   prior_trt = normal(scale = 100))
smk_fit_FE
# Fitting a random effects model
smk_fit_RE <- nma(smk_net,</pre>
                  trt_effects = "random",
                   prior_intercept = normal(scale = 100),
                   prior_trt = normal(scale = 100),
                   prior_het = normal(scale = 5))
smk_fit_RE
# Fitting an unrelated mean effects (inconsistency) model
smk_fit_RE_UME <- nma(smk_net,</pre>
                       consistency = "ume",
                       trt_effects = "random",
                       prior_intercept = normal(scale = 100),
                       prior_trt = normal(scale = 100),
                       prior_het = normal(scale = 5))
```

```
# Fitting all possible node-splitting models
smk_fit_RE_nodesplit <- nma(smk_net,</pre>
                             consistency = "nodesplit",
                            trt_effects = "random",
                             prior_intercept = normal(scale = 100),
                             prior_trt = normal(scale = 100),
                             prior_het = normal(scale = 5))
# Summarise the node-splitting results
summary(smk_fit_RE_nodesplit)
## Plaque psoriasis ML-NMR
# Set up plaque psoriasis network combining IPD and AgD
library(dplyr)
pso_ipd <- filter(plaque_psoriasis_ipd,</pre>
                  studyc %in% c("UNCOVER-1", "UNCOVER-2", "UNCOVER-3"))
pso_agd <- filter(plaque_psoriasis_agd,</pre>
                  studyc == "FIXTURE")
head(pso_ipd)
head(pso_agd)
pso_ipd <- pso_ipd %>%
  mutate(# Variable transformations
   bsa = bsa / 100,
   prevsys = as.numeric(prevsys),
   psa = as.numeric(psa),
   weight = weight / 10,
    durnpso = durnpso / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                          trtn == 4 ~ "TNFa blocker"),
    # Check complete cases for covariates of interest
    complete = complete.cases(durnpso, prevsys, bsa, weight, psa)
  )
pso_agd <- pso_agd %>%
  mutate(
    # Variable transformations
   bsa_mean = bsa_mean / 100,
   bsa_sd = bsa_sd / 100,
   prevsys = prevsys / 100,
   psa = psa / 100,
```

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smk_fit_RE_UME

```
weight_mean = weight_mean / 10,
   weight_sd = weight_sd / 10,
   durnpso_mean = durnpso_mean / 10,
    durnpso_sd = durnpso_sd / 10,
    # Treatment classes
    trtclass = case_when(trtn == 1 ~ "Placebo",
                         trtn %in% c(2, 3, 5, 6) ~ "IL blocker",
                         trtn == 4 ~ "TNFa blocker")
 )
# Exclude small number of individuals with missing covariates
pso_ipd <- filter(pso_ipd, complete)</pre>
pso_net <- combine_network(</pre>
 set_ipd(pso_ipd,
          study = studyc,
          trt = trtc,
          r = pasi75,
          trt_class = trtclass),
  set_agd_arm(pso_agd,
              study = studyc,
              trt = trtc,
              r = pasi75_r,
              n = pasi75_n,
              trt_class = trtclass)
)
# Print network details
pso_net
# Add integration points to the network
pso_net <- add_integration(pso_net,</pre>
 durnpso = distr(qgamma, mean = durnpso_mean, sd = durnpso_sd),
 prevsys = distr(qbern, prob = prevsys),
 bsa = distr(qlogitnorm, mean = bsa_mean, sd = bsa_sd),
 weight = distr(qgamma, mean = weight_mean, sd = weight_sd),
 psa = distr(qbern, prob = psa),
 n_{int} = 1000)
# Fitting a ML-NMR model.
# Specify a regression model to include effect modifier interactions for five
# covariates, along with main (prognostic) effects. We use a probit link and
# specify that the two-parameter Binomial approximation for the aggregate-level
# likelihood should be used. We set treatment-covariate interactions to be equal
# within each class. We narrow the possible range for random initial values with
# init_r = 0.1, since probit models in particular are often hard to initialise.
# Using the QR decomposition greatly improves sampling efficiency here, as is
# often the case for regression models.
pso_fit <- nma(pso_net,</pre>
               trt_effects = "fixed",
```

link = "probit", likelihood = "bernoulli2",

```
regression = ~(durnpso + prevsys + bsa + weight + psa)*.trt,
class_interactions = "common",
prior_intercept = normal(scale = 10),
prior_trt = normal(scale = 10),
prior_reg = normal(scale = 10),
init_r = 0.1,
QR = TRUE)
```

```
pso_fit
```

nma_data-class The nma_data class

Description

The nma_data class contains the data for a NMA in a standard format, created using the functions set_ipd(), set_agd_arm(), set_agd_contrast(), or combine_network(). The sub-class mlnmr_data is created by the function add_integration(), and further contains numerical integration points for the aggregate data.

Details

Objects of class nma_data have the following components:

agd_arm data from studies with aggregate data (arm format)

agd_contrast data from studies with aggregate data (contrast format)

ipd data from studies with individual patient data

treatments treatment coding factor for entire network

classes treatment class coding factor (same length as treatments for entire network)

studies study coding factor for entire network

outcome outcome type for each data source, named list

The agd_arm, agd_contrast, and ipd components are tibbles with the following columns:

- .study study (as factor)
- .trt treatment (as factor)
- .trtclass treatment class (as factor), if specified
- .y continuous outcome
- .se standard error (continuous)
- .r event count (discrete)
- .n event count denominator (discrete, agd_arm only)
- .E time at risk (discrete)
- .surv event/censoring time, of type Surv (time-to-event)

nma_dic-class

.sample_size sample size (agd_* only)

... other columns (typically covariates) from the original data frame

Objects of class mlnmr_data additionally have components:

n_int number of numerical integration points

int_names names of covariates with numerical integration points

int_cor correlation matrix for covariates used to generate numerical integration points

The agd_arm and agd_contrast tibbles have additional list columns with prefix .int_, one for each covariate, which contain the numerical integration points nested as length-n_int vectors within each row.

See Also

print.nma_data() for the print method displaying details of the network, and plot.nma_data()
for network plots.

nma_dic-class The nma_dic class

Description

The nma_dic class contains details of the Deviance Information Criterion (DIC), produced using the dic() function.

Details

Objects of class nma_dic have the following components:

dic The DIC value

pd The effective number of parameters

resdev The total residual deviance

pointwise A list of data frames containing the pointwise contributions for the IPD and AgD.

resdev_array A 3D MCMC array [Iterations, Chains, Parameters] of posterior residual deviance samples.

See Also

dic(), print.nma_dic(), plot.nma_dic().

Description

The nma_nodesplit and nma_nodesplit_df classes contains the results from running a node-splitting model with the function nma().

Details

Objects of class nma_nodesplit inherit from the stan_nma class, and contain the results of fitting a single node-split model. They have one additional component, nodesplit, which gives the comparison that was node-split as a length 2 vector.

Objects of class nma_nodesplit_df are tibble data frames with one row for each node-split comparison and columns:

trt1, trt2 Treatments forming the comparison

model A list column containing the results of each model as a nma_nodesplit object

Optionally, there will be an additional row for the consistency model if this was fitted (e.g. by get_nodesplits(.,include_consistency = TRUE)) with trt1 and trt2 both NA.

nma_prior-class The nma_prior class

Description

The nma_prior class is used to specify prior distributions.

Details

Objects of class nma_prior have the following components:

- dist Distribution name
- fun Name of constructor function, as string (e.g. "normal")
- ... Parameters of the distribution

The distribution parameters, specified as named components in ..., match those in the constructor functions (see priors).

nma_summary-class The nma_summary class

Description

The nma_summary class contains posterior summary statistics of model parameters or other quantities of interest, and the draws used to obtain these statistics.

Details

Objects of class nma_summary have the following components:

- **summary** A data frame containing the computed summary statistics. If a regression model was fitted with effect modifier interactions with treatment, these summaries will be study-specific. In this case, the corresponding study population is indicated in a column named .study.
- sims A 3D array [Iteration, Chain, Parameter] of MCMC simulations
- **studies** (Optional) A data frame containing study information, printed along with the corresponding summary statistics if summary contains a .study column. Should have a matching .study column.

The following attributes may also be set:

xlab Label for x axis in plots, usually either "Treatment" or "Contrast".

ylab Label for y axis in plots, usually used for the scale e.g. "log Odds Ratio".

The subclass nma_rank_probs is used by the function posterior_rank_probs(), and contains posterior rank probabilities. This subclass does not have a sims component, as the rank probabilities are themselves posterior summaries of the ranks (i.e. they do not have a posterior distribution). The posterior ranks from which the rank probabilities are calculated may be obtained from posterior_ranks().

nodesplit_summary-class

The nodesplit_summary class

Description

The nodesplit_summary class contains posterior summary statistics for node-splitting models, as a result of calling summary() on a nma_nodesplit or nma_nodesplit_df object.

Details

Objects of class nodesplit_summary are tibble data frames, with one row for each node-split comparison and columns:

- trt1, trt2 Treatments forming the comparison
- summary A list column containing nma_summary objects with the posterior summaries and draws for each of the node-splitting parameters
- p_value Bayesian p-value for inconsistency
- dic A list column containing nma_dic objects, giving the model fit statistics

The parameters included in summary are:

d_net Network estimate from the corresponding consistency model, if available

d_dir Direct estimate from the node-splitting model

- d_ind Indirect estimate from the node-splitting model
- omega Inconsistency factor $\omega = d_{\rm dir} d_{\rm ind}$
- tau Heterogeneity standard deviation from the node-splitting model, if a random effects model was fitted
- tau_consistency Heterogeneity standard deviation from the corresponding consistency model, if available and if a random effects model was fitted

pairs.stan_nma Matrix of plots for a stan_nma object

Description

A pairs() method for stan_nma objects, which calls bayesplot::mcmc_pairs() on the underlying stanfit object.

Usage

S3 method for class 'stan_nma'
pairs(x, ..., pars, include = TRUE)

Arguments

x	An object of class stan_nma
	Other arguments passed to bayesplot::mcmc_pairs()
pars	Optional character vector of parameter names to include in output. If not specified, all parameters are used.
include	Logical, are parameters in pars to be included (TRUE, default) or excluded (FALSE)?

parkinsons

Value

A grid of ggplot objects produced by bayesplot::mcmc_pairs().

Examples

```
## Not run:
## Parkinson's mean off time reduction
park_net <- set_agd_arm(parkinsons,</pre>
                        study = studyn,
                        trt = trtn,
                        y = y,
                        se = se,
                        sample_size = n)
# Fitting a RE model
park_fit_RE <- nma(park_net,</pre>
                   trt_effects = "random",
                   prior_intercept = normal(scale = 100),
                   prior_trt = normal(scale = 100),
                   prior_het = half_normal(scale = 5))
# We see a small number of divergent transition errors
# These do not go away entirely when adapt_delta is increased
# Try to diagnose with a pairs plot
pairs(park_fit_RE, pars = c("mu[4]", "d[3]", "delta[4: 3]", "tau"))
# Transforming tau onto log scale
pairs(park_fit_RE, pars = c("mu[4]", "d[3]", "delta[4: 3]", "tau"),
      transformations = list(tau = "log"))
# The divergent transitions occur in the upper tail of the heterogeneity
# standard deviation. In this case, with only a small number of studies, there
# is not very much information to estimate the heterogeneity standard deviation
# and the prior distribution may be too heavy-tailed. We could consider a more
# informative prior distribution for the heterogeneity variance to aid
# estimation.
```

```
## End(Not run)
```

parkinsons

Mean off-time reduction in Parkison's disease

Description

Data frame containing the mean off-time reduction in patients given dopamine agonists as adjunct therapy in Parkinson's disease, from 7 trials comparing four active drugs and placebo (Dias et al. 2011).

Usage

parkinsons

Format

A data frame with 15 rows and 7 variables:

studyn numeric study ID

trtn numeric treatment code (placebo = 1)

y mean off-time reduction

se standard error

n sample size

diff mean difference vs. treatment in reference arm

se_diff standard error of mean difference, see details

Details

This dataset may be analysed using either an arm-based likelihood using y and se, or a contrastbased likelihood using diff and se_diff (or a combination of the two across different studies).

The contrast-based data is formatted as described in set_agd_contrast(). That is, for the chosen reference arm in each study, the mean difference diff is set to NA, and se_diff is set to the standard error se of the outcome on the reference arm.

References

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

plaque_psoriasis_ipd Plaque psoriasis data

Description

Two data frames, plaque_psoriasis_ipd and plaque_psoriasis_agd, containing (simulated) individual patient data from four studies and aggregate data from five studies (Phillippo 2019). Outcomes are binary success/failure to achieve 75%, 90%, or 100% reduction in symptoms on the Psoriasis Area and Severity Index (PASI) scale.

Usage

plaque_psoriasis_ipd

plaque_psoriasis_agd

Format

The individual patient data are contained in a data frame plaque_psoriasis_ipd with 4118 rows, one per individual, and 16 variables:

studyc study name trtc_long treatment name (long format) **trtc** treatment name trtn numeric treatment code pasi75 binary PASI 75 outcome pasi90 binary PASI 90 outcome pasi100 binary PASI 100 outcome age age (years) **bmi** body mass index (BMI) pasi_w0 PASI score at week 0 male male sex (TRUE or FALSE) **bsa** body surface area (percent) weight weight (kilograms) durnpso duration of psoriasis (years) prevsys previous systemic treatment (TRUE or FALSE) psa psoriatic arthritis (TRUE or FALSE)

The aggregate data are contained in a data frame plaque_psoriasis_agd with 15 rows, one per study arm, and 26 variables:

studyc study name trtc_long treatment name (long format) **trtc** treatment name trtn numeric treatment code pasi75_r, pasi75_n PASI 75 outcome count and denominator pasi90_r, pasi90_n PASI 75 outcome count and denominator pasi100_r, pasi100_n PASI 75 outcome count and denominator sample_size_w0 sample size at week zero age mean, age sd mean and standard deviation of age (years) bmi_mean, bmi_sd mean and standard deviation of BMI pasi_w0_mean, pasi_w0_sd mean and standard deviation of PASI score at week 0 male percentage of males bsa_mean, bsa_sd mean and standard deviation of body surface area (percent) weight_mean, weight_sd mean and standard deviation of weight (kilograms) **durnpso mean, durnpso sd** mean and standard deviation of duration of psoriasis (years) prevsys percentage of individuals with previous systemic treatment psa percentage of individuals with psoriatic arthritis

An object of class data. frame with 15 rows and 26 columns.

References

Phillippo DM (2019). *Calibration of Treatment Effects in Network Meta-Analysis using Individual Patient Data*. Ph.D. thesis, University of Bristol. Available from https://research-information.bris.ac.uk/.

plot.nma_data Network plots

Description

Create a network plot from a nma_data network object.

Usage

```
## S3 method for class 'nma_data'
plot(
    x,
    ...,
    layout,
    circular,
    weight_edges = TRUE,
    weight_nodes = FALSE,
    show_trt_class = FALSE
)
```

Arguments

х	A nma_data object to plot
	Additional arguments passed to ggraph() and on to the layout function
layout	The type of layout to create. Any layout accepted by ggraph() may be used, including all of the layout functions provided by igraph.
circular	Whether to use a circular representation. See ggraph().
weight_edges	Weight edges by the number of studies? Default is TRUE.
weight_nodes	Weight nodes by the total sample size? Default is FALSE.
show_trt_class	Colour treatment nodes by class, if trt_class is set? Default is FALSE.

Details

The default is equivalent to layout = "linear" and circular = TRUE, which places the treatment nodes on a circle in the order defined by the treatment factor variable. An alternative layout which may give good results for simple networks is "sugiyama", which attempts to minimise the number of edge crossings.

weight_nodes = TRUE requires that sample sizes have been specified for any aggregate data in the network, using the sample_size option of set_agd_*().

plot.nma_dic

Value

A ggplot object, as produced by ggraph().

Examples

```
## Stroke prevention in atrial fibrillation
# Setting up the network
af_net <- set_agd_arm(atrial_fibrillation,</pre>
                      study = studyc,
                      trt = abbreviate(trtc, minlength = 3),
                      r = r,
                      n = n,
                      trt_class = trt_class)
af_net
# Basic plot
plot(af_net)
# Turn off weighting edges by number of studies
plot(af_net, weight_edges = FALSE)
# Turn on weighting nodes by sample size
plot(af_net, weight_nodes = TRUE)
# Colour treatment nodes by class
plot(af_net, weight_nodes = TRUE, show_trt_class = TRUE)
# Output may be customised using standard ggplot commands
# For example, to display the legends below the plot:
plot(af_net, weight_nodes = TRUE, show_trt_class = TRUE) +
  ggplot2::theme(legend.position = "bottom",
                 legend.box = "vertical",
                 legend.margin = ggplot2::margin(0, 0, 0, 0),
                 legend.spacing = ggplot2::unit(0.5, "lines"))
# Choosing a different ggraph layout, hiding some legends
plot(af_net, weight_nodes = TRUE, show_trt_class = TRUE,
     layout = "star") +
  ggplot2::guides(edge_width = "none", size = "none")
```

plot.nma_dic

Plots of model fit diagnostics

Description

The plot() method for nma_dic objects produced by dic() produces several useful diagnostic plots for checking model fit and model comparison. Further detail on these plots and their interpretation is given by Dias et al. (2011).

Usage

```
## S3 method for class 'nma_dic'
plot(
    x,
    y,
    ...,
    show_uncertainty = TRUE,
    stat = "pointinterval",
    orientation = c("vertical", "horizontal", "x", "y")
)
```

Arguments

x	A nma_dic object	
У	(Optional) A second nma_dic object, to produce "dev-dev" plots for model com- parison.	
	Additional arguments passed on to other methods	
show_uncertainty		
	Logical, show uncertainty with a ggdist plot stat? Default TRUE.	
stat	Character string specifying the ggdist plot stat to use if show_uncertainty = TRUE, default "pointinterval". If y is provided, currently only "pointinterval" is supported.	
orientation	Whether the ggdist geom is drawn horizontally ("horizontal") or vertically ("vertical"). Only used for residual deviance plots, default "vertical".	

Details

When a single nma_dic object is given, a plot of the residual deviance contribution for each data point is produced. For a good fitting model, each data point is expected to have a residual deviance of 1; larger values indicate data points that are fit poorly by the model.

When two nma_dic objects are given, a "dev-dev" plot comparing the residual deviance contributions under each model is produced. Data points with residual deviance contributions lying on the line of equality are fit equally well under either model. Data points lying below the line of equality indicate better fit under the second model (y); conversely, data points lying above the line of equality indicate better fit under the first model (x). A common use case is to compare a standard consistency model (fitted using nma() with consistency = "consistency") with an unrelated mean effects (UME) inconsistency model (fitted using nma() with consistency = "ume"), to check for potential inconsistency.

See Dias et al. (2011) for further details.

Value

A ggplot object.

plot.nma_dic

References

Dias S, Welton NJ, Sutton AJ, Ades AE (2011). "NICE DSU Technical Support Document 2: A generalised linear modelling framework for pair-wise and network meta-analysis of randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Examples

```
## Smoking cessation
# Run smoking FE NMA example if not already available
if (!exists("smk_fit_FE")) example("example_smk_fe", run.donttest = TRUE)
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
# Compare DIC of FE and RE models
(smk_dic_FE <- dic(smk_fit_FE))</pre>
(smk_dic_RE <- dic(smk_fit_RE)) # substantially better fit</pre>
# Plot residual deviance contributions under RE model
plot(smk_dic_RE)
# Further customisation is possible using ggplot commands
# For example, highlighting data points with residual deviance above a certain threshold
plot(smk_dic_RE) +
 ggplot2::aes(colour = ifelse(..y.. > 1.5, "darkorange", "black")) +
 ggplot2::scale_colour_identity()
# Or by posterior probability, for example here a central probability of 0.6
# corresponds to a lower tail probability of (1 - 0.6)/2 = 0.2
plot(smk_dic_RE, .width = c(0.6, 0.95)) +
 ggplot2::aes(colour = ifelse(..ymin.. > 1, "darkorange", "black")) +
 ggplot2::scale_colour_identity()
# Check for inconsistency using UME model
# Run smoking UME NMA example if not already available
if (!exists("smk_fit_RE_UME")) example("example_smk_ume", run.donttest = TRUE)
# Compare DIC
smk_dic_RE
(smk_dic_RE_UME <- dic(smk_fit_RE_UME)) # no difference in fit</pre>
# Compare residual deviance contributions with a "dev-dev" plot
plot(smk_dic_RE, smk_dic_RE_UME)
# By default the dev-dev plot can be a little cluttered
```

```
# Hiding the credible intervals
plot(smk_dic_RE, smk_dic_RE_UME, show_uncertainty = FALSE)
# Changing transparency
plot(smk_dic_RE, smk_dic_RE_UME, point_alpha = 0.5, interval_alpha = 0.1)
```

plot.nma_summary Plots of summary results

Description

The plot method for nma_summary objects is used to produce plots of parameter estimates (when called on a stan_nma object or its summary), relative effects (when called on the output of relative_effects()), absolute predictions (when called on the output of predict.stan_nma()), posterior ranks and rank probabilities (when called on the output of posterior_ranks() or posterior_rank_probs()).

Usage

```
## S3 method for class 'nma_summary'
plot(
 х,
  . . . .
  stat = "pointinterval",
 orientation = c("horizontal", "vertical", "y", "x"),
  ref_line = NA_real_
)
## S3 method for class 'nma_parameter_summary'
plot(
 х,
  ...,
  stat = "pointinterval",
 orientation = c("horizontal", "vertical", "y", "x"),
  ref_line = NA_real_
)
## S3 method for class 'nma_rank_probs'
```

```
plot(x, ...)
```

Arguments

х	A nma_summary object
	Additional arguments passed on to the underlying ggdist plot stat, see Details
stat	Character string specifying the ggdist plot stat to use, default "pointinterval"
orientation	Whether the ggdist geom is drawn horizontally ("horizontal") or vertically ("vertical"), default "horizontal"

ref_line Numeric vector of positions for reference lines, by default no reference lines are drawn

Details

Plotting is handled by ggplot2 and the stats and geoms provided in the ggdist package. As a result, the output is very flexible. Any plotting stats provided by ggdist may be used, via the argument stat. The default uses ggdist::stat_pointinterval(), to produce medians and 95% Credible Intervals with 66% inner bands. Additional arguments in ... are passed to the ggdist stat, to customise the output. For example, to produce means and Credible Intervals, specify point_interval = "mean_qi". To produce an 80% Credible Interval with no inner band, specify .width = c(0, 0.8).

Alternative stats can be specified to produce different summaries. For example, specify stat = "[half]eye" to produce (half) eye plots, or stat = "histinterval" to produce histograms with intervals.

A full list of options and examples is found in the ggdist vignette vignette("slabinterval", package = "ggdist").

A ggplot object is returned which can be further modified through the usual ggplot2 functions to add further aesthetics, geoms, themes, etc.

Value

A ggplot object.

Examples

```
## Smoking cessation
```

```
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
```

```
# Produce relative effects
smk_releff_RE <- relative_effects(smk_fit_RE)
plot(smk_releff_RE, ref_line = 0)</pre>
```

```
# Customise plot options
plot(smk_releff_RE, ref_line = 0, stat = "halfeye")
```

```
# Further customisation is possible with ggplot commands
plot(smk_releff_RE, ref_line = 0, stat = "halfeye", slab_alpha = 0.6) +
ggplot2::aes(slab_fill = ifelse(..x.. < 0, "darkred", "grey60"))</pre>
```

```
# Produce posterior ranks
smk_rank_RE <- posterior_ranks(smk_fit_RE, lower_better = FALSE)
plot(smk_rank_RE)</pre>
```

```
# Produce rank probabilities
smk_rankprob_RE <- posterior_rank_probs(smk_fit_RE, lower_better = FALSE)
plot(smk_rankprob_RE)</pre>
```

plot.nodesplit_summary

Plots of node-splitting models

Description

Produce summary plots of node-splitting models

Usage

```
## S3 method for class 'nodesplit_summary'
plot(
    x,
    ...,
    pars = "d",
    stat = "dens_overlay",
    orientation = c("horizontal", "vertical", "y", "x"),
    ref_line = NA_real_
)
```

Arguments

х	A nodesplit_summary object.
	Additional arguments passed on to the underlying ggdist plot stat, see Details.
pars	Character vector specifying the parameters to include in the plot, choices include "d" for the direct, indirect, and network estimates of relative effects, "omega" for the inconsistency factor, and "tau" for heterogeneity standard deviation in random effects models. Default is "d".
stat	Character string specifying the ggdist plot stat to use. The default "dens_overlay" is a special case, producing an overlaid density plot.
orientation	Whether the ggdist geom is drawn horizontally ("horizontal") or vertically ("vertical"), default "horizontal".
ref_line	Numeric vector of positions for reference lines, by default no reference lines are drawn.

Details

Plotting is handled by ggplot2 and the stats and geoms provided in the ggdist package. As a result, the output is very flexible. Any plotting stats provided by ggdist may be used, via the argument stat. The default "dens_overlay" is a special exception, which uses ggplot2::geom_density(), to plot overlaid densities. Additional arguments in ... are passed to the ggdist stat, to customise the output.

Alternative stats can be specified to produce different summaries. For example, specify stat = "[half]eye" to produce (half) eye plots, or stat = "pointinterval" to produce point estimates and credible intervals.

A full list of options and examples is found in the ggdist vignette vignette("slabinterval", package = "ggdist").

A ggplot object is returned which can be further modified through the usual ggplot2 functions to add further aesthetics, geoms, themes, etc.

Value

A ggplot object.

See Also

summary.nma_nodesplit_df()

Examples

```
# Run smoking node-splitting example if not already available
if (!exists("smk_fit_RE_nodesplit")) example("example_smk_nodesplit", run.donttest = TRUE)
# Summarise the node-splitting results
(smk_nodesplit_summary <- summary(smk_fit_RE_nodesplit))
# Plot the node-splitting results
plot(smk_nodesplit_summary)
# Plot the inconsistency factors instead, change the plot stat to half-eye,
# and add a reference line at 0
plot(smk_nodesplit_summary, pars = "omega", stat = "halfeye", ref_line = 0)
# Plot a comparison of the heterogeneity under the node-split models vs.
# the consistency model
plot(smk_nodesplit_summary, pars = "tau")
```

plot_integration_error

Plot numerical integration error

Description

For ML-NMR models, plot the estimated numerical integration error over the entire posterior distribution, as the number of integration points increases. See (Phillippo et al. 2020; Phillippo 2019) for details.

Usage

```
plot_integration_error(
    x,
    ...,
    stat = "violin",
    orientation = c("vertical", "horizontal", "x", "y"),
    show_expected_rate = TRUE
)
```

Arguments

х	An object of type stan_mlnmr
	Additional arguments passed to the ggdist plot stat.
stat	Character string specifying the ggdist plot stat used to summarise the integra- tion error over the posterior. Default is "violin", which is equivalent to "eye" with some cosmetic tweaks.
orientation	Whether the ggdist geom is drawn horizontally ("horizontal") or vertically ("vertical"), default "vertical"
show_expected_rate	
	Logical, show typical convergence rate $1/N?$ Default TRUE.

Details

The total number of integration points is set by the n_int argument to add_integration(), and the intervals at which integration error is estimated are set by the int_thin argument to nma(). The typical convergence rate of Quasi-Monte Carlo integration (as used here) is 1/N, which by default is displayed on the plot output.

The integration error at each thinning interval N_{thin} is estimated for each point in the posterior distribution by subtracting the final estimate (using all n_int points) from the estimate using only the first N_{thin} points.

Value

A ggplot object.

plot_prior_posterior

Examples

```
## Plaque psoriasis ML-NMR
# Run plaque psoriasis ML-NMR example if not already available
if (!exists("pso_fit")) example("example_pso_mlnmr", run.donttest = TRUE)
```

```
# Plot numerical integration error
plot_integration_error(pso_fit)
```

plot_prior_posterior Plot prior vs posterior distribution

Description

Produce plots comparing the prior and posterior distributions of model parameters.

Usage

```
plot_prior_posterior(
    x,
    ...,
    prior = NULL,
    post_args = list(),
    prior_args = list(),
    overlay = c("prior", "posterior"),
    ref_line = NA_real_
)
```

Arguments

х	A stan_nma object
	Additional arguments passed on to methods
prior	Character vector selecting the prior and posterior distribution(s) to plot. May include "intercept", "trt", "het", "reg", or "aux", as appropriate.
post_args	List of arguments passed on to ggplot2::geom_histogram to control plot output for the posterior distribution
prior_args	List of arguments passed on to ggplot2::geom_path to control plot output for the prior distribution. Additionally, n controls the number of points the density curve is evaluated at (default 500), and p_limits controls the endpoints of the curve as quantiles (default c(.001,.999)).
overlay	String, should prior or posterior be shown on top? Default "prior".
ref_line	Numeric vector of positions for reference lines, by default no reference lines are drawn

Details

Prior distributions are displayed as lines, posterior distributions are displayed as histograms.

Value

A ggplot object.

Examples

Smoking cessation NMA
Run smoking RE NMA example if not already available

```
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
# Plot prior vs. posterior, by default all parameters are plotted
plot_prior_posterior(smk_fit_RE)
# Plot prior vs. posterior for heterogeneity SD only
plot_prior_posterior(smk_fit_RE, prior = "het")
# Customise plot
```

Description

Produce posterior treatment rankings and rank probabilities from a fitted NMA model. When a meta-regression is fitted with effect modifier interactions with treatment, these will differ by study population.

Usage

```
posterior_ranks(
    x,
    newdata = NULL,
    study = NULL,
    lower_better = TRUE,
    probs = c(0.025, 0.25, 0.5, 0.75, 0.975),
    sucra = FALSE,
    summary = TRUE
)
```

```
posterior_rank_probs(
    x,
    newdata = NULL,
    study = NULL,
    lower_better = TRUE,
    cumulative = FALSE,
    sucra = FALSE
)
```

```
.
```

Arguments

х	A stan_nma object created by nma()
newdata	Only used if a regression model is fitted. A data frame of study details, one row per study, giving the covariate values at which to produce relative effects. Column names must match variables in the regression model. If NULL, relative effects are produced for all studies in the network.
study	Column of newdata which specifies study names, otherwise studies will be la- belled by row number.
lower_better	Logical, are lower treatment effects better (TRUE; default) or higher better (FALSE)? See details.
probs	Numeric vector of quantiles of interest to present in computed summary, default c(0.025,0.25,0.5,0.75,0.975)
sucra	Logical, calculate the surface under the cumulative ranking curve (SUCRA) for each treatment? Default FALSE.
summary	Logical, calculate posterior summaries? Default TRUE.
cumulative	Logical, return cumulative rank probabilities? Default is FALSE, return posterior probabilities of each treatment having a given rank. If TRUE, cumulative posterior rank probabilities are returned for each treatment having a given rank or better.

Details

The function posterior_ranks() produces posterior rankings, which have a distribution (e.g. mean/median rank and 95% Credible Interval). The function posterior_rank_probs() produces rank probabilities, which give the posterior probabilities of being ranked first, second, etc. out of all treatments.

The argument lower_better specifies whether lower treatment effects or higher treatment effects are preferred. For example, with a negative binary outcome lower (more negative) log odds ratios are preferred, so lower_better = TRUE. Conversely, for example, if treatments aim to increase the rate of a positive outcome then lower_better = FALSE.

Value

A nma_summary object if summary = TRUE, otherwise a list containing a 3D MCMC array of samples and (for regression models) a data frame of study information.

See Also

plot.nma_summary() for plotting the ranks and rank probabilities.

Examples

```
## Smoking cessation
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
# Produce posterior ranks
smk_rank_RE <- posterior_ranks(smk_fit_RE, lower_better = FALSE)</pre>
smk_rank_RE
plot(smk_rank_RE)
# Produce rank probabilities
smk_rankprob_RE <- posterior_rank_probs(smk_fit_RE, lower_better = FALSE)</pre>
smk_rankprob_RE
plot(smk_rankprob_RE)
# Produce cumulative rank probabilities
smk_cumrankprob_RE <- posterior_rank_probs(smk_fit_RE, lower_better = FALSE,</pre>
                                            cumulative = TRUE)
smk_cumrankprob_RE
plot(smk_cumrankprob_RE)
# Further customisation is possible with ggplot commands
plot(smk_cumrankprob_RE) +
  ggplot2::facet_null() +
  ggplot2::aes(colour = Treatment)
## Plaque psoriasis ML-NMR
# Run plaque psoriasis ML-NMR example if not already available
if (!exists("pso_fit")) example("example_pso_mlnmr", run.donttest = TRUE)
# Produce population-adjusted rankings for all study populations in
# the network
# Ranks
pso_rank <- posterior_ranks(pso_fit)</pre>
pso_rank
plot(pso_rank)
# Rank probabilities
pso_rankprobs <- posterior_rank_probs(pso_fit)</pre>
pso_rankprobs
plot(pso_rankprobs)
```

predict.stan_nma

```
# Cumulative rank probabilities
pso_cumrankprobs <- posterior_rank_probs(pso_fit, cumulative = TRUE)</pre>
pso_cumrankprobs
plot(pso_cumrankprobs)
# Produce population-adjusted rankings for a different target
# population
new_agd_means <- data.frame(</pre>
  bsa = 0.6,
  prevsys = 0.1,
  psa = 0.2,
  weight = 10,
  durnpso = 3)
# Ranks
posterior_ranks(pso_fit, newdata = new_agd_means)
# Rank probabilities
posterior_rank_probs(pso_fit, newdata = new_agd_means)
# Cumulative rank probabilities
posterior_rank_probs(pso_fit, newdata = new_agd_means,
                      cumulative = TRUE)
```

predict.stan_nma Predictions of absolute effects from NMA models

Description

Obtain predictions of absolute effects from NMA models fitted with nma(). For example, if a model is fitted to binary data with a logit link, predicted outcome probabilities or log odds can be produced.

Usage

```
## S3 method for class 'stan_nma'
predict(
   object,
    ...,
   baseline = NULL,
   newdata = NULL,
   study = NULL,
   trt_ref = NULL,
   type = c("link", "response"),
   level = c("aggregate", "individual"),
   baseline_type = c("link", "response"),
   baseline_level = c("individual", "aggregate"),
   probs = c(0.025, 0.25, 0.5, 0.75, 0.975),
   predictive_distribution = FALSE,
```

predict.stan_nma

summary = TRUE
)

Arguments

object	A stan_nma object created by nma().
	Additional arguments, passed to uniroot() for regression models if baseline_level = "aggregate".
baseline	An optional distr() distribution for the baseline response (i.e. intercept), about which to produce absolute effects. If NULL, predictions are produced using the baseline response for each study in the network with IPD or arm-based AgD. For regression models, this may be a list of distr() distributions of the same length as the number of studies in newdata (possibly named by the study names,
	or otherwise in order of appearance in newdata). Use the baseline_type and baseline_level arguments to specify whether this distribution is on the response or linear predictor scale, and (for ML-NMR or models including IPD) whether this applies to an individual at the reference level of the covariates or over the entire newdata population, respectively. For example, in a model with a logit link with baseline_type = "link", this would be a distribution for the baseline log odds of an event. Use the trt_ref argument to specify which treatment this distribution applies
newdata	to. Only required if a regression model is fitted and baseline is specified. A data frame of covariate details, for which to produce predictions. Column names must match variables in the regression model.
	If level = "aggregate" this should either be a data frame with integration points as produced by add_integration() (one row per study), or a data frame with individual covariate values (one row per individual) which are summarised over.
	If level = "individual" this should be a data frame of individual covariate values, one row per individual.
	If NULL, predictions are produced for all studies with IPD and/or arm-based AgD in the network, depending on the value of level.
study	Column of newdata which specifies study names or IDs. When not specified: if newdata contains integration points produced by add_integration(), studies will be labelled sequentially by row; otherwise data will be assumed to come from a single study.
trt_ref	Treatment to which the baseline response distribution refers, if baseline is specified. By default, the baseline response distribution will refer to the network reference treatment. Coerced to character string.
type	Whether to produce predictions on the "link" scale (the default, e.g. log odds) or "response" scale (e.g. probabilities).
level	The level at which predictions are produced, either "aggregate" (the default), or "individual". If baseline is not specified, predictions are produced for all IPD studies in the network if level is "individual" or "aggregate", and for all arm-based AgD studies in the network if level is "aggregate".

baseline_type	When a baseline distribution is given, specifies whether this corresponds to the "link" scale (the default, e.g. log odds) or "response" scale (e.g. probabili- ties).		
baseline_level	When a baseline distribution is given, specifies whether this corresponds to an individual at the reference level of the covariates ("individual", the default), or from an (unadjusted) average outcome on the reference treatment in the newdata population ("aggregate"). Ignored for AgD NMA, since the only option is "aggregate" in this instance.		
probs	Numeric vector of quantiles of interest to present in computed summary, default $c(0.025, 0.25, 0.5, 0.75, 0.975)$		
predictive_distribution			
	Logical, when a random effects model has been fitted, should the predictive distribution for absolute effects in a new study be returned? Default FALSE.		
summary	Logical, calculate posterior summaries? Default TRUE.		

Value

A nma_summary object if summary = TRUE, otherwise a list containing a 3D MCMC array of samples and (for regression models) a data frame of study information.

See Also

plot.nma_summary() for plotting the predictions.

Examples

Smoking cessation

```
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
```

```
# Predicted log odds of success in each study in the network
predict(smk_fit_RE)
```

```
# Predicted probabilities of success in each study in the network
predict(smk_fit_RE, type = "response")
```

Predicted probabilities in a population with a baseline log odds of # response on No Intervention given a Normal distribution with mean -2

```
# and SD 0.13, using `baseline_type = "link"` (the default)
# Note: this is approximately equivalent to the above Beta distribution on
# the baseline probability
(smk_pred_RE2 <- predict(smk_fit_RE,</pre>
                         baseline = distr(qnorm, mean = -2, sd = 0.13),
                         type = "response"))
plot(smk_pred_RE2, ref_line = c(0, 1))
## Plaque psoriasis ML-NMR
# Run plaque psoriasis ML-NMR example if not already available
if (!exists("pso_fit")) example("example_pso_mlnmr", run.donttest = TRUE)
# Predicted probabilities of response in each study in the network
(pso_pred <- predict(pso_fit, type = "response"))</pre>
plot(pso_pred, ref_line = c(0, 1))
# Predicted probabilites of response in a new target population, with means
# and SDs or proportions given by
new_agd_int <- data.frame(</pre>
 bsa_mean = 0.6,
 bsa_sd = 0.3,
 prevsys = 0.1,
 psa = 0.2,
 weight_mean = 10,
 weight_sd = 1,
 durnpso_mean = 3,
 durnpso_sd = 1
)
# We need to add integration points to this data frame of new data
# We use the weighted mean correlation matrix computed from the IPD studies
new_agd_int <- add_integration(new_agd_int,</pre>
                           durnpso = distr(qgamma, mean = durnpso_mean, sd = durnpso_sd),
                               prevsys = distr(qbern, prob = prevsys),
                               bsa = distr(qlogitnorm, mean = bsa_mean, sd = bsa_sd),
                              weight = distr(qgamma, mean = weight_mean, sd = weight_sd),
                               psa = distr(qbern, prob = psa),
                               cor = pso_net$int_cor,
                               n_{int} = 1000)
# Predicted probabilities of achieving PASI 75 in this target population, given
# a Normal(-1.75, 0.08^2) distribution on the baseline probit-probability of
# response on Placebo (at the reference levels of the covariates), are given by
(pso_pred_new <- predict(pso_fit,</pre>
                         type = "response",
                         newdata = new_agd_int,
                         baseline = distr(qnorm, -1.75, 0.08)))
plot(pso_pred_new, ref_line = c(0, 1))
```

Description

Print details of networks stored as nma_data objects, as created by set_ipd(), set_agd_arm(), set_agd_contrast(), or combine_network().

Usage

```
## S3 method for class 'nma_data'
print(x, ..., n = 10)
```

S3 method for class 'mlnmr_data'
print(x, ..., n = 10)

Arguments

х	nma_data object
	other options (not used)
n	number of studies of each type to print

|--|--|

Description

Print details of DIC model fit statistics, computed by dic() function.

Usage

S3 method for class 'nma_dic'
print(x, digits = 1, ...)

Arguments

х	An object of class nma_dic	
digits	An integer passed to round()	
	Ignored	

Value

x is returned invisibly.

print.nma_nodesplit_df

Print nma_nodesplit_df objects

Description

Print nma_nodesplit_df objects

Usage

```
## S3 method for class 'nma_nodesplit_df'
print(x, ...)
```

```
## S3 method for class 'nma_nodesplit'
print(x, ...)
```

Arguments

Х	A nma_nodesplit_df object
	Further arguments passed to print.stanfit()

See Also

The summary method summary.nma_nodesplit_df() summarises the node-splitting results.

print.nma_summary Methods for nma_summary objects

Description

The as.data.frame(), as_tibble(), and as.tibble() methods return the posterior summary statistics in a data frame or tibble. The as.matrix() method returns a matrix of posterior draws. The as.array() method returns a 3D array [Iteration, Chain, Parameter] of posterior draws (as class mcmc_array).

Usage

```
## S3 method for class 'nma_summary'
print(x, ..., digits = 2, pars, include = TRUE)
## S3 method for class 'nma_summary'
as.data.frame(x, ...)
## S3 method for class 'nma_summary'
as.tibble(x, ...)
```

```
## S3 method for class 'nma_summary'
as_tibble(x, ...)
## S3 method for class 'nma_summary'
as.array(x, ...)
## S3 method for class 'nma_summary'
as.matrix(x, ...)
## S3 method for class 'nma_rank_probs'
as.array(x, ...)
## S3 method for class 'nma_rank_probs'
```

as.matrix(x, ...)

Arguments

х	A nma_summary object
	Additional arguments passed on to other methods
digits	Integer number of digits to display
pars	Character vector of parameters to display in the printed summary
include	Logical, are parameters named in pars included (TRUE) or excluded (FALSE)

Value

A data.frame for as.data.frame(), a tbl_df for as.tibble() and as_tibble(), a matrix for as.matrix(), and an mcmc_array for as.array().

The print() method returns x invisibly.

See Also

plot.nma_summary()

print.nodesplit_summary

Methods for nodesplit_summary objects

Description

The as.data.frame(), as_tibble(), and as.tibble() methods return the node-splitting summaries in a data frame or tibble.

Usage

```
## S3 method for class 'nodesplit_summary'
print(x, ..., digits = 2)
## S3 method for class 'nodesplit_summary'
as_tibble(x, ..., nest = FALSE)
as.tibble.nodesplit_summary(x, ..., nest = FALSE)
## S3 method for class 'nodesplit_summary'
as.data.frame(x, ...)
```

Arguments

х	A nodesplit_summary object
	Additional arguments passed on to other methods
digits	Integer number of digits to display
nest	Whether to return a nested tibble, with the full nma_summary and nma_dic objects, or to unnest their summaries, default FALSE

Value

```
A data.frame for as.data.frame(), a tbl_df for as.tibble() and as_tibble().
The print() method returns x invisibly.
```

See Also

plot.nodesplit_summary()

print.stan_nma Print stan_nma objects

Description

Print stan_nma objects

Usage

S3 method for class 'stan_nma'
print(x, ...)

Arguments

х	A stan_nma object
	Further arguments passed to print.stanfit()

priors

Description

These functions are used to specify prior distributions for the model parameters.

Usage

```
normal(location = 0, scale)
half_normal(scale)
log_normal(location, scale)
cauchy(location = 0, scale)
half_cauchy(scale)
student_t(location = 0, scale, df)
half_student_t(scale, df)
exponential(scale = 1/rate, rate = 1/scale)
```

flat()

Arguments

location	Prior location. Typically prior mean (see details).
scale	Prior scale. Typically prior standard deviation (see details).
df	Prior degrees of freedom.
rate	Prior rate.

Details

The location and scale parameters are typically the prior mean and standard deviation, with the following exceptions:

- For the Cauchy distribution location is the prior median and scale is the prior scale.
- For the log-Normal distribution, location and scale are the prior mean and standard deviation of the logarithm.

Compatibility with model parameters:

The following table summarises which prior distributions may be used with which model parameters. Essentially, priors that take only non-negative values (e.g. half-Normal) may only be used

qbern

for non-negative parameters (heterogeneity SD/variance/precision, and any auxiliary parameter). If a real-valued prior distribution is specified for a non-negative parameter, it will be truncated at 0 to be non-negative.

	Intercept prior_intercept	Treatment effects prior_trt	Heterogeneity prior
Normal normal()	Yes	Yes	Yes
<pre>half-Normal half_normal()</pre>	-	-	Yes
<pre>log-Normal log_normal()</pre>	-	-	Yes
Cauchy cauchy()	Yes	Yes	Yes
<pre>half-Cauchy half_cauchy()</pre>	-	-	Yes
<pre>Student t student_t()</pre>	Yes	Yes	Yes
<pre>half-Student t half_student_t()</pre>	-	-	Yes
Exponential exponential()	-	-	Yes
Flat flat()	Yes	Yes	Yes

The flat() prior is a special case where no prior information is added to the model, resulting in an implicit flat uniform prior distribution over the entire support for a parameter. This will be an improper prior if the parameter is unbounded, and is not generally advised. See the Stan user's guide for more details.

Value

Object of class nma_prior.

See Also

summary.nma_prior() for summarising details of prior distributions. plot_prior_posterior()
for plots comparing the prior and posterior distributions of model parameters.

qbern

The Bernoulli Distribution

Description

The quantile function qbern for a Bernoulli distribution, with success probability prob. This is equivalent to qbinom(p,1,prob).

Usage

```
qbern(p, prob, lower.tail = TRUE, log.p = FALSE)
pbern(q, prob, lower.tail = TRUE, log.p = FALSE)
dbern(x, prob, log = FALSE)
```

qgamma

Arguments

р	vector of probabilities
prob	probability of success
lower.tail, log	g.p,log
	see stats::Binomial
x,q	vector of quantiles

qgamma

The Gamma distribution

Description

We provide convenient extensions of the [dpq]gamma functions, which allow the distribution to be specified in terms of its mean and standard deviation, instead of shape and rate/scale.

Usage

```
qgamma(
 p,
  shape,
 rate = 1,
  scale = 1/rate,
  lower.tail = TRUE,
 log.p = FALSE,
 mean,
 sd
)
dgamma(x, shape, rate = 1, scale = 1/rate, log = FALSE, mean, sd)
pgamma(
  q,
  shape,
  rate = 1,
  scale = 1/rate,
  lower.tail = TRUE,
  log.p = FALSE,
 mean,
  sd
)
```

Arguments

p vector of probabilities shape, rate, scale, log, lower.tail, log.p see stats::GammaDist

relative_effects

mean, sd	mean and standard deviation, overriding shape and rate or scale if specified
x, q	vector of quantiles

qlogitnorm	The logit Normal distribution
------------	-------------------------------

Description

We provide convenient extensions of the [dpq]logitnorm functions in the package logitnorm, which allow the distribution to be specified in terms of its mean and standard deviation, instead of its logit-mean and logit-sd.

Usage

qlogitnorm(p, mu = 0, sigma = 1, ..., mean, sd)
dlogitnorm(x, mu = 0, sigma = 1, ..., mean, sd)
plogitnorm(q, mu = 0, sigma = 1, ..., mean, sd)

Arguments

p, x	vector of quantiles
mu, sigma,	see logitnorm
mean, sd	mean and standard deviation, overriding mu and sigma if specified
q	vector of probabilities

relative_effects Relative treatment effects

Description

Generate (population-average) relative treatment effects. If a ML-NMR or meta-regression model was fitted, these are specific to each study population.

```
relative_effects(
    x,
    newdata = NULL,
    study = NULL,
    all_contrasts = FALSE,
    trt_ref = NULL,
    probs = c(0.025, 0.25, 0.5, 0.75, 0.975),
    predictive_distribution = FALSE,
    summary = TRUE
)
```

x	A stan_nma object created by nma()	
newdata	Only used if a regression model is fitted. A data frame of study details, one row per study, giving the covariate values at which to produce relative effects. Column names must match variables in the regression model. If NULL, relative effects are produced for all studies in the network.	
study	Column of newdata which specifies study names, otherwise studies will be la- belled by row number.	
all_contrasts	Logical, generate estimates for all contrasts (TRUE), or just the "basic" contrasts against the network reference treatment (FALSE)? Default FALSE.	
trt_ref	Reference treatment to construct relative effects against, if all_contrasts = FALSE. By default, relative effects will be against the network reference treatment. Coerced to character string.	
probs	Numeric vector of quantiles of interest to present in computed summary, default $c(0.025, 0.25, 0.5, 0.75, 0.975)$	
predictive_distribution		
	Logical, when a random effects model has been fitted, should the predictive distribution for relative effects in a new study be returned? Default FALSE.	
summary	Logical, calculate posterior summaries? Default TRUE.	

Value

A nma_summary object if summary = TRUE, otherwise a list containing a 3D MCMC array of samples and (for regression models) a data frame of study information.

See Also

plot.nma_summary() for plotting the relative effects.

Examples

```
## Smoking cessation
```

```
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
```

```
# Produce relative effects
smk_releff_RE <- relative_effects(smk_fit_RE)
smk_releff_RE
plot(smk_releff_RE, ref_line = 0)</pre>
```

```
# Relative effects for all pairwise comparisons
relative_effects(smk_fit_RE, all_contrasts = TRUE)
```

```
# Relative effects against a different reference treatment
relative_effects(smk_fit_RE, trt_ref = "Self-help")
```

```
# Transforming to odds ratios
# We work with the array of relative effects samples
LOR_array <- as.array(smk_releff_RE)</pre>
OR_array <- exp(LOR_array)</pre>
# mcmc_array objects can be summarised to produce a nma_summary object
smk_OR_RE <- summary(OR_array)</pre>
# This can then be printed or plotted
smk_OR_RE
plot(smk_OR_RE, ref_line = 1)
## Plaque psoriasis ML-NMR
# Run plaque psoriasis ML-NMR example if not already available
if (!exists("pso_fit")) example("example_pso_mlnmr", run.donttest = TRUE)
# Produce population-adjusted relative effects for all study populations in
# the network
pso_releff <- relative_effects(pso_fit)</pre>
pso_releff
plot(pso_releff, ref_line = 0)
# Produce population-adjusted relative effects for a different target
# population
new_agd_means <- data.frame(</pre>
  bsa = 0.6,
  prevsys = 0.1,
  psa = 0.2,
  weight = 10,
  durnpso = 3)
relative_effects(pso_fit, newdata = new_agd_means)
```

```
RE_cor
```

Random effects structure

Description

Use RE_cor to generate the random effects correlation matrix, under the assumption of common heterogeneity variance (i.e. all within-study correlations are 0.5). Use which_RE to return a vector of IDs for the RE deltas (0 means no RE delta on this arm).

Usage

```
RE_cor(study, trt, contrast, type = c("reftrt", "blshift"))
which_RE(study, trt, contrast, type = c("reftrt", "blshift"))
```

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set_agd_arm

Arguments

study	A vector of study IDs (integer, character, or factor)
trt	A factor vector of treatment codes (or coercible as such), with first level indicat- ing the reference treatment
contrast	A logical vector, of the same length as study and trt, indicating whether the corresponding data are in contrast rather than arm format.
type	Character string, whether to generate RE structure under the "reference treat- ment" parameterisation, or the "baseline shift" parameterisation.

Value

For RE_cor(), a correlation matrix of dimension equal to the number of random effects deltas (excluding those that are set equal to zero).

For which_RE(), an integer vector of IDs indexing the rows and columns of the correlation matrix returned by RE_cor().

Examples

```
RE_cor(smoking$studyn, smoking$trtn, contrast = rep(FALSE, nrow(smoking)))
RE_cor(smoking$studyn, smoking$trtn, contrast = rep(FALSE, nrow(smoking)), type = "blshift")
which_RE(smoking$studyn, smoking$trtn, contrast = rep(FALSE, nrow(smoking)))
which_RE(smoking$studyn, smoking$trtn, contrast = rep(FALSE, nrow(smoking)), type = "blshift")
```

Set up ann bused aggregate date	set_agd_arm	Set up arm-based aggregate data
---------------------------------	-------------	---------------------------------

Description

Set up a network containing arm-based aggregate data (AgD), such as event counts or mean outcomes on each arm. Multiple data sources may be combined once created using combine_network().

```
set_agd_arm(
   data,
   study,
   trt,
   y = NULL,
   se = NULL,
   r = NULL,
   n = NULL,
   E = NULL,
   sample_size = NULL,
   trt_ref = NULL,
   trt_class = NULL
)
```

data	a data frame
study	column of data specifying the studies, coded using integers, strings, or factors
trt	column of data specifying treatments, coded using integers, strings, or factors
У	column of data specifying a continuous outcome
se	column of data specifying the standard error for a continuous outcome
r	column of data specifying a binary or Binomial outcome count
n	column of data specifying Binomial outcome numerator
E	column of data specifying the total time at risk for Poisson outcomes
sample_size	column of data giving the sample size in each arm. Optional, see details.
trt_ref	reference treatment for the network, as a single integer, string, or factor. If not specified, a reasonable well-connected default will be chosen (see details).
trt_class	column of data specifying treatment classes, coded using integers, strings, or factors. By default, no classes are specified.

Details

By default, trt_ref = NULL and a network reference treatment will be chosen that attempts to maximise computational efficiency and stability. If an alternative reference treatment is chosen and the model runs slowly or has low effective sample size (ESS) this may be the cause - try letting the default reference treatment be used instead. Regardless of which treatment is used as the network reference at the model fitting stage, results can be transformed afterwards: see the trt_ref argument of relative_effects() and predict.stan_nma().

The sample_size argument is optional, but when specified:

- Enables automatic centering of predictors (center = TRUE) in nma() when a regression model is given for a network combining IPD and AgD
- Enables production of study-specific relative effects, rank probabilities, etc. for studies in the network when a regression model is given
- Nodes in plot.nma_data() may be weighted by sample size

If a Binomial outcome is specified and sample_size is omitted, n will be used as the sample size by default. If a Multinomial outcome is specified and sample_size is omitted, the sample size will be determined automatically from the supplied counts by default.

All arguments specifying columns of data accept the following:

- A column name as a character string, e.g. study = "studyc"
- A bare column name, e.g. study = studyc
- dplyr::mutate() style semantics for inline variable transformations, e.g. study = paste(author, year)

Value

An object of class nma_data

set_agd_contrast

See Also

set_ipd() for individual patient data, set_agd_contrast() for contrast-based aggregate data, and combine_network() for combining several data sources in one network.

print.nma_data() for the print method displaying details of the network, and plot.nma_data()
for network plots.

Examples

set_agd_contrast Set up contrast-based aggregate data

Description

Set up a network containing contrast-based aggregate data (AgD), i.e. summaries of relative effects between treatments such as log Odds Ratios. Multiple data sources may be combined once created using combine_network().

```
set_agd_contrast(
  data,
  study,
  trt,
  y = NULL,
  se = NULL,
  sample_size = NULL,
  trt_ref = NULL,
  trt_class = NULL
)
```

data	a data frame
study	column of data specifying the studies, coded using integers, strings, or factors
trt	column of data specifying treatments, coded using integers, strings, or factors
У	column of data specifying a continuous outcome
se	column of data specifying the standard error for a continuous outcome
sample_size	column of data giving the sample size in each arm. Optional, see details.
trt_ref	reference treatment for the network, as a single integer, string, or factor. If not specified, a reasonable well-connected default will be chosen (see details).
trt_class	column of data specifying treatment classes, coded using integers, strings, or factors. By default, no classes are specified.

Details

Each study should have a single reference/baseline treatment, against which relative effects in the other arm(s) are given. For the reference arm, include a data row with continuous outcome y equal to NA. If a study has three or more arms (so two or more relative effects), set the standard error se for the reference arm data row equal to the standard error of the mean outcome on the reference arm (this determines the covariance of the relative effects, when expressed as differences in mean outcomes between arms).

All arguments specifying columns of data accept the following:

- A column name as a character string, e.g. study = "studyc"
- A bare column name, e.g. study = studyc
- dplyr::mutate() style semantics for inline variable transformations, e.g. study = paste(author, year)

By default, trt_ref = NULL and a network reference treatment will be chosen that attempts to maximise computational efficiency and stability. If an alternative reference treatment is chosen and the model runs slowly or has low effective sample size (ESS) this may be the cause - try letting the default reference treatment be used instead. Regardless of which treatment is used as the network reference at the model fitting stage, results can be transformed afterwards: see the trt_ref argument of relative_effects() and predict.stan_nma().

The sample_size argument is optional, but when specified:

- Enables automatic centering of predictors (center = TRUE) in nma() when a regression model is given for a network combining IPD and AgD
- Enables production of study-specific relative effects, rank probabilities, etc. for studies in the network when a regression model is given
- Nodes in plot.nma_data() may be weighted by sample size

Value

An object of class nma_data

set_ipd

See Also

set_ipd() for individual patient data, set_agd_arm() for arm-based aggregate data, and combine_network()
for combining several data sources in one network.

print.nma_data() for the print method displaying details of the network, and plot.nma_data()
for network plots.

Examples

```
# Set up network of Parkinson's contrast data
head(parkinsons)
```

```
park_net <- set_agd_contrast(parkinsons,</pre>
```

```
study = studyn,
trt = trtn,
y = diff,
se = se_diff,
sample_size = n)
# Print details
```

```
park_net
```

Plot network
plot(park_net)

set_ipd

Set up individual patient data

Description

Set up a network containing individual patient data (IPD). Multiple data sources may be combined once created using combine_network().

```
set_ipd(
  data,
  study,
  trt,
  y = NULL,
  r = NULL,
  E = NULL,
  trt_ref = NULL,
  trt_class = NULL
)
```

data	a data frame
study	column of data specifying the studies, coded using integers, strings, or factors
trt	column of data specifying treatments, coded using integers, strings, or factors
У	column of data specifying a continuous outcome
r	column of data specifying a binary outcome or Poisson outcome count
E	column of data specifying the total time at risk for Poisson outcomes
trt_ref	reference treatment for the network, as a single integer, string, or factor. If not specified, a reasonable well-connected default will be chosen (see details).
trt_class	column of data specifying treatment classes, coded using integers, strings, or factors. By default, no classes are specified.

Details

By default, trt_ref = NULL and a network reference treatment will be chosen that attempts to maximise computational efficiency and stability. If an alternative reference treatment is chosen and the model runs slowly or has low effective sample size (ESS) this may be the cause - try letting the default reference treatment be used instead. Regardless of which treatment is used as the network reference at the model fitting stage, results can be transformed afterwards: see the trt_ref argument of relative_effects() and predict.stan_nma().

All arguments specifying columns of data accept the following:

- A column name as a character string, e.g. study = "studyc"
- A bare column name, e.g. study = studyc
- dplyr::mutate() style semantics for inline variable transformations, e.g. study = paste(author, year)

Value

An object of class nma_data

See Also

set_agd_arm() for arm-based aggregate data, set_agd_contrast() for contrast-based aggregate
data, and combine_network() for combining several data sources in one network.

print.nma_data() for the print method displaying details of the network, and plot.nma_data()
for network plots.

Examples

smoking

```
# Print network details
pso_net
# Plot network
plot(pso_net)
# Setting a different reference treatment
set_ipd(plaque_psoriasis_ipd,
        study = studyc,
        trt = trtc,
        r = pasi75,
        trt_ref = "PBO")
```

smoking

Smoking cessation data

Description

Data frame containing the results of 24 trials of 4 smoking cessation treatments (Hasselblad 1998; Dias et al. 2011).

Usage

smoking

Format

A data frame with 50 rows and 5 variables:

studyn numeric study ID

trtn numeric treatment code

trtc treatment name

- r total number of events
- **n** total number of individuals

References

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE (2011). "NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Hasselblad V (1998). "Meta-analysis of Multitreatment Studies." *Medical Decision Making*, **18**(1), 37–43. doi: 10.1177/0272989x9801800110.

stan_nma-class

Description

The stan_nma and stan_mlnmr classes contains the results from running a model with the function nma().

Details

Objects of class stan_nma and stan_mlnmr have the following components:

network The network data from which the model was run (class nma_data for stan_nma, or class mlnmr_data for stan_mlnmr)

stanfit The stanfit object returned by calling sampling() for the model

trt_effects Whether fixed or random effects were used (character string)

consistency The consistency/inconsistency model used (character string)

regression The regression model used (formula)

class_interactions If treatment classes and a regression model are specified, the model used for interactions within each class (common, exchangeable, or independent)

xbar A named vector of values used for centering

likelihood The likelihood used (character string)

link The link function used (character string)

priors A list containing the priors used (as nma_prior objects)

The stan_mlnmr sub-class inherits from stan_nma, and differs only in the class of the network object.

statins

Statins for cholesterol lowering

Description

Data frame containing the results of 19 trials comparing statins to placebo or usual care (Dias et al. 2011). The number of deaths (all-cause mortality) are recorded. In some studies the aim was primary prevention (patients had no previous heart disease), and in others the aim was secondary prevention (patients had previous heart disease).

Usage

statins

Format

A data frame with 38 rows and 7 variables:

studyn numeric study ID

studyc study name

trtn numeric treatment code

trtc treatment name

prevention primary or secondary prevention study

r number of deaths

n sample size

References

Dias S, Sutton AJ, Welton NJ, Ades AE (2011). "NICE DSU Technical Support Document 3: Heterogeneity: subgroups, meta-regression, bias and bias-adjustment." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

summary.nma_nodesplit_df

Summarise the results of node-splitting models

Description

Posterior summaries of node-splitting models (nma_nodesplit and nma_nodesplit_df objects) can be produced using the summary() method, and plotted using the plot() method.

```
## S3 method for class 'nma_nodesplit_df'
summary(
    object,
    consistency = NULL,
    ...,
    probs = c(0.025, 0.25, 0.5, 0.75, 0.975)
)
## S3 method for class 'nma_nodesplit'
summary(
    object,
    consistency = NULL,
    ...,
    probs = c(0.025, 0.25, 0.5, 0.75, 0.975)
)
## S3 method for class 'nma_nodesplit'
```

```
plot(x, consistency = NULL, ...)
## S3 method for class 'nma_nodesplit_df'
plot(x, consistency = NULL, ...)
```

consistency	Optional, a stan_nma object for the corresponding fitted consistency model, to display the network estimates alongside the direct and indirect estimates. The fitted consistency model present in the nma_nodesplit_df object will be used if this is present (see get_nodesplits()).
	Additional arguments passed on to other methods
probs	Numeric vector of specifying quantiles of interest, default c(0.025,0.25,0.5,0.75,0.975)
x,object	A nma_nodesplit or nma_nodesplit_df object

Details

The plot() method is a shortcut for plot(summary(nma_nodesplit)). For details of plotting options, see plot.nodesplit_summary().

Value

A nodesplit_summary object

See Also

plot.nodesplit_summary()

Examples

Run smoking node-splitting example if not already available if (!exists("smk_fit_RE_nodesplit")) example("example_smk_nodesplit", run.donttest = TRUE)

Summarise the node-splitting results
summary(smk_fit_RE_nodesplit)

Plot the node-splitting results
plot(smk_fit_RE_nodesplit)

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summary.nma_prior Summary of prior distributions

Description

Print a summary of prior distribution details.

Usage

```
## S3 method for class 'nma_prior'
summary(object, ..., probs = c(0.5, 0.95), digits = 2, trunc = NULL)
```

Arguments

object	Prior distribution as a nma_prior object
	Additional arguments, not used
probs	Numeric vector of probabilities to calculate prior intervals
digits	Number of digits to display
trunc	Optional numeric vector of length 2, giving the truncation limits of the prior distribution. Useful if a real-valued prior is assigned to a positive-valued parameter, then trunc = $c(0, Inf)$ will give the correct prior intervals. By default, truncation is not used.

Value

A data frame is returned invisibly, giving the prior intervals

Examples

```
summary(normal(location = 0, scale = 1))
summary(half_normal(scale = 1))
summary(log_normal(location = -3.93, scale = 1.51))
```

```
# Truncation limits may be set, for example to restrict a prior to positive values summary(normal(location = 0.5, scale = 1), trunc = c(0, Inf))
```

```
summary.stan_nma
```

Description

Posterior summaries of model parameters in stan_nma objects may be produced using the summary() method and plotted with the plot() method. NOTE: To produce relative effects, absolute predictions, or posterior ranks, see relative_effects(), predict.stan_nma(), posterior_ranks(), posterior_rank_probs().

Usage

```
## S3 method for class 'stan_nma'
summary(object, ..., pars, include, probs = c(0.025, 0.25, 0.5, 0.75, 0.975))
## S3 method for class 'stan_nma'
plot(
    x,
    ...,
    pars,
    include,
    stat = "pointinterval",
    orientation = c("horizontal", "vertical", "y", "x"),
    ref_line = NA_real_
)
```

Arguments

•••	Additional arguments passed on to other methods
pars, include	See rstan::extract()
probs	Numeric vector of specifying quantiles of interest, default c(0.025,0.25,0.5,0.75,0.975)
x, object	A stan_nma object
stat	Character string specifying the ggdist plot stat to use, default "pointinterval"
orientation	Whether the ggdist geom is drawn horizontally ("horizontal") or vertically ("vertical"), default "horizontal"
ref_line	Numeric vector of positions for reference lines, by default no reference lines are drawn
summary	Logical, calculate posterior summaries? Default TRUE.

Details

The plot() method is a shortcut for plot(summary(stan_nma)). For details of plotting options, see plot.nma_summary().

theme_multinma

Value

A nma_summary object

See Also

plot.nma_summary(), relative_effects(), predict.stan_nma(), posterior_ranks(), posterior_rank_probs()

Examples

Smoking cessation

```
# Run smoking RE NMA example if not already available
if (!exists("smk_fit_RE")) example("example_smk_re", run.donttest = TRUE)
# Summary and plot of all model parameters
summary(smk_fit_RE)
plot(smk_fit_RE)
# Summary and plot of heterogeneity tau only
summary(smk_fit_RE, pars = "tau")
plot(smk_fit_RE, pars = "tau")
# Customising plot output
plot(smk_fit_RE,
    pars = c("d", "tau"),
    stat = "halfeye",
    ref_line = 0)
```

theme_multinma Plot theme for multinma plots

Description

A simple ggplot2 theme for plots in the multinma package.

Usage

```
theme_multinma(...)
```

Arguments

Arguments passed to ggplot2::theme_light()

Value

A ggplot2 theme

See Also

ggplot2::theme(),ggplot2::theme_set()

Examples

```
library(ggplot2)
theme_set(theme_multinma())
```

thrombolytics Thrombolytic treatments data

Description

Data frame containing the results of 50 trials of 8 thrombolytic drugs (streptokinase, SK; alteplase, t-PA; accelerated alteplase, Acc t-PA; streptokinase plus alteplase, SK+tPA; reteplase, r-PA; tenocteplase, TNK; urokinase, UK; anistreptilase, ASPAC) plus per-cutaneous transluminal coronary angioplasty (PTCA) (Boland et al. 2003; Lu and Ades 2006; Dias et al. 2011). The number of deaths in 30 or 35 days following acute myocardial infarction are recorded.

Usage

thrombolytics

Format

A data frame with 102 rows and 5 variables:

studyn numeric study ID

trtn numeric treatment code

trtc treatment name

- r total number of events
- **n** total number of individuals

References

Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mota RM, Walley T, Dickson R (2003). "Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation." *Health Technology Assessment*, **7**(15). doi: 10.3310/hta7150.

Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE (2011). "NICE DSU Technical Support Document 4: Inconsistency in networks of evidence based on randomised controlled trials." National Institute for Health and Care Excellence. https://nicedsu.sites.sheffield.ac.uk.

Lu GB, Ades AE (2006). "Assessing evidence inconsistency in mixed treatment comparisons." *Journal of the American Statistical Association*, **101**(474), 447–459. doi: 10.1198/016214505000001302.

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transfusion

Granulocyte transfusion in patients with neutropenia or neutrophil dysfunction

Description

Data frame containing the number of deaths in 6 trials comparing transfusion of granulocytes (white blood cells) to control (Stanworth et al. 2005). Previously used to demonstrate informative prior distributions for the heterogeneity variance by Turner et al. (2012).

Usage

transfusion

Format

A data frame with 12 rows and 4 variables:

studyc study name

trtc treatment name

r total number of deaths

n total number of individuals

References

Stanworth S, Massey E, Hyde C, Brunskill SJ, Navarette C, Lucas G, Marks D, Paulus U (2005). "Granulocyte transfusions for treating infections in patients with neutropenia or neutrophil dysfunction." *Cochrane Database of Systematic Reviews*. ISSN 1465-1858, doi: 10.1002/14651858.CD005339.

Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JPT (2012). "Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews." *International Journal of Epidemiology*, **41**(3), 818–827. doi: 10.1093/ije/dys041.

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