Package ‘cobenrich’

July 22, 2025

Type Package

Title Using Multiple Continuous Biomarkers for Patient Enrichment in Two-Stage Clinical Designs

Version 1.0.1

Description Enrichment strategies play a critical role in modern clinical trial design, especially as precision medicine advances the focus on patient-specific efficacy. Recent developments in enrichment design have introduced biomarker randomness and accounted for the correlation structure between treatment effect and biomarker, resulting in a two-stage threshold enrichment design. We propose novel two-stage enrichment designs capable of handling two or more continuous biomarkers.
See Zhang, F. and Gou, J. (2025). Using multiple biomarkers for patient enrichment in two-stage clinical designs. Technical Report.

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Encoding UTF-8

Depends R (>= 4.2.0)

Imports tmvtnorm (>= 1.2), stats (>= 4.0.0)

RoxygenNote 7.3.2

NeedsCompilation no

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Repository CRAN

Date/Publication 2025-04-15 19:30:12 UTC

Contents

`avetrteff2` *Compute the average subpopulation treatment effect and the standardized average subpopulation treatment effect when two biomarkers are involved*

Description

Compute the average subpopulation treatment effect and the standardized average subpopulation treatment effect when two biomarkers are involved

Usage

```
avetrteff2(z1z2, kappa, rhovec, sigma, muminusmu0)
```

Arguments

`z1z2`	a numeric vector of two numbers that are standardized biomarker values
`kappa`	a number of the correlation coefficient between two biomarkers
`rhovec`	a numeric vector of two correlation coefficients between the output and two biomarkers
`sigma`	a number of the standard deviation of outcome
`muminusmu0`	a number of the difference between the mean of outcome and the minimal clinically important treatment effect

Value

a list of three numbers: `delta` is the average subpopulation treatment effect, `lambda` is the standardized average subpopulation treatment effect, and `cVar` is the variance with respect to the truncated distribution with specified cutoff values

Author(s)

Jiangtao Gou

References

Zhang, F. and Gou, J. (2025). Using multiple biomarkers for patient enrichment in two-stage clinical designs. Technical Report.

Examples

```
x1x2 <- c(2, 1)
nu1nu2 <- c(0,0)
tau1tau2 <- c(1,1)
z1z2 <- (x1x2 - nu1nu2)/tau1tau2
muminusmu0 <- 1.8
kappa <- 0.1
```

```
sigma <- 1
rhovec <- c(0.1, 0.2)
avetrteff2(z1z2, kappa, rhovec, sigma, muminusmu0)
```

`findATE2` *Find the cutoff values of biomarkers based on the average subpopulation treatment effect*

Description

Find the cutoff values of biomarkers based on the average subpopulation treatment effect

Usage

```
findATE2(z2interval, kkk, muminusmu0, kappa, rhovec, sigma, cDel)
```

Arguments

`z2interval`	a numeric vector of two values, including the lower and upper limits of the initial interval for z2
`kkk`	the researchers' weighting preference between the two biomarkers
`muminusmu0`	a number of the difference between the mean of outcome and the minimal clinically important treatment effect
`kappa`	a number of the correlation coefficient between two biomarkers
`rhovec`	a numeric vector of two correlation coefficients between the output and two biomarkers
`sigma`	a number of the standard deviation of outcome
`cDel`	the desired average subpopulation treatment effect

Value

a numeric vector of two values which are the cutoff values for z1 and z2

Author(s)

Jiangtao Gou

Fengqing Zhang

References

Zhang, F. and Gou, J. (2025). Using multiple biomarkers for patient enrichment in two-stage clinical designs. Technical Report.

Examples

```
z2interval <- c(-5, 5)
kkk <- 1
muminusmu0 <- 1.8
kappa <- 0.1
rhovec <- c(0.1, 0.2)
sigma <- 1
cDel <- 2.5
findATE2(z2interval, kkk, muminusmu0, kappa, rhovec, sigma, cDel)
```

`findSATE2` *Find the cutoff values of biomarkers based on the standardized average subpopulation treatment effect*

Description

Find the cutoff values of biomarkers based on the standardized average subpopulation treatment effect

Usage

```
findSATE2(z2interval, kkk, muminusmu0, kappa, rhovec, sigma, cLam)
```

Arguments

`z2interval`	a numeric vector of two values, including the lower and upper limits of the initial interval for z2
`kkk`	the researchers' weighting preference between the two biomarkers
`muminusmu0`	a number of the difference between the mean of outcome and the minimal clinically important treatment effect
`kappa`	a number of the correlation coefficient between two biomarkers
`rhovec`	a numeric vector of two correlation coefficients between the output and two biomarkers
`sigma`	a number of the standard deviation of outcome
`cLam`	the desired standardized average subpopulation treatment effect

Value

a numeric vector of two values which are the cutoff values for z1 and z2

Author(s)

Jiangtao Gou

Fengqing Zhang

References

Zhang, F. and Gou, J. (2025). Using multiple biomarkers for patient enrichment in two-stage clinical designs. Technical Report.

Examples

```
z2interval <- c(-4, 4)
kkk <- 1
muminusmu0 <- 1.8
kappa <- 0.1
rhovec <- c(0.1, 0.2)
sigma <- 1
cLam <- 2.5
findSATE2(z2interval, kkk, muminusmu0, kappa, rhovec, sigma, cLam)
```

`targetDel` *Find the difference between the average subpopulation treatment effect and the desired one*

Description

Find the difference between the average subpopulation treatment effect and the desired one

Usage

```
targetDel(z2, kkk, muminusmu0, kappa, rhovec, sigma, cDel)
```

Arguments

`z2`	the standardized biomarker value of the second biomarker
`kkk`	the researchers' weighting preference between the two biomarkers
`muminusmu0`	a number of the difference between the mean of outcome and the minimal clinically important treatment effect
`kappa`	a number of the correlation coefficient between two biomarkers
`rhovec`	a numeric vector of two correlation coefficients between the output and two biomarkers
`sigma`	a number of the standard deviation of outcome
`cDel`	the desired average subpopulation treatment effect

Value

the difference between the average subpopulation treatment effect and the desired one

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`targetLam` *Find the difference between the standardized average subpopulation treatment effect and the desired one*

Description

Find the difference between the standardized average subpopulation treatment effect and the desired one

Usage

```
targetLam(z2, kkk, muminusmu0, kappa, rhovec, sigma, cLam)
```

Arguments

`z2`	the standardized biomarker value of the second biomarker
`kkk`	the researchers' weighting preference between the two biomarkers
`muminusmu0`	a number of the difference between the mean of outcome and the minimal clinically important treatment effect
`kappa`	a number of the correlation coefficient between two biomarkers
`rhovec`	a numeric vector of two correlation coefficients between the output and two biomarkers
`sigma`	a number of the standard deviation of outcome
`cLam`	the desired standardized average subpopulation treatment effect

Value

the difference between the standardized average subpopulation treatment effect and the desired one

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