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 multiple 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.

SystemRequirements Java (>= 8)

Depends survival,
    R (>= 3.5.0)

Imports dplyr,
    ggplot2,
    ggdist,
    gridExtra,
    meta,
    EmpiricalCalibration,
    rJava,
    BeastJar,
    Cyclops (>= 3.1.0),
    HDInterval,
    coda,
    rlang,
    methods

Suggests knitr,
    rmarkdown,
    testthat,
    sn

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URL https://ohdsi.github.io/EvidenceSynthesis/, https://github.com/OHDSI/EvidenceSynthesis

BugReports https://github.com/OHDSI/EvidenceSynthesis/issues

VignetteBuilder knitr

RoxygenNote 7.2.3

Roxygen list(markdown = TRUE)

Encoding UTF-8

LazyData true

R topics documented:

---

approximateHierarchicalNormalPosterior
                        Approximate Bayesian posterior for hierarchical Normal model

---

Description

Approximate a Bayesian posterior from a set of Cyclops likelihood profiles under a hierarchical normal model using the Markov chain Monte Carlo engine BEAST.

Usage

```
approximateHierarchicalNormalPosterior(
  likelihoodProfiles,
  chainLength = 1100000,
  burnIn = 1e+05,
  subSampleFrequency = 100,
  effectPriorMean = 0,
  effectPriorSd = 0.5,
  nu0 = 1,
  sigma0 = 1,
  effectStartingValue = 0,
  precisionStartingValue = 1,
  seed = 1
)
```

Arguments

`likelihoodProfiles`
        List of grid likelihoods profiled with `Cyclops`.

`chainLength`   Number of MCMC iterations.

`burnIn`   Number of MCMC iterations to consider as burn in.

`subSampleFrequency`
        Subsample frequency for the MCMC.

`effectPriorMean`
        Prior mean for global parameter

`effectPriorSd`   Prior standard deviation for the global parameter

`nu0`   Prior "sample size" for precision (with precision ~ gamma(nu0/2, nu0*sigma0/2))

`sigma0`   Prior "variance" for precision (with precision ~ gamma(nu0/2, nu0*sigma0/2))

`effectStartingValue`
        Initial value for global & local parameter

`precisionStartingValue`
        Initial value for the precision

`seed`   Seed for the random number generator.

Value

A data frame with the point estimates and 95% credible intervals for the the global and local parameter, as well as the global precision. Attributes of the data frame contain the MCMC trace for diagnostics.

Examples

```
#TBD
```

approximateLikelihood   *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

cyclopsFit	A model fitted using the Cyclops::fitCyclopsModel() function.
parameter	The parameter in the cyclopsFit object to profile.
approximation	The type of approximation. Valid options are 'normal', 'skew normal', 'custom', 'grid', or 'adaptive grid'.
bounds	The bounds on the effect size used to fit the approximation.

Value

A vector of parameters of the likelihood approximation.

See Also

computeConfidenceInterval, computeFixedEffectMetaAnalysis, computeBayesianMetaAnalysis

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()

cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                          data = populations[[1]],
                                          modelType = "cox")
cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
approximation <- approximateLikelihood(cyclopsFit, "x")
approximation

# (Estimates in this example will vary due to the random simulation)
```

---

approximateSimplePosterior

Approximate simple Bayesian posterior

Description

Approximate a Bayesian posterior from a `Cyclops` likelihood profile and normal prior using the Markov chain Monte Carlo engine BEAST.

Usage

```
approximateSimplePosterior(
  likelihoodProfile,
  chainLength = 1100000,
  burnIn = 1e+05,
  subSampleFrequency = 100,
  priorMean = 0,
  priorSd = 0.5,
  startingValue = 0,
  seed = 1
)
```

Arguments

likelihoodProfile	Named vector containing grid likelihood data from `Cyclops`.
chainLength	Number of MCMC iterations.
burnIn	Number of MCMC iterations to consider as burn in.
subSampleFrequency	Subsample frequency for the MCMC.
priorMean	Prior mean for the regression parameter
priorSd	Prior standard deviation for the regression parameter
startingValue	Initial state for regression parameter
seed	Seed for the random number generator.

Value

A data frame with the point estimates and 95% credible intervals for the regression parameter. Attributes of the data frame contain the MCMC trace for diagnostics.

Examples

```
# Simulate some data for this example:
population <- simulatePopulations(createSimulationSettings(nSites = 1))[[1]]

# Fit a Cox regression at each data site, and approximate likelihood function:
cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                          data = population,
                                          modelType = "cox")
cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
```

```
likelihoodProfile <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "grid")

# Run MCMC
mcmcTraces <- approximateSimplePosterior(likelihoodProfile = likelihoodProfile,
                                         priorMean = 0, priorSd = 100)

# Report posterior expectation
mean(mcmcTraces$theta)

# (Estimates in this example will vary due to the random simulation)
```

---

biasCorrectionInference

Bias Correction with Inference

Description

Perform Bayesian posterior inference regarding an outcome of interest with bias correction using negative control analysis. There is an option to not perform bias correction so that un-corrected results can be obtained.

Usage

```
biasCorrectionInference(
  likelihoodProfiles,
  ncLikelihoodProfiles = NULL,
  biasDistributions = NULL,
  priorMean = 0,
  priorSd = 1,
  numsamps = 10000,
  thin = 10,
  doCorrection = TRUE,
  seed = 1,
  ...
)
```

Arguments

likelihoodProfiles
:   A list of grid profile likelihoods for the outcome of interest.

ncLikelihoodProfiles
:   Likelihood profiles for the negative control outcomes. Must be a list of lists of profile likelihoods; if there is only one analysis period, then this must be a length-1 list, with the first item as a list all outcome-wise profile likelihoods.

biasDistributions
:   Pre-saved bias distribution(s), formatted as the output from [fitBiasDistribution()](#) or [sequentialFitBiasDistribution()](#). If NULL, then ncLikelihoodProfiles must be provided.

priorMean
:   Prior mean for the effect size (log rate ratio).

priorSd
:   Prior standard deviation for the effect size (log rate ratio).

numsamps	Total number of MCMC samples needed.
thin	Thinning frequency: how many iterations before another sample is obtained?
doCorrection	Whether or not to perform bias correction; default: TRUE.
seed	Seed for the random number generator.
...	Arguments to be passed to [sequentialFitBiasDistribution()](#) to fit bias distributions if biasDistributions is NULL.

Value

A dataframe with five columns, including posterior median and mean of log RR effect size estimates, 95% credible intervals (ci95Lb and ci95Ub), posterior probability that log RR > 0 (p1), and the period or group ID (Id).

It is accompanied by the following attributes:

- samplesCorrected: all MCMC samples for the bias corrected log RR effect size estimate.

- samplesRaw: all MCMC samples for log RR effect size estimate, without bias correction.

- biasDistributions: the learned empirical bias distribution from negative control analysis.

- summaryRaw: a summary dataframe (same format as in the main result) without bias correction.

- corrected: a logical flag indicating if bias correction has been performed; = TRUE if doCorrection = TRUE.

See Also

[approximateSimplePosterior](#), [fitBiasDistribution](#)

Examples

```
# load example data
data("ncLikelihoods")
data("ooiLikelihoods")

# perform sequential analysis with bias correction, using the t model
# NOT RUN
# bbcResults = biasCorrectionInference(ooiLikelihoods,
#                                      ncLikelihoodProfiles = ncLikelihoods,
#                                      robust = TRUE,
#                                      seed = 42)

# check out analysis summary
# bbcResults
```

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,
  robust = FALSE,
  seed = 1
)
```

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.
robust	Whether or not to use a t-distribution model; default: FALSE.
seed	The seed for the random number generator.

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()

# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                            data = population,
                                            modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
  approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
  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)
estimate

# (Estimates in this example will vary due to the random simulation)
```

---

computeConfidenceInterval

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

```
# Simulate some data for this example:
populations <- simulatePopulations()

cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                          data = populations[[1]],
                                          modelType = "cox")
cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
approximation <- approximateLikelihood(cyclopsFit, "x")
computeConfidenceInterval(approximation)
```

---

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

approximateLikelihood, computeBayesianMetaAnalysis

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()

# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                            data = population,
                                            modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
 approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
  return(approximation)
```

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

# At study coordinating center, perform meta-analysis using per-site approximations:
computeFixedEffectMetaAnalysis(approximations)

# (Estimates in this example will vary due to the random simulation)
```

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

nSites	Number of database sites to simulate.
n	Number of subjects per site. Either a single number, or a vector of length nSites.
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

```
settings <- createSimulationSettings(nSites = 1, hazardRatio = 2)
populations <- simulatePopulations(settings)

# Fit a Cox regression for the simulated data site:
cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                          data = populations[[1]],
                                          modelType = "cox")
cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
coef(cyclopsFit)

# (Estimates in this example will vary due to the random simulation)
```

---

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)
```

detectApproximationType

Detect the type of likelihood approximation based on the data format

Description

Detect the type of likelihood approximation based on the data format

Usage

```
detectApproximationType(data, verbose = TRUE)
```

Arguments

data	The approximation data. Can be a single approximation, or approximations from multiple sites.
verbose	Should the detected type be communicated to the user?

Value

A character vector with one of the following values: "normal", "custom", "skew normal", "pooled", "grid", or "adaptive grid".

Examples

```
detectApproximationType(data.frame(logRr = 1, seLogRr = 0.1))
```

fitBiasDistribution

Fit Bias Distribution

Description

Learn an empirical distribution on estimation bias by simultaneously analyzing a large set of negative control outcomes by a Bayesian hierarchical model through MCMC. Analysis is based on a list of extracted likelihood profiles.

Usage

```
fitBiasDistribution(
  likelihoodProfiles,
  priorSds = c(2, 0.5),
  numsamps = 10000,
  thin = 10,
  minNCs = 5,
  robust = FALSE,
  seed = 1
)
```

Arguments

likelihoodProfiles

> A list of grid profile likelihoods regarding negative controls.

priorSds   A two-dimensional vector with the standard deviation of the prior for the average
                    bias and the sd/scale parameter, respectively.

numsamps   Total number of MCMC samples needed.

thin   Thinning frequency: how many iterations before another sample is obtained?

minNCs   Minimum number of negative controls needed to fit a bias distribution; default
                    (also recommended): 5.

robust   Whether or not to use a t-distribution model; default: FALSE.

seed   Seed for the random number generator.

Value

A dataframe with three columns and numsamps number of rows. Column mean includes MCMC
samples for the average bias, scale for the sd/scale parameter, and bias for predictive samples of
the bias.

See Also

[computeBayesianMetaAnalysis](#)

Examples

```
# load example data
data("ncLikelihoods")

# fit a bias distributions by analyzing a set of negative control outcomes
# for example, for the 5th analysis period, and using the t model
# NOT RUN
# biasDistribution = fitBiasDistribution(ncLikelihoods[[5]], robust = TRUE)
```

---

ncLikelihoods   *Example profile likelihoods for negative control outcomes*

Description

A list that contain profile likelihoods a large set of negative control outcomes. They are extracted
from a real-world observational healthcare database, with the likelihoods profiled using adaptive
grids using the Cyclops package.

Usage

```
ncLikelihoods
```

Format

An object of class list containing 12 lists, where each list includes several dataframes ith column
point and value for adaptive grid profile likelihoods.

References

Schuemie et al. (2022). Vaccine safety surveillance using routinely collected healthcare data—an empirical evaluation of epidemiological designs. Frontiers in Pharmacology.

Examples

```
data("ncLikelihoods")
ncLikEx = ncLikelihoods[["5"]][[1]]
plot(value ~ point, data = ncLikEx)
```

---

ooiLikelihoods | *Example profile likelihoods for a synthetic outcome of interest*

Description

A list that contain profile likelihoods for a synthetic outcome of interest. They are extracted from a real-world observational healthcare database, with the likelihoods profiled using adaptive grids using the `Cyclops` package.

Usage

```
ooiLikelihoods
```

Format

An objects of class `list`; the list contains 12 lists, where each list includes several dataframes with column `point` and `value` for adaptive grid profile likelihoods.

References

Schuemie et al. (2022). Vaccine safety surveillance using routinely collected healthcare data—an empirical evaluation of epidemiological designs. Frontiers in Pharmacology.

Examples

```
data("ooiLikelihoods")
ooiLikEx = ooiLikelihoods[["5"]][[1]]
plot(value ~ point, data = ooiLikEx)
```

plotBiasCorrectionInference

Plot bias correction inference

Description

Plot bias correction inference

Usage

```
plotBiasCorrectionInference(
  bbcResult,
  type = "raw",
  ids = bbcResult$Id,
  limits = c(-3, 3),
  logScale = FALSE,
  numericId = TRUE,
  fileName = NULL
)
```

Arguments

bbcResult	A (sequential) analysis object generated by the biasCorrectionInference() function.
type	The type of plot. Must be one of c("corrected", "raw", "compare").
ids	IDs of the periods/groups to plot result for; default is all IDs.
limits	The limits on log RR for plotting.
logScale	Whether or not to show bias in log-RR; default FALSE (shown in RR).
numericId	Whether or not to treat Id as a numeric variable; default: TRUE.
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

Plot empirical bias distributions learned from analyzing negative controls.

Value

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

See Also

biasCorrectionInference

Examples

```
# Perform sequential analysis using Bayesian bias correction for this example:
data("ncLikelihoods")
data("ooiLikelihoods")
# NOT RUN
# bbcSequential = biasCorrectionInference(ooiLikelihoods, ncLikelihoodProfiles = ncLikelihoods)

# Plot it
# NOT RUN
# plotBiasCorrectionInference(bbcSequential, type = "corrected")
```

---

plotBiasDistribution   *Plot bias distributions*

Description

Plot bias distributions

Usage

```
plotBiasDistribution(
  biasDist,
  limits = c(-2, 2),
  logScale = FALSE,
  numericId = TRUE,
  fileName = NULL
)
```

Arguments

biasDist	A bias distribution object generated by the fitBiasDistribution() or sequentialFitBiasDistri function.
limits	The lower and upper limits in log-RR to plot.
logScale	Whether or not to show bias in log-RR; default FALSE (shown in RR).
numericId	(For sequential or group case only) whether or not to treat Id as a numeric variable; default: TRUE.
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

Plot empirical bias distributions learned from analyzing negative controls.

Value

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

See Also

fitBiasDistribution, sequentialFitBiasDistribution

Examples

```
# Fit a bias distribution for this example:
data("ncLikelihoods")
# NOT RUN
# singleBiasDist = fitBiasDistribution(ncLikelihoods[[5]], seed = 1)

# Plot it
# NOT RUN
# plotBiasDistribution(singleBiasDist)
```

---

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.
afterLabel	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.

Value

A Ggplot object. Use the ggplot2::ggsave.

Examples

```
# Some example data:
balance1 <- data.frame(beforeMatchingStdDiff = rnorm(1000, 0.1, 0.1),
                       afterMatchingStdDiff = rnorm(1000, 0, 0.01))
balance2 <- data.frame(beforeMatchingStdDiff = rnorm(1000, 0.2, 0.1),
                       afterMatchingStdDiff = rnorm(1000, 0, 0.05))
balance3 <- data.frame(beforeMatchingStdDiff = rnorm(1000, 0, 0.1),
                       afterMatchingStdDiff = rnorm(1000, 0, 0.03))
plotCovariateBalances(balances = list(balance1, balance2, balance3),
                      labels = c("Site A", "Site B", "Site C"))
```

---

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(lower bound 95 percent confidence interval) - l og(effect estimate))/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.

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)
```

---

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

```
# Simulate a single database population:
population <- simulatePopulations(createSimulationSettings(nSites = 1))[[1]]

# Approximate the likelihood:
cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                          data = population,
                                          modelType = "cox")
cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")

plotLikelihoodFit(approximation, cyclopsFit, parameter = "x")
```

---

plotMcmcTrace   *Plot MCMC trace*

Description

Plot MCMC trace

Usage

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

Arguments

estimate	An object as generated using the [computeBayesianMetaAnalysis()](#) function.
showEstimate	Show the parameter estimates (mode) and 95 percent confidence intervals?
dataCutoff	This fraction of the data at both tails will be removed.
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

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()

# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                            data = population,
                                            modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
 approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
  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)
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,
  showLikelihood = TRUE,
  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).
showLikelihood	Show the likelihood curve for each estimate?
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.

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()
labels <- paste("Data site", LETTERS[1:length(populations)])

# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                            data = population,
                                            modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
 approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
  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)
plotMetaAnalysisForest(approximations, labels, estimate)

# (Estimates in this example will vary due to the random simulation)
```

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

estimate	An object as generated using the computeBayesianMetaAnalysis() function.
showEstimate	Show the parameter estimates (mode) and 95 percent confidence intervals?
dataCutoff	This fraction of the data at both tails will be removed.
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

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

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()

# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                            data = population,
                                            modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
 approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
  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)
plotPerDbMcmcTrace(estimate)
```

---

plotPerDbPosterior   *Plot posterior density per database*

Description

Plot posterior density per database

Usage

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

Arguments

estimate	An object as generated using the computeBayesianMetaAnalysis() function.
showEstimate	Show the parameter estimates (mode) and 95 percent confidence intervals?
dataCutoff	This fraction of the data at both tails will be removed.
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

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.

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()

# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                            data = population,
                                            modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
  approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
```

```
  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)
```

---

plotPosterior   *Plot posterior density*

Description

Plot posterior density

Usage

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

Arguments

estimate	An object as generated using the computeBayesianMetaAnalysis() function.
showEstimate	Show the parameter estimates (mode) and 95 percent confidence intervals?
dataCutoff	This fraction of the data at both tails will be removed.
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

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

computeBayesianMetaAnalysis

Examples

```
# Simulate some data for this example:
populations <- simulatePopulations()

# Fit a Cox regression at each data site, and approximate likelihood function:
fitModelInDatabase <- function(population) {
  cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                            data = population,
                                            modelType = "cox")
  cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
  approximation <- approximateLikelihood(cyclopsFit, parameter = "x", approximation = "custom")
  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)
plotPosterior(estimate)
```

---

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() function.

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.

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)
```

---

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.

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)
```

---

sequentialFitBiasDistribution

Fit Bias Distribution Sequentially or in Groups

Description

Learn empirical bias distributions sequentially or in groups; for each sequential step or analysis group, bias distributions is learned by by simultaneously analyzing a large set of negative control outcomes by a Bayesian hierarchical model through MCMC.

Usage

```
sequentialFitBiasDistribution(LikelihoodProfileList, ...)
```

Arguments

LikelihoodProfileList

> A list of lists, each of which is a set of grid profile likelihoods regarding negative controls, indexed by analysis period ID for sequential analyses or group ID for group analyses.

... Arguments passed to the [fitBiasDistribution()](fitBiasDistribution) function.

Value

A (long) dataframe with four columns. Column mean includes MCMC samples for the average bias, scale for the sd/scale parameter, bias for predictive samples of the bias, and Id for the period ID or group ID.

See Also

[fitBiasDistribution](#), [computeBayesianMetaAnalysis](#)

Examples

```
# load example data
data("ncLikelihoods")

# fit bias distributions over analysis periods
# NOT RUN
# biasDistributions = sequentialFitBiasDistribution(ncLikelihoods, seed = 42)
```

---

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.

Examples

```
settings <- createSimulationSettings(nSites = 1, hazardRatio = 2)
populations <- simulatePopulations(settings)

# Fit a Cox regression for the simulated data site:
cyclopsData <- Cyclops::createCyclopsData(Surv(time, y) ~ x + strata(stratumId),
                                          data = populations[[1]],
                                          modelType = "cox")
cyclopsFit <- Cyclops::fitCyclopsModel(cyclopsData)
coef(cyclopsFit)

# (Estimates in this example will vary due to the random simulation)
```

---

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 likelihood for the given x.

References

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

Examples

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

---

supportsJava8   *Determine if Java virtual machine supports Java*

Description

Tests Java virtual machine (JVM) java.version system property to check if version >= 8.

Usage

```
supportsJava8()
```

Value

Returns TRUE if JVM supports Java >= 8.

Examples

```
supportsJava8()
```

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