Package 'EvidenceSynthesis'

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```
Type Package
Title Synthesizing Causal Evidence in a Distributed Research Network
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Maintainer Martijn Schuemie <schuemie@ohdsi.org>
Description Routines for combining causal effect estimates and study diagnostics across multi-
      ple data sites in a distributed study, without sharing patient-level data.
      Allows for normal and non-normal approximations of the data-
      site likelihood of the effect parameter.
Depends survival,
      R (>= 3.5.0)
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      EmpiricalCalibration,
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      BeastJar,
      Cyclops (>= 3.1.0),
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 ${\it approximate }\ a\ likelihood\ function$

Description

Approximate the likelihood function using a parametric (normal, skew-normal, or custom parametric), or grid approximation. The approximation does not reveal person-level information, and can therefore be shared among data sites. When counts are low, a normal approximation might not be appropriate.

Usage

```
approximateLikelihood(
  cyclopsFit,
  parameter = 1,
  approximation = "custom",
  bounds = c(log(0.1), log(10))
)
```

Arguments

Value

A vector of parameters of the likelihood approximation.

See Also

computeConfidenceInterval, computeFixedEffectMetaAnalysis, computeBayesianMetaAnalysis

Examples

computeBayesianMetaAnalysis

Compute a Bayesian random-effects meta-analysis

Description

Compute a Bayesian meta-analysis using the Markov chain Monte Carlo (MCMC) engine BEAST. A normal and half-normal prior are used for the mu and tau parameters, respectively, with standard deviations as defined by the priorSd argument.

Usage

```
computeBayesianMetaAnalysis(
  data,
  chainLength = 1100000,
  burnIn = 1e+05,
  subSampleFrequency = 100,
  priorSd = c(2, 0.5),
  alpha = 0.05
)
```

Arguments

data A data frame containing either normal, skew-normal, custom parametric, or grid

likelihood data, with one row per database.

chainLength Number of MCMC iterations.

burnIn Number of MCMC iterations to consider as burn in.

subSampleFrequency

Subsample frequency for the MCMC.

priorSd A two-dimensional vector with the standard deviation of the prior for mu and

tau, respectively.

alpha The alpha (expected type I error) used for the credible intervals.

Value

A data frame with the point estimates and 95% credible intervals for the mu and tau parameters (the mean and standard deviation of the distribution from which the per-site effect sizes are drawn). Attributes of the data frame contain the MCMC trace and the detected approximation type.

See Also

approximateLikelihood, computeFixedEffectMetaAnalysis

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()</pre>
# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {</pre>
  cyclopsData \leftarrow Cyclops::createCyclopsData(Surv(time, y) \sim x + strata(stratumId),
                                               data = population,
                                               modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)</pre>
 approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
  return(approximation)
approximations <- lapply(populations, fitModelInDatabase)</pre>
approximations <- do.call("rbind", approximations)</pre>
# At study coordinating center, perform meta-analysis using per-site approximations:
estimate <- computeBayesianMetaAnalysis(approximations)</pre>
estimate
# (Estimates in this example will vary due to the random simulation)
```

compute Confidence Interval

Compute the point estimate and confidence interval given a likelihood function approximation

Description

Compute the point estimate and confidence interval given a likelihood function approximation

Usage

```
computeConfidenceInterval(approximation, alpha = 0.05)
```

Arguments

approximation An approximation of the likelihood function as fitted using the approximateLikelihood()

function.

alpha The alpha (expected type I error).

Details

Compute the point estimate and confidence interval given a likelihood function approximation.

Value

A data frame containing the point estimate, and upper and lower bound of the confidence interval.

Examples

```
computeFixedEffectMetaAnalysis
```

Compute a fixed-effect meta-analysis

Description

Compute a fixed-effect meta-analysis using a choice of various likelihood approximations.

Usage

```
computeFixedEffectMetaAnalysis(data, alpha = 0.05)
```

Arguments

data A data frame containing either normal, skew-normal, custom parametric, or grid

likelihood data. One row per database.

alpha The alpha (expected type I error) used for the confidence intervals.

Value

The meta-analytic estimate, expressed as the point estimate hazard ratio (rr), its 95 percent confidence interval (lb, ub), as well as the log of the point estimate (logRr), and the standard error (seLogRr).

See Also

approximate Likelihood, compute Bayesian Meta Analysis

Examples

createSimulationSettings

Create simulation settings

Description

Create an object specifying a simulation. Currently only Cox proportional hazard models are supported.

Usage

```
createSimulationSettings(
  nSites = 5,
  n = 10000,
  treatedFraction = 0.2,
  nStrata = 10,
  minBackgroundHazard = 2e-07,
  maxBackgroundHazard = 2e-05,
  hazardRatio = 2,
  randomEffectSd = 0
)
```

Arguments

n

nSites Number of database sites to simulate.

Number of subjects per site. Either a single number, or a vector of length nSites.

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treatedFraction

Fraction of subjects that is treated. Either a single number, or a vector of length

nSites.

nStrata Number of strata per site. Either a single number, or a vector of length nSites.

minBackgroundHazard

Minimum background hazard. Either a single number, or a vector of length

nSites.

maxBackgroundHazard

Maximum background hazard. Either a single number, or a vector of length

nSites.

hazardRatio Hazard ratio.

randomEffectSd Standard deviation of the log(hazardRatio). Fixed effect if equal to 0.

Value

An object of type simulationSettings, to be used in the simulatePopulations() function.

See Also

simulatePopulations

Examples

 ${\it customFunction}$

A custom function to approximate a log likelihood function

Description

A custom function to approximate a log likelihood function

Usage

```
customFunction(x, mu, sigma, gamma)
```

Arguments

x The log(hazard ratio) for which to approximate the log likelihood.

mu The position parameter.
sigma The scale parameter.
gamma The skew parameter.

Details

A custom parametric function designed to approximate the shape of the Cox log likelihood function. When gamma = 0 this function is the normal distribution.

Value

The approximate log likelihood for the given x.

Examples

```
customFunction(x = 0:3, mu = 0, sigma = 1, gamma = 0)
```

plotCovariateBalances Plot covariate balances

Description

Plots the covariate balance before and after matching for multiple data sources.

Usage

```
plotCovariateBalances(
  balances,
  labels,
  threshold = 0,
  beforeLabel = "Before matching",
  afterLabel = "After matching",
  fileName = NULL
)
```

Arguments

balances A list of covariate balance objects as created using the computeCovariateBalance()

function in the CohortMethod package. Each balance object is expected to be a data frame with at least these two columns: beforeMatchingStdDiff and

afterMatchingStdDiff.

labels A vector containing the labels for the various sources.

threshold Show a threshold value for the standardized difference.

beforeLabel Label for before matching / stratification / trimming.

Label for after matching / stratification / trimming.

fileName Name of the file where the plot should be saved, for example 'plot.png'. See the

function ggplot2::ggsave for supported file formats.

Details

Creates a plot showing the covariate balance before and after matching. Balance distributions are displayed as box plots combined with scatterplots.

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Value

A Ggplot object. Use the ggplot2::ggsave.

Examples

plotEmpiricalNulls

Plot empirical null distributions

Description

Plot the empirical null distribution for multiple data sources.

Usage

```
plotEmpiricalNulls(
  logRr,
  seLogRr,
  labels,
  xLabel = "Relative risk",
  limits = c(0.1, 10),
  showCis = TRUE,
  fileName = NULL
)
```

Arguments

logRr	A numeric vector of effect estimates for the negative controls on the log scale.
seLogRr	The standard error of the log of the effect estimates. Hint: often the standard error = $(\log(\text{lower bound 95 percent confidence interval}) - 1 \log(\text{effect estimate}))/\text{qnorm}(0.025)$.
labels	A vector containing the labels for the various sources. Should be of equal length as logRr and seLogRr.
xLabel	The label on the x-axis: the name of the effect estimate.
limits	The limits of the effect size axis.
showCis	Show the 95 percent confidence intervals on the null distribution and distribution parameter estimates?
fileName	Name of the file where the plot should be saved, for example 'plot.png'. See the function ggplot2::ggsave() for supported file formats.

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Details

Creates a plot showing the empirical null distributions. Distributions are shown as mean plus minus one standard deviation, as well as a distribution plot.

Value

A Ggplot object. Use the ggplot2::ggsave() function to save to file.

See Also

EmpiricalCalibration::fitNull, EmpiricalCalibration::fitMcmcNull

Examples

```
# Some example data:
site1 <- EmpiricalCalibration::simulateControls(n = 50, mean = 0, sd = 0.1, trueLogRr = 0)
site1$label <- "Site 1"
site2 <- EmpiricalCalibration::simulateControls(n = 50, mean = 0.1, sd = 0.2, trueLogRr = 0)
site2$label <- "Site 2"
site3 <- EmpiricalCalibration::simulateControls(n = 50, mean = 0.15, sd = 0.25, trueLogRr = 0)
site3$label <- "Site 3"
sites <- rbind(site1, site2, site3)

plotEmpiricalNulls(logRr = sites$logRr, seLogRr = sites$seLogRr, labels = sites$label)</pre>
```

plotLikelihoodFit

Plot the likelihood approximation

Description

Plot the likelihood approximation

Usage

```
plotLikelihoodFit(
  approximation,
  cyclopsFit,
  parameter = "x",
  logScale = TRUE,
  xLabel = "Hazard Ratio",
  limits = c(0.1, 10),
  fileName = NULL
)
```

Arguments

```
approximation An approximation of the likelihood function as fitted using the approximateLikelihood() function.

cyclopsFit A model fitted using the Cyclops::fitCyclopsModel() function.

The parameter in the cyclopsFit object to profile.
```

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logScale Show the y-axis on the log scale?

xLabel The title of the x-axis.

limits The limits on the x-axis.

fileName Name of the file where the plot should be saved, for example 'plot.png'. See the

function ggplot2::ggsave in the ggplot2 package for supported file formats.

Details

Plots the (log) likelihood and the approximation of the likelihood. Allows for reviewing the approximation.

Value

A Ggplot object. Use the ggplot2::ggsave function to save to file.

Examples

plotMcmcTrace

Plot MCMC trace

Description

Plot MCMC trace

Usage

```
plotMcmcTrace(
   estimate,
   showEstimate = TRUE,
   dataCutoff = 0.01,
   fileName = NULL
)
```

Arguments

An object as generated using the computeBayesianMetaAnalysis() function.

ShowEstimate Show the parameter estimates (mode) and 95 percent confidence intervals?

This fraction of the data at both tails will be removed.

Name of the file where the plot should be saved, for example 'plot.png'. See the function ggplot2::ggsave in the ggplot2 package for supported file formats.

Details

Plot the samples of the posterior distribution of the mu and tau parameters. Samples are taken using Markov-chain Monte Carlo (MCMC).

Value

A Ggplot object. Use the ggplot2::ggsave function to save to file.

See Also

computeBayesianMetaAnalysis

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()</pre>
# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {</pre>
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),</pre>
                                               data = population,
                                              modelType = "cox")
 cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)</pre>
 approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
 return(approximation)
}
approximations <- lapply(populations, fitModelInDatabase)</pre>
approximations <- do.call("rbind", approximations)</pre>
# At study coordinating center, perform meta-analysis using per-site approximations:
estimate <- computeBayesianMetaAnalysis(approximations)</pre>
plotMcmcTrace(estimate)
```

plotMetaAnalysisForest

Create a forest plot

Description

Creates a forest plot of effect size estimates, including the summary estimate.

Usage

```
plotMetaAnalysisForest(
  data,
  labels,
  estimate,
  xLabel = "Relative risk",
  summaryLabel = "Summary",
  limits = c(0.1, 10),
  alpha = 0.05,
  fileName = NULL
)
```

Arguments

data	A data frame containing either normal, skew-normal, custom parametric, or grid likelihood data. One row per database.
labels	A vector of labels for the data sources.
estimate	The meta-analytic estimate as created using either ['computeFixedEffectMeta-Analysis()] or [computeBayesianMetaAnalysis()'] function.
xLabel	The label on the x-axis: the name of the effect estimate.
summaryLabel	The label for the meta-analytic estimate.
limits	The limits of the effect size axis.
alpha	The alpha (expected type I error).
fileName	Name of the file where the plot should be saved, for example 'plot.png'. See the function ggplot2::ggsave ifor supported file formats.

Details

Creates a forest plot of effect size estimates, including a meta-analysis estimate.

Value

A Ggplot object. Use the ggplot2::ggsave function to save to file.

```
# Simulate some data for this example:
populations <- simulatePopulations()</pre>
labels <- paste("Data site", LETTERS[1:length(populations)])</pre>
\mbox{\tt\#} Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {</pre>
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),</pre>
                                               data = population,
                                               modelType = "cox")
 cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)</pre>
 approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")</pre>
  return(approximation)
approximations <- lapply(populations, fitModelInDatabase)</pre>
approximations <- do.call("rbind", approximations)</pre>
# At study coordinating center, perform meta-analysis using per-site approximations:
estimate <- computeBayesianMetaAnalysis(approximations)</pre>
plotMetaAnalysisForest(approximations, labels, estimate)
# (Estimates in this example will vary due to the random simulation)
```

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plotPerDbMcmcTrace

Plot MCMC trace for individual databases

Description

Plot MCMC trace for individual databases

Usage

```
plotPerDbMcmcTrace(
   estimate,
   showEstimate = TRUE,
   dataCutoff = 0.01,
   fileName = NULL
)
```

Arguments

An object as generated using the computeBayesianMetaAnalysis() function.

ShowEstimate Show the parameter estimates (mode) and 95 percent confidence intervals?

This fraction of the data at both tails will be removed.

Name of the file where the plot should be saved, for example 'plot.png'. See the function ggplot2::ggsave in the ggplot2 package for supported file formats.

Details

Plot the samples of the posterior distribution of the theta parameter (the estimated log hazard ratio) at each site. Samples are taken using Markov-chain Monte Carlo (MCMC).

Value

A Ggplot object. Use the ggplot2::ggsave function to save to file.

See Also

computeBayesianMetaAnalysis

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```
approximations <- do.call("rbind", approximations)

# At study coordinating center, perform meta-analysis using per-site approximations:
estimate <- computeBayesianMetaAnalysis(approximations)
plotPerDbMcmcTrace(estimate)</pre>
```

plotPerDbPosterior

Plot posterior density per database

Description

Plot posterior density per database

Usage

```
plotPerDbPosterior(
  estimate,
  showEstimate = TRUE,
  dataCutoff = 0.01,
  fileName = NULL
)
```

Arguments

An object as generated using the computeBayesianMetaAnalysis() function.

showEstimate Show the parameter estimates (mode) and 95 percent confidence intervals?

This fraction of the data at both tails will be removed.

Name of the file where the plot should be saved, for example 'plot.png'. See the function ggplot2::ggsave in the ggplot2 package for supported file formats.

Details

Plot the density of the posterior distribution of the theta parameter (the estimated log hazard ratio) at each site.

Value

A Ggplot object. Use the ggplot2::ggsave function to save to file.

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```
return(approximation)
}
approximations <- lapply(populations, fitModelInDatabase)
approximations <- do.call("rbind", approximations)

# At study coordinating center, perform meta-analysis using per-site approximations:
estimate <- computeBayesianMetaAnalysis(approximations)
plotPerDbPosterior(estimate)</pre>
```

plotPosterior

Plot posterior density

Description

Plot posterior density

Usage

```
plotPosterior(
   estimate,
   showEstimate = TRUE,
   dataCutoff = 0.01,
   fileName = NULL
)
```

Arguments

An object as generated using the computeBayesianMetaAnalysis() function.

ShowEstimate Show the parameter estimates (mode) and 95 percent confidence intervals?

This fraction of the data at both tails will be removed.

Name of the file where the plot should be saved, for example 'plot.png'. See the function ggplot2::ggsave in the ggplot2 package for supported file formats.

Details

Plot the density of the posterior distribution of the mu and tau parameters.

Value

A Ggplot object. Use the ggplot2::ggsave function to save to file.

See Also

compute Bayesian Meta Analysis

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Examples

plotPreparedPs

Plot the propensity score distribution

Description

Plot the propensity score distribution

Usage

```
plotPreparedPs(
  preparedPsPlots,
  labels,
  treatmentLabel = "Target",
  comparatorLabel = "Comparator",
  fileName = NULL
)
```

Arguments

preparedPsPlots

list of prepared propensity score data as created by the preparePsPlot() func-

labels A vector containing the labels for the various sources.

treatmentLabel A label to us for the treated cohort. comparatorLabel

A label to us for the comparator cohort.

fileName Name of the file where the plot should be saved, for example 'plot.png'. See the

function ggplot2::ggsave for supported file formats.

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Value

A ggplot object. Use the ggplot2::ggsave function to save to file in a different format.

See Also

```
preparePsPlot
```

Examples

```
# Simulate some data for this example:
treatment <- rep(0:1, each = 100)
propensityScore <- c(rnorm(100, mean = 0.4, sd = 0.25), rnorm(100, mean = 0.6, sd = 0.25))
data <- data.frame(treatment = treatment, propensityScore = propensityScore)
data <- data[data$propensityScore > 0 & data$propensityScore < 1, ]
preparedPlot <- preparePsPlot(data)

# Just reusing the same data three times for demonstration purposes:
preparedPsPlots <- list(preparedPlot, preparedPlot, preparedPlot)
labels <- c("Data site A", "Data site B", "Data site C")

plotPreparedPs(preparedPsPlots, labels)</pre>
```

preparePsPlot

Prepare to plot the propensity score distribution

Description

Prepare to plot the propensity (or preference) score distribution. It computes the distribution, so the output does not contain person-level data.

Usage

```
preparePsPlot(data, unfilteredData = NULL, scale = "preference")
```

Arguments

data A data frame with at least the two columns described below

unfilteredData To be used when computing preference scores on data from which subjects have already been removed, e.g. through trimming and/or matching. This data frame should have the same structure as data.

scale The scale of the graph. Two scales are supported: scale = 'propensity' or scale = 'preference'. The preference score scale is defined by Walker et al. (2013).

Details

The data frame should have a least the following two columns:

• **treatment** (integer): Column indicating whether the person is in the treated (1) or comparator (0) group. - **propensityScore** (numeric): Propensity score.

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Value

A data frame describing the propensity score (or preference score) distribution at 100 equally-spaced points.

References

Walker AM, Patrick AR, Lauer MS, Hornbrook MC, Marin MG, Platt R, Roger VL, Stang P, and Schneeweiss S. (2013) A tool for assessing the feasibility of comparative effectiveness research, Comparative Effective Research, 3, 11-20

See Also

plotPreparedPs

Examples

```
# Simulate some data for this example:
treatment <- rep(0:1, each = 100)
propensityScore <- c(rnorm(100, mean = 0.4, sd = 0.25), rnorm(100, mean = 0.6, sd = 0.25))
data <- data.frame(treatment = treatment, propensityScore = propensityScore)
data <- data[data$propensityScore > 0 & data$propensityScore < 1, ]
preparedPlot <- preparePsPlot(data)</pre>
```

simulatePopulations

Simulate survival data for multiple databases

Description

Simulate survival data for multiple databases

Usage

```
simulatePopulations(settings = createSimulationSettings())
```

Arguments

settings

An object of type simulationSettings, created by the createSimulationSettings() function.

Value

A object of class simulation, which is a list of populations, each a data frame with columns rowId, stratumId, x, time, and y.

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Examples

skewNormal

The skew normal function to approximate a log likelihood function

Description

The skew normal function to approximate a log likelihood function

Usage

```
skewNormal(x, mu, sigma, alpha)
```

Arguments

x The log(hazard ratio) for which to approximate the log likelihood.

mu The position parameter.
sigma The scale parameter.
alpha The skew parameter.

Details

The skew normal function. When alpha = 0 this function is the normal distribution.

Value

The approximate log likehood for the given x.

References

Azzalini, A. (2013). The Skew-Normal and Related Families. Institute of Mathematical Statistics Monographs. Cambridge University Press.

```
skewNormal(x = 0:3, mu = 0, sigma = 1, alpha = 0)
```

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