Package 'barthgn'

October 16, 2025

Type Package

Title Bartlett correction and bootstrap adjustment methods for likelihood-based inference in the hypergeometric-normal random-effects model for rare event meta-analysis

Version 1.1-1

Date 2025-10-13

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Description The hypergeometric–normal random-effects model is widely used in meta-analyses of binary outcomes, providing a direct framework for modeling arm-level data from individual studies. This approach has proven particularly effective for meta-analyses involving rare events, offering relatively accurate estimation of treatment effects. However, when the number of studies is small or when many trials include zero events, large-sample approximations may break down, and the resulting inferences can be unreliable. To address these issues, this package implements higher-order asymptotic inference for the hypergeometric–normal random-effects model using Bartlett correction and bootstrap. Two improved approaches are provided: an analytic correction method and parametric bootstrap-based approaches.

Depends R (>= 3.5.0)

Imports stats, doSNOW, doParallel, parallel, foreach, BiasedUrn

Suggests statmod, testthat

License GPL-3

Encoding UTF-8

LazyData true

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ESCI_mu_RE_boot *Confidence interval by the bootstrap test using score statistic for the hypergeometric-normal random-effects model*

Description

Constructs a confidence interval of μ by the bootstrap test using score statistic under the hypergeometric-normal random-effects model. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
ESCI_mu_RE_boot(d1, n1, d2, n2, data, cl = 0.95, B=1000, seed=11111, nCores=NULL,
 start.L=NULL, start.U=NULL)
```

Arguments

d1	Number of events in the treatment group (numeric vector).
n1	Number of participants in the treatment group (numeric vector).
d2	Number of events in the control group (numeric vector).
n2	Number of participants in the control group (numeric vector).
data	Optional data.frame containing d1, n1, d2, n2.
cl	Confidence level (default: 0.95).
B	Number of bootstrap resampling.
seed	Seed of random numbers.
nCores	Number of cores for paralell computation (default: min(10, maximum number of the computer minus 1)).
start.L	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the lower bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.
start.U	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the upper bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.

Value

Confidence intervals of the summary log OR and OR are provided.

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
ESCI_mu_RE_boot(d1, n1, d2, n2)
detach(rosiglitazonemi)
```

`EST_mu_RE_boot` *Bootstrap test using the score statistic of the hypergeometric-normal random-effects model*

Description

Performs a bootstrap test using score statistic of μ under the hypergeometric-normal random-effects model using parametric bootstrap. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
EST_mu_RE_boot(d1, n1, d2, n2, data, mu0 = 0, B=1000, seed=11111, nCores=NULL)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`mu0`	Null value for μ.
`B`	Number of bootstrap resampling.
`seed`	Seed of random numbers.
`nCores`	Number of cores for paralell computation (default: min(10, maximum number of the computer minus 1)).

Value

Results of the bootstrap test are provided.

statistic Corrected score statistic for μ.

p_value P-value (df = 1).

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
EST_mu_RE_boot(d1, n1, d2, n2, mu0=0)
detach(rosiglitazonemi)
```

`exact_hgn_RE` *Conditional inference of the hypergeometric-normal random-effects model*

Description

Fits an hypergeometric-normal random-effects model with exact conditional likelihood for meta-analysis of binary outcomes.

Usage

```
exact_hgn_RE(d1, n1, d2, n2, data)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.

Value

Results of the synthesis analysis are provided; the conditional maximum likelihood estimates of `mu` (grand mean), `sigma` (heterogeneity SD), `tau2` (heterogeneity variance), and the Wald test and confidence interval of the summary odds ratio, etc.

References

Jackson, D., Law, M., Stijnen, T., Viechtbauer, W., and White, I. R. (2018). A comparison of seven random-effects models for meta-analyses that estimate the summary odds ratio. *Statistics in Medicine.* **37**: 1059-1085.

Stijnen, T., Hamza, T. H., and Özdemir, P. (2010). Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Statistics in Medicine.* **29**: 3046-3067.

van Houwelingen, H. C., Zwinderman, K. H., and Stijnen, T. (1993). A bivariate approach to meta-analysis. *Statistics in Medicine.* **12**: 2273-2284.

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
exact_hgn_RE(d1, n1, d2, n2)
detach(rosiglitazonemi)
```

`LRCI_mu_RE` *Confidence interval by the likelihood ratio test for the hypergeometric-normal random-effects model*

Description

Constructs a confidence interval of μ by likelihood ratio test (LRT) under the hypergeometric-normal random-effects model. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
LRCI_mu_RE(d1, n1, d2, n2, data, cl = 0.95, start.L=NULL, start.U=NULL)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`cl`	Confidence level (default: 0.95).
`start.L`	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the lower bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.
`start.U`	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the upper bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.

Value

Confidence intervals of the summary log OR and OR are provided.

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRCI_mu_RE(d1, n1, d2, n2)
detach(rosiglitazonemi)
```

LRCI_mu_RE_bartbs *Confidence interval by the bootstrap-based Bartlett correction for the hypergeometric-normal random-effects model*

Description

Constructs a confidence interval of μ by the bootstrap-based Bartlett correction under the hypergeometric-normal random-effects model. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
LRCI_mu_RE_bartbs(d1, n1, d2, n2, data, cl = 0.95, B=1000, seed=11111, nCores=NULL,
 start.L=NULL, start.U=NULL)
```

Arguments

d1	Number of events in the treatment group (numeric vector).
n1	Number of participants in the treatment group (numeric vector).
d2	Number of events in the control group (numeric vector).
n2	Number of participants in the control group (numeric vector).
data	Optional data.frame containing d1, n1, d2, n2.
cl	Confidence level (default: 0.95).
B	Number of bootstrap resampling.
seed	Seed of random numbers.
nCores	Number of cores for paralell computation (default: min(10, maximum number of the computer minus 1)).
start.L	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the lower bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.
start.U	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the upper bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.

Value

Confidence intervals of the summary log OR and OR are provided.

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRCI_mu_RE_bartbs(d1, n1, d2, n2)
detach(rosiglitazonemi)
```

`LRCI_mu_RE_Bartlett` *Confidence interval by the Bartlett correction for the hypergeometric-normal random-effects model*

Description

Constructs a confidence interval of μ by the Bartlett correction under the hypergeometric-normal random-effects model. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
LRCI_mu_RE_Bartlett(d1, n1, d2, n2, data, cl = 0.95, start.L=NULL, start.U=NULL)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`cl`	Confidence level (default: 0.95).
`start.L`	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the lower bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.
`start.U`	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the upper bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.

Value

Confidence intervals of the summary log OR and OR are provided.

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRCI_mu_RE_Bartlett(d1, n1, d2, n2)
detach(rosiglitazonemi)
```

LRCI_mu_RE_boot *Confidence interval by the bootstrap test using likelihood ratio statistic for the hypergeometric-normal random-effects model*

Description

Constructs a confidence interval of μ by the bootstrap test using likelihood ratio statistic under the hypergeometric-normal random-effects model. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
LRCI_mu_RE_boot(d1, n1, d2, n2, data, cl = 0.95, B=1000, seed=11111, nCores=NULL,
 start.L=NULL, start.U=NULL)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`cl`	Confidence level (default: 0.95).
`B`	Number of bootstrap resampling.
`seed`	Seed of random numbers.
`nCores`	Number of cores for paralell computation (default: min(10, maximum number of the computer minus 1)).
`start.L`	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the lower bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.
`start.U`	When computing confidence limits via the bisection method, the initial bracket is set using the MLE and a point located 5 times the distance from the MLE to the upper bound of the Wald confidence interval. If convergence is not achieved, this argument can be used to manually adjust the initial value.

Value

Confidence intervals of the summary log OR and OR are provided.

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRCI_mu_RE_boot(d1, n1, d2, n2)
detach(rosiglitazonemi)
```

LRT_mu_RE — *Likelihood ratio test for the hypergeometric-normal random-effects model*

Description

Performs a likelihood ratio test (LRT) of μ under the hypergeometric-normal random-effects model. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fall-back grid).

Usage

```
LRT_mu_RE(d1, n1, d2, n2, data, mu0 = 0)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`mu0`	Null value for μ.

Value

Results of the LRT are provided.

statistic LRT statistic for μ.

p_value P-value (df = 1).

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRT_mu_RE(d1, n1, d2, n2, mu0 = 0)
detach(rosiglitazonemi)
```

LRT_mu_RE_bartbs — *Bootstrap-based Bartlett correction for the likelihood ratio test of the hypergeometric-normal random-effects model*

Description

Performs a likelihood ratio test (LRT) with Bartlett correction of μ under the hypergeometric-normal random-effects model using parametric bootstrap. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
LRT_mu_RE_boot(d1, n1, d2, n2, data, mu0 = 0, B=1000, seed=11111, nCores=NULL)
```

Arguments

d1	Number of events in the treatment group (numeric vector).
n1	Number of participants in the treatment group (numeric vector).
d2	Number of events in the control group (numeric vector).
n2	Number of participants in the control group (numeric vector).
data	Optional data.frame containing d1, n1, d2, n2.
mu0	Null value for μ.
B	Number of bootstrap resampling.
seed	Seed of random numbers.
nCores	Number of cores for paralell computation (default: min(10, maximum number of the computer minus 1)).

Value

Results of the LRT with bootstrap-based Bartlett correction are provided.

statistic Corrected LRT statistic for μ.

p_value P-value (df = 1).

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRT_mu_RE_boot(d1, n1, d2, n2, mu0=0)
detach(rosiglitazonemi)
```

LRT_mu_RE_Bartlett *Likelihood ratio test with Bartlett correction for the hypergeometric-normal random-effects model*

Description

Performs a likelihood ratio test (LRT) with Bartlett correction of μ under the hypergeometric-normal random-effects model. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
LRT_mu_RE_Bartlett(d1, n1, d2, n2, data, mu0 = 0)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`mu0`	Null value for μ.

Value

Results of the LRT with Bartlett correction are provided.

statistic Corrected LRT statistic for μ.

p_value P-value (df = 1).

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRT_mu_RE_Bartlett(d1, n1, d2, n2, mu0=0)
detach(rosiglitazonemi)
```

`LRT_mu_RE_boot` *Bootstrap test using the likelihood ratio statistic of the hypergeometric-normal random-effects model*

Description

Performs a bootstrap test using likelihood ratio statistic of μ under the hypergeometric-normal random-effects model using parametric bootstrap. The marginal likelihood is evaluated with deterministic Gauss–Hermite quadrature (or a safe fallback grid).

Usage

```
LRT_mu_RE_boot(d1, n1, d2, n2, data, mu0 = 0, B=1000, seed=11111, nCores=NULL)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`mu0`	Null value for μ.
`B`	Number of bootstrap resampling.
`seed`	Seed of random numbers.
`nCores`	Number of cores for paralell computation (default: min(10, maximum number of the computer minus 1)).

Value

Results of the bootstrap test are provided.

statistic Corrected LRT statistic for μ.

p_value P-value (df = 1).

Examples

```
data(rosiglitazonemi)
attach(rosiglitazonemi)
LRT_mu_RE_boot(d1, n1, d2, n2, mu0=0)
detach(rosiglitazonemi)
```

`resample_hgn` *Parametric bootstrap resampling from the hypergeometric-normal random-effects model*

Description

Performs parametric bootstrap resampling from the hypergeometric-normal random-effects model, specified the grand mean to a null value (under H_0) and the heterogeneity variance to the constrained maximum likelihood estimate under H_0.

Usage

```
resample_hgn(d1, n1, d2, n2, data, mu0, tau2_hat)
```

Arguments

`d1`	Number of events in the treatment group (numeric vector).
`n1`	Number of participants in the treatment group (numeric vector).
`d2`	Number of events in the control group (numeric vector).
`n2`	Number of participants in the control group (numeric vector).
`data`	Optional data.frame containing `d1`, `n1`, `d2`, `n2`.
`mu0`	Null value for μ.
`tau2_hat`	The constrained maximum likelihood estimate of tau2 (heterogeneity variance) under H_0.

Value

Random numbers by the parametric bootstrap are generated.

`rosiglitazone` *Meta-analysis for effect of rosiglitazone on the risk of death from cardiovascular causes*

Description

This dataset is drawn from Nissen and Wolski (2007), a meta-analysis of 42 randomized trials comparing rosiglitazone with placebo or active comparators; here we focus on the outcome "death from cardiovascular causes." The authors used fixed-effect (Peto) odds ratios because many trials had few events, time-to-event data were unavailable, and myocardial infarction and cardiovascular death were analyzed and reported separately.

- `id`: Study ID
- `d1`: Number of cardiovascular death in rosiglitazone group
- `n1`: Sample size in control group
- `d2`: Number of cardiovascular death in rosiglitazone group
- `n2`: Sample size in control group

Usage

```
data(rosiglitazone)
```

Format

A data frame with 42 rows and 6 variables

References

Nissen, S. E., and Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine.* **356**: 2457-2471.

`rosiglitazonemi` *Meta-analysis for effect of rosiglitazone on the risk of myocardial infarction*

Description

This dataset is drawn from Nissen and Wolski (2007), a meta-analysis of 42 randomized trials comparing rosiglitazone with placebo or active comparators; here we focus on the outcome "myocardial infarction." The authors used fixed-effect (Peto) odds ratios because many trials had few events, time-to-event data were unavailable, and myocardial infarction and cardiovascular death were analyzed and reported separately.

- `id`: Study ID
- `d1`: Number of myocardial infarction in rosiglitazone group
- `n1`: Sample size in control group
- `d2`: Number of myocardial infarction in rosiglitazone group
- `n2`: Sample size in control group

Usage

```
data(rosiglitazonemi)
```

Format

A data frame with 42 rows and 6 variables

References

Nissen, S. E., and Wolski, K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine.* **356**: 2457-2471.

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