Package ‘factorial2x2’

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Type Package

Title Design and Analysis of a 2x2 Factorial Trial

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Description Used for the design and analysis of a 2x2 factorial trial for a time-to-event endpoint. It performs power calculations and significance testing as well as providing estimates of the relevant hazard ratios and the corresponding 95% confidence intervals. Important reference papers include
Slud EV. (1994) <`https://www.ncbi.nlm.nih.gov/pubmed/8086609`>
Lin DY, Gong J, Gallo P, Bunn PH, Couper D. (2016) <DOI:10.1111/biom.12507>
Leifer ES, Troendle JF, Kolecki A, Follmann DA. (2020)
<`https://github.com/EricSLeifer/factorial2x2/blob/master/Leifer%20et%20al.%20paper.pdf`>.

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`cor2x2` *Hazard ratios and correlations for the 2x2 statistics*

Description

Computes the hazard ratios, confidence intervals, p-values, and correlations for the overall A, simple A, and simple AB logrank statistics.

Usage

```
cor2x2(time, event, indA, indB, covmat)
```

Arguments

`time`	follow-up times
`event`	event indicators (0/1)
`indA`	treatment A indicators (0/1)
`indB`	treatment B indicators (0/1)
`covmat`	matrix of covariates; one row per subject. NOTE!! Factor variables must use 0/1 indicator variables

Details

This function computes (i) correlation between the overall A test and the simple A test (ii) correlation between the overall A test and the simple AB test (iii) correaltion between the simple A and simple AB test. The correlation estimates are derived in Lin, Gong, Gallo, et al. (Biometrics 2016).

Value

`loghrA`	overall A log hazard ratio
`seA`	standard error of the overall A log hazard ratio
`hrA`	overall A hazard ratio
`ciA`	95% confidence interval for overall A hazard ratio

`pvalA`	two-sided p-value for overall A hazard ratio
`loghra`	simple A log hazard ratio
`sea`	standard error of the simple A log hazard ratio
`hra`	simple A hazard ratio
`cia`	95% confidence interval for simple A hazard ratio
`pvala`	two-sided p-value for simple A hazard ratio
`loghrab`	simple AB log hazard ratio
`seab`	standard error of the simple AB log hazard ratio
`hrab`	simple AB hazard ratio
`ciab`	95% confidence interval for simple AB hazard ratio
`pvalab`	two-sided p-value for simple AB hazard ratio
`corAa`	correlation between the overall A and simple A test statistics
`corAab`	correlation between the overall A and simple AB test statistics
`coraab`	correlation between the simple A and simple AB test statistics

References

Lin, D.Y., Glong , J., Gallo, P., Bunn, P.H., Couper, D. Simultaneous inference on treatment effects in survival studies with factorial designs. Biometrics, 2016; 72: 1078-1085.

Examples

```
# First load the simulated data variables. The "simdat" file is
# a 100-by-9 matrix which is loaded with the factorial2x2 package.
time <- simdat[, "time"]
event <- simdat[, "event"]
indA <- simdat[, "indA"]
indB <- simdat[, "indB"]
covmat <- simdat[, 6:10]

cor2x2(time, event, indA, indB, covmat)
# $loghrA
# [1] 0.05613844

# $seA
# [1] 0.4531521

# $hrA
# [1] 1.057744

# $ciA
# [1] 0.4351608 2.5710556

# $pvalA
# [1] 0.9014069

# $loghra
```

```
# [1] 0.1987329

# $sea
# [1] 0.6805458

# $hra
# [1] 1.219856

# $cia
# [1] 0.3213781 4.6302116

# $pvala
# [1] 0.7702714

# $loghrab
# [1] 0.2864932

# $seab
# [1] 0.6762458

# $hrab
# [1] 1.331749

# $ciab
# [1] 0.3538265 5.0125010

# $pvalab
# [1] 0.6718193

# $corAa
# [1] 0.6123399

# $corAab
# [1] 0.5675396

# $coraab
# [1] 0.4642737
```

`crit2x2` *Critical values for the Equal Allocation 3, Proportional Allocation 2, and Equal Allocation 2 procedures*

Description

Computes the critical values for null hypotheses rejection and corresponding nominal two-sided significance levels for the Equal Allocation 3, Proportional Allocation 2, and Equal Allocation 2 procedures

Usage

```
crit2x2(
  corAa,
  corAab,
  coraab,
  dig = 2,
  alpha = 0.05,
  niter = 5,
  abseps = 1e-05,
  tol = 1e-04
)
```

Arguments

`corAa`	correlation between the overall A and simple A log hazard ratio estimates
`corAab`	correlation between the overall A and simple AB log hazard ratio estimates
`coraab`	correlation between the simple A and simple AB log hazard ratio estimates
`dig`	number of decimal places to which we `roundDown` the critical value
`alpha`	two-sided familywise error level to control
`niter`	number of times we compute the critical values to average out the randomness from the `pmvnorm` function call
`abseps`	`abseps` setting in the `pmvnorm` function call
`tol`	`tol` setting in the uniroot function call

Details

This function computes the Dunnett-corrected critical values based on the asymptotic correlations of the overall A, simple A, and simple AB logrank statistics as described in Leifer, Troendle, et al. (2020) and are derived in Lin, Gong, et al. (2016) and Slud (1994). `pmvnorm` uses a random seed in its algorithm. To smooth out the randomness, `pmvnorm` is called `niter` times. The `roundDown` function is used in conjunction with the `dig` argument to insure that any rounding of the (negative) critical values will be done conservatively to control the familywise type I error at the desired level.

Value

`critEA3`	Equal Allocation 3 procedure's critical value for all three test statistics
`sigEA3`	two-sided nominal significance level corresponding to `critEA3`
`critPA2A`	Proportional Allocation 2 procedure's critical value for the overall A statistic
`sigPA2A`	two-sided nominal significance level corresponding to `critPA2A`
`critPA2ab`	Proportional Allocation 2 procedure's critical value for the simple AB statistic
`sigPA2ab`	two-sided nominal significance level corresponding to `critPA2ab`
`critEA2`	Equal Allocation 2 procedure's critical value for the simple A and AB statistics
`sigEA2`	two-sided nominal significance level corresponding to `critEA2`

References

Leifer, E.S., Troendle, J.F., Kolecki, A., Follmann, D. Joint testing of overall and simple effect for the two-by-two factorial design. 2020. Submitted.

Lin, D-Y., Gong, J., Gallo, P., et al. Simultaneous inference on treatment effects in survival studies with factorial designs. Biometrics. 2016; 72: 1078-1085.

Slud, E.V. Analysis of factorial survival experiments. Biometrics. 1994; 50: 25-38.

See Also

`roundDown`. `eventProb`, `lgrkPower`, `strLgrkPower`, `pmvnorm`

Examples

```
# Example 1:  Compute the nominal significance levels for rejection using
# the asymptotic correlations derived in Slud (1994)
corAa  <- 1/sqrt(2)
corAab <- 1/sqrt(2)
coraab <- 1/2

crit2x2(corAa, corAab, coraab, dig = 2, alpha = 0.05, niter = 5)
# critEA3
# [1] -2.32

# sigEA3
# [1] 0.02034088

# critPA2A
# [1] -2.13

# sigPA2A
# [1] 0.03317161

# critPA2ab
# [1] -2.24

# sigPA2ab
# [1] 0.02509092

# critEA2
# [1] -2.22

# sigEA2
# [1] 0.02641877

# Example 2:  Compute the nominal critical values and significance levels for rejection
# using the estimated correlations for simdat.
corAa  <- 0.6123399
corAab <- 0.5675396
coraab <- 0.4642737

crit2x2(corAa, corAab, coraab, dig = 2, alpha = 0.05, niter = 5)
```

```
# $critEA3
# [1] -2.34

# $critPA2A
# [1] -2.13

# $sigPA2A
# [1] 0.03317161

# $critPA2ab
# [1] -2.3

# $sigPA2ab
# [1] 0.02144822
#
# $sigEA3
# [1] 0.01928374

# $critEA2
# [1] -2.22

# $sigEA2
# [1] 0.02641877
```

`eventProb` *Calculate event probabilities*

Description

Calculates the event probabilities for each of the four factorial groups C, A, B, AB. The time unit is in years, but of course, any time unit could be used. Average event probabilities across various combinations of the groups are also calculated. The event times are assumed to be exponentially distributed. The censoring times are assumed to be uniformly distributed and indepedent of the event times.

Usage

```
eventProb(rateC, hrA, hrB, hrAB, mincens, maxcens)
```

Arguments

`rateC`	group C one year event rate
`hrA`	group A to group C hazard ratio
`hrB`	group B to group C hazard ratio
`hrAB`	group AB to group C hazard ratio
`mincens`	minimum censoring time
`maxcens`	maximum censoring time

Value

`hazC`	group C's exponential hazard rate
`probC`	event probability of the C group
`probA`	event probability of the A group
`probB`	event probability of the B group
`probAB`	event probability of the AB group
`avgprob`	average event probability across all factorial groups
`probA_C`	average event probablity of the A and C groups
`probAB_C`	average event probablity of the AB and C groups

Examples

```
# Corresponds to scenario 5 of Table 2 from Leifer, Troendle, et al. (2019).
rateC <- 0.0445
hrA <- 0.80
hrB <- 0.80
hrAB <- 0.72
mincens <- 4.0
maxcens <- 8.4
eventProb(rateC, hrA, hrB, hrAB, mincens, maxcens)
# hazC
# [1] 0.04552052

# probC
# [1] 0.2446365

# probA
# [1] 0.201254

# probB
# [1] 0.201254

# probAB
# [1] 0.1831806

# avgprob
# [1] 0.2075813

# probAB_C
# [1] 0.2139086
```

`fac2x2analyze` *Significance testing for the Proportional Allocation 2, Equal Allocation 3, Equal Allocation 2 procedures*

Description

Performs significance testing for the Proportional Allocation 2, Equal Allocation 3, Equal Allocation 2 procedures. Also reports the hazard ratios, 95% confidence intervals, p-values, nominal significance levels, and correlations for the overall and simple test statistics.

Usage

```
fac2x2analyze(time, event, indA, indB, covmat, alpha, dig = 2, niter = 5)
```

Arguments

`time`	follow-up times
`event`	event indicators (0/1)
`indA`	treatment A indicators (0/1)
`indB`	treatment B indicators (0/1)
`covmat`	covariate matrix, must be non-NULL. Factor variables MUST use 0/1 dummy variables
`alpha`	two-sided familywise significance level
`dig`	number of decimal places to which we `roundDown` the critical value
`niter`	number of interations passed to `crit2x2` function call

Details

For each of the three multiple testing procedures, the critical values for the overall A (respectively, simple A) logrank statistics may be slightly different from the overall B (respectively, simple B) logrank statistics. This is due to their slightly different correlations with each other (i.e., correlation between overall A and simple A, respectively, overall B and simple B, statistics) as well as with the simple AB statistic.

Value

`loghrAoverall`	overall A log hazard ratio
`seAoverall`	standard error of the overall A log hazard ratio
`ZstatAoverall`	Z-statistic for the overall A log hazard ratio
`pvalAoverall`	two-sided p-value for the overall hazard ratio
`hrAoverall`	overall A hazard ratio
`ciAoverall`	95% confidence interval for the overall A hazard ratio
`loghrAsimple`	simple A log hazard ratio
`seAsimple`	standard error of the simple A log hazard ratio
`ZstatAsimple`	Z-statistic for the simple A log hazard ratio
`pvalAsimple`	two-sided p-value for the simple A hazard ratio
`hrAsimple`	simple A hazard ratio
`ciAsimple`	95% confidence interval for the simple A hazard ratio

`loghrABsimple`	simple AB log hazard ratio
`seABsimple`	standard error of the simple AB log hazard ratio
`ZstatABsimple`	Z-statistic for the simple AB log hazard ratio
`pvalABsimple`	two-sided p-value for the simple AB hazard ratio
`hrABsimple`	simple AB hazard ratio
`ciABsimple`	95% confidence interval for the simple AB hazard ratio
`critEA3_A`	Equal Allocation 3's critical value for the overall A simple A, and simple AB hypotheses
`sigEA3_A`	Equal Allocation 3's p-value rejection criterion for the overall A, simple A, and simple AB hypotheses
`resultEA3_A`	Equal Allocation 3's accept/reject decisions for the overall A, simple A, and simple AB hypotheses
`critPA2overallA`	Proportional Allocation 2's critical value for the overall A statistic
`sigPA2overallA`	Proportional Allocation 2's p-value rejection criterion for the overall A hypothesis
`critPA2simpleAB`	Proportional Allocation 2's critical value for the simple AB hypothesis
`sigPA2simpleAB`	Proportional Allocation 2 procedure's p-value rejection criterion for the simple AB hypothesis
`resultPA2_A`	Proportional Allocation 2 procedure's accept/reject decisions for the overall A and simple A hypotheses
`critEA2_A`	Equal Allocation 2 procedure's critical value for the simple A and simple AB hypotheses
`sigEA2_A`	Equal Allocation 2 procedure's p-value rejection criterion for the simple A and simple AB hypotheses
`resultEA2_A`	Equal Allocation 2 procedure's accept/reject decisions for the simple A and simple AB hypotheses
`corAa`	correlation between the overall A and simple A logrank statistics
`corAab`	correlation between the overall A and simple AB logrank statistics
`coraab`	correlation between the simple A and simple AB logrank statistics

Author(s)

Eric Leifer, James Troendle

References

Leifer, E.S., Troendle, J.F., Kolecki, A., Follmann, D. Joint testing of overall and simple effect for the two-by-two factorial design. (2020). Submitted.

Lin, D-Y., Gong, J., Gallo, P., et al. Simultaneous inference on treatment effects in survival studies with factorial designs. Biometrics. 2016; 72: 1078-1085.

Slud, E.V. Analysis of factorial survival experiments. Biometrics. 1994; 50: 25-38.

Examples

```
 # First load the simulated data variables. The "simdataSub" file is
 # a 100-by-9 matrix which is loaded with the factorial2x2 package.
 time <- simdataSub[, "time"]
 event <- simdataSub[, "event"]
 indA <- simdataSub[, "indA"]
 indB <- simdataSub[, "indB"]
 covmat <- simdataSub[, 6:10]
 fac2x2analyze(time, event, indA, indB, covmat, alpha = 0.05, niter = 5)
#  $loghrA
# [1] 0.05613844

# $seA
# [1] 0.4531521

# $ZstatA
# [1] 0.1238843

# $pvalA
# [1] 0.9014069

# $hrA
# [1] 1.057744

# $ciA
# [1] 0.4351608 2.5710556

# $loghra
# [1] 0.1987329

# $sea
# [1] 0.6805458

# $Zstata
# [1] 0.2920198

# $pvala
# [1] 0.7702714

# $hra
# [1] 1.219856

# $cia
# [1] 0.3213781 4.6302116

# $loghrab
# [1] 0.2864932

# $seab
# [1] 0.6762458

# $Zstatab
```

```
# [1] 0.4236525

# $pvalab
# [1] 0.6718193

# $hrab
# [1] 1.331749

# $ciab
# [1] 0.3538265 5.0125010

# $critPA2A
# [1] -2.129

# $sigPA2A
# [1] 0.03325426

# $critPA2ab
# [1] -2.299

# $sigPA2ab
# [1] 0.02150494

# $result23
# [1] "accept overall A" "accept simple AB"

# $critEA3
# [1] -2.338

# $sigEA3
# [1] 0.01938725

# $result13
# [1] "accept overall A" "accept simple A"  "accept simple AB"

# $critEA2
# [1] -2.216

# $sigEA2
# [1] 0.0266915

# $result12
# [1] "accept simple A"  "accept simple AB"

# $corAa
# [1] 0.6123399

# $corAab
# [1] 0.5675396

# $coraab
# [1] 0.4642737
```

`fac2x2design` *Power for the Equal Allocation 3, Proportional Allocation 2, and Equal Allocation 2 procedures.*

Description

Power for the Equal Allocation 3, Proportional Allocation 2, and Equal Allocation 2 procedures.

Usage

```
fac2x2design(
  n,
  rateC,
  hrA,
  hrB,
  hrAB,
  mincens,
  maxcens,
  dig = 2,
  alpha = 0.05,
  niter = 5,
  abseps = 0.001,
  corAa = 1/sqrt(2),
  corAab = 1/sqrt(2),
  coraab = 1/2
)
```

Arguments

`n`	total sample size
`rateC`	group C one year event rate
`hrA`	group A to group C hazard ratio
`hrB`	group B to group C hazard ratio
`hrAB`	group AB to group C hazard ratio
`mincens`	minimum censoring time
`maxcens`	maximum censoring time
`dig`	number of decimal places to `roundDown` the critical value to
`alpha`	two-sided significance level
`niter`	number of times we call `pmvnorm` to average out its randomness
`abseps`	`abseps` setting in the `pmvnorm` call
`corAa`	correlation between the overall A and simple A log hazard ratio estimates
`corAab`	correlation between the overall A and simple AB log hazard ratio estimates
`coraab`	correlation between the simple A and simple AB log hazard ratio estimates

Value

`events`	expected number of events
`evtprob`	event probabilities for the C, A, B, and AB groups, respectively
`powerEA3overallA`	Equal Allocation 3's power to detect the overall A effect
`powerEA3simpleA`	Equal Allocation 3's power to detect the simple A effect
`powerEA3simpleAB`	Equal Allocation 3's power to detect the simple AB effect
`powerEA3anyA`	Equal Allocation 3's power to detect the simple A or AB effects
`powerPA2overallA`	Proportional Allocation 2's power to detect the overall A effect
`powerPA2simpleAB`	Proportional Allocation 2's power to detect the simple AB effect
`powerEA2simpleA`	Equal Allocation 2's power to detect the simple A effect
`powerEA2simpleAB`	Equal Allocation 2's power to detect the simple AB effect
`powerA`	power to detect the overall A effect at the two-sided `alpha` level
`powerB`	power to detect the overall B effect at the two-sided `alpha` level

References

Leifer, E.S., Troendle, J.F., Kolecki, A., Follmann, D. Joint testing of overall and simple effect for the two-by-two factorial design. (2019). Submitted.

Slud, E.V. Analysis of factorial survival experiments. Biometrics. 1994; 50: 25-38.

See Also

`eventProb`, `crit2x2`, `lgrkPower` `strLgrkPower`, `powerEA3`, `powerPA2`, `powerEA2`

Examples

```
# Corresponds to scenario 4 in Table 2 from Leifer, Troendle, et al. (2019).
n <- 4600
rateC <- 0.0445
hrA <- 0.80
hrB <- 0.80
hrAB <- 0.72
mincens <- 4.0
maxcens <- 8.4

fac2x2design(n, rateC, hrA, hrB, hrAB, mincens, maxcens, dig = 2, alpha = 0.05, niter = 1)
# $events
# [1] 954.8738

# $evtprob
```

```
# probC     probA     probB    probAB
# 0.2446365 0.2012540 0.2012540 0.1831806

# $powerEA3overallA
# [1] 0.5861992

# $powerEA3simpleA
# [1] 0.5817954

# $powerEA3simplAB
# [1] 0.9071236

# $powerEA3anyA
# [1] 0.7060777
# $powerPA2overallA
# [1] 0.6582819

# $powerPA2simpleAB
# [1] 0.9197286

# $powerEA2simpleA
# [1] 0.6203837
#
# $powerEA2simpleAB
# [1] 0.9226679

# $powerA
# [1] 0.7182932

# $powerB
# [1] 0.7182932
```

`lgrkPower` *Unstratified (ordinary) logrank power*

Description

Computes the power for the unstratified (ordinary) logrank statistic for two group comparison.

Usage

```
lgrkPower(hr, nevent, alpha = 0.05, rprob = 0.5)
```

Arguments

`hr`	hazard ratio
`nevent`	expected number of events
`alpha`	two-sided significance level
`rprob`	randomization probability

Details

Uses the formula at the bottom of p.317 from Schoenfeld (Biometrika, 1981) where the beta should be 1 - beta. The formula is modified to assume that values of the hazard ratio less than 1 correspond to treatment efficacy. We do this because we only want to include the probability of rejecting the null in favor of efficacy, not inferiority as well.

Value

`power`	logrank power

Author(s)

Eric Leifer, James Troendle

References

Schoenfeld, D. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika. 1981; 68: 316-319.

Examples

```
hr <- 0.5
nevent <- 98
lgrkPower(hr, nevent, alpha = 0.05,  rprob = 0.5)
# $power
# [1] 0.9293463
```

`powerEA2` *Power of the Equal Allocation 2 procedure*

Description

Computes the Equal Allocation 2's procedure power to detect the simple A effect and the simple AB effect, respectively.

Usage

```
powerEA2(n, hrA, hrAB, probA_C, probAB_C, crit12)
```

Arguments

`n`	total subjects with n/4 subjects in each of the C, A, B, and AB groups
`hrA`	group A to group C hazard ratio; `hrA` < 1 corresponds to group A superiority
`hrAB`	group AB to group C hazard ratio; `hrAB` < 1 corresponds to group AB superiority
`probA_C`	event probability averaged across the A and C groups
`probAB_C`	event probability averaged across the AB and C groups
`crit12`	logrank statistic critical value for both the simple A and simple AB effects

Details

For a 2-by-2 factorial design, this function computes the probability that either the simple A, respectively, simple AB logrank statistics reject their null hypotheses using a Dunnett-corrected `crit12` critical value. When the two-sided familywise type I error is 0.05, we may use `crit2x2` to compute `crit12` = -2.22 which corresponds to a 0.0264 two-sided significance level. This is described in Leifer, Troendle, et al. (2020).

Value

`powerEA2simpleA`	power to detect the simple A effect
`powerEA2simpleAB`	power to detect the simple AB effect

References

Leifer, E.S., Troendle, J.F., Kolecki, A., Follmann, D. Joint testing of overall and simple effect for the two-by-two factorial design. (2020). Submitted.

Lin, D-Y., Gong, J., Gallo, P., et al. Simultaneous inference on treatment effects in survival studies with factorial designs. Biometrics. 2016; 72: 1078-1085.

Slud, E.V. Analysis of factorial survival experiments. Biometrics. 1994; 50: 25-38.

See Also

`crit2x2`, `lgrkPower`

Examples

```
# Corresponds to scenario 4 in Table 2 from Leifer, Troendle, et al. (2020).
rateC <- 0.0445  # one-year C group event rate
hrA <- 0.80
hrB <- 0.80
hrAB <- 0.72
mincens <- 4.0
maxcens <- 8.4
evtprob <- eventProb(rateC, hrA, hrB, hrAB, mincens, maxcens)
probA_C <- evtprob$probA_C
probAB_C <- evtprob$probAB_C
corAa  <- 1/sqrt(2)
corAab <- 1/sqrt(2)
coraab <- 1/2
dig <- 2
alpha <- 0.05
critEA2 <- crit2x2(corAa, corAab, coraab, dig, alpha)$critEA2
n <- 4600
powerEA2(n, hrA, hrAB, probA_C, probAB_C, critEA2)

# $powerEA2simpleA
# [1] 0.6203837
```

```
# $powerEA2simpleAB
# [1] 0.9226679
```

---

powerEA3 *Power of the Equal Allocation 3 procedure*

Description

Computes the Equal Allocation 3 procedure's power to detect the overall A effect, the simple A effect, or the simple AB effect, respectively.

Usage

```
powerEA3(
  n,
  hrA,
  hrB,
  hrAB,
  avgprob,
  probA_C,
  probAB_C,
  critEA3,
  dig,
  cormat12 = matrix(c(1, sqrt(0.5), sqrt(0.5), 1), byrow = T, nrow = 2),
  niter = 5,
  abseps = 0.001
)
```

Arguments

`n`	total subjects with n/4 subjects in each of the C, A, B, and AB groups
`hrA`	group A to group C hazard ratio; `hrA` < 1 corresponds to group A superiority
`hrB`	group B to group C hazard ratio; `hrA` < 1 corresponds to group A superiority
`hrAB`	group AB to group C hazard ratio; `hrAB` < 1 corresponds to group AB superiority
`avgprob`	event probability averaged across the C, A, B, and AB groups
`probA_C`	event probability averaged across the A and C groups
`probAB_C`	event probability averaged across the AB and C groups
`critEA3`	rejection critical value for the overall A, simple A, and simple AB logrank statistics
`dig`	number of decimal places to `roundDown` the critical value to
`cormat12`	asymptotic correlation matrix for the overall A and simple A, respectively, simple AB logrank statistics
`niter`	number of times we call `pmvnorm` to average out its randomness
`abseps`	abseps setting in the `pmvnorm` call

Details

For a 2-by-2 factorial design, this function computes the probability that either the overall A or the simple A or the simple AB logrank statistics reject their null hypotheses at the Dunnet-corrected `critEA3` critical value. As described in Leifer, Troendle, et al. (2019), the `critEA3` = -2.32 critical value corresponds to controlling the famiywise error of the Equal Allocation 3 procedure at the two-sided 0.05 significance level. The critical value -2.32 may be computed using the `crit2x2` function. The `pmvnorm` function from the `mvtnorm` package is used to calculate the power for simultaneously detecting the overall and simple A effects. This is used to compute the power for detecting the overall A and/or simple A effects, which is computed as the sum of the powers for each of the effects minus the power for simultaneously detecting both effects. Since the power for simultaneously detecting both effects involves bivariate normal integration over an unbounded region in R^2, `pmvnorm` uses a random seed for these computations. Note that cRAN suggested we not include the random seed as an argument in this function. To smooth out the randomness, `pmvnorm` is called `niter` times and the average value over the `niter` calls is taken to be those powers.

Value

`powerEA3overallA`	power to detect the overall A effect
`powerEA3simpleA`	power to detect the simple A effect
`powerEA3simpleAB`	power to detect the simple AB effect
`powerEA3anyA`	power to detect either the overall A or simple A effects

References

Leifer, E.S., Troendle, J.F., Kolecki, A., Follmann, D. Joint testing of overall and simple effect for the two-by-two factorial design. (2020). Submitted.

Lin, D-Y., Gong, J., Gallo, P., et al. Simultaneous inference on treatment effects in survival studies with factorial designs. Biometrics. 2016; 72: 1078-1085.

Slud, E.V. Analysis of factorial survival experiments. Biometrics. 1994; 50: 25-38.

See Also

`crit2x2`, `lgrkPower`, `strLgrkPower`, `pmvnorm`

Examples

```
# Corresponds to scenario 5 in Table 2 from Leifer, Troendle, et al. (2020).
rateC <- 0.0445
hrA <- 0.80
hrB <- 0.80
hrAB <- 0.72
mincens <- 4.0
maxcens <- 8.4
evtprob <- eventProb(rateC, hrA, hrB, hrAB, mincens, maxcens)
```

```
avgprob <- evtprob$avgprob
probAB_C <- evtprob$probAB_C
probA_C <- evtprob$probA_C
dig <- 2
alpha <- 0.05
corAa  <- 1/sqrt(2)
corAab <- 1/sqrt(2)
coraab <- 1/2
critEA3 <- crit2x2(corAa, corAab, coraab, dig, alpha)$critEA3
n <- 4600
powerEA3(n, hrA, hrB, hrAB, avgprob, probA_C, probAB_C,
  critEA3, dig, cormat12 = matrix(c(1, sqrt(0.5), sqrt(0.5), 1), byrow = TRUE,
  nrow = 2), niter = 1, abseps = 1e-03)

# $powerEA3overallA
# [1] 0.5861992

# $powerEA3simpleA
# [1] 0.5817954

# $powerAB
# [1] 0.9071236

# $powerEA3anyA
# [1] 0.7060777
```

`powerPA2` *Power of the Proportional Allocation 2 procedure*

Description

Computes the Proportional Allocation 2 procedure's power to detect the overall A effect or the simple AB effect, respectively.

Usage

```
powerPA2(n, hrA, hrB, hrAB, avgprob, probAB_C, critPA2A, critPA2ab, dig)
```

Arguments

`n`	total subjects with n/4 subjects in each of the C, A, B, and AB groups
`hrA`	group A to group C hazard ratio; `hrA` < 1 corresponds to group A superiority
`hrB`	group B to group C hazard ratio; `hrA` < 1 corresponds to group A superiority
`hrAB`	group AB to group C hazard ratio; `hrAB` < 1 corresponds to group AB superiority
`avgprob`	event probability averaged across the C, A, B, and AB groups
`probAB_C`	event probability averaged across the AB and C groups
`critPA2A`	rejection critical value for the overall A stratified logrank statistic

`critPA2ab`	rejection critical value for the simple AB ordinary logrank statistic
`dig`	number of decimal places to which we `roundDown` the critical value for the overall A test as calculated in `powerPA2` by `strLgrkPower`

Details

The Proportional Allocation 2 procedure uses a two-sided 2/3 * alpha significance level to test the overall A effect and the remaining Dunnett-corrected type 1 error to thest the simple AB effect. When the familywise error is alpha = 0.05, this corresponds to a critical value `critPA2A` = -2.13. Then `crit2x2` is used to compute a critical value `critPA2ab` = -2.24 to test the simple AB effect. This corresponds to a two-sided 0.0251 significance level. This controls the asymptotic familywise type I error for the two hypothesis tests at the two-sided 0.05 level. This is because of the `1/sqrt(2)` asymptotic correlation between the logrank test statistics for the overall A and simple AB effects (Slud, 1994). The overall A effect's significance level 2/3 * 0.05 is prespecified and the simple AB effect's significance level 0.0251 is computed using `crit2x2`.

Value

`powerPA2overallA`	power to detect the overall A effect
`powerPA2simpleAB`	power to detect the simple AB effect

Author(s)

Eric Leifer, James Troendle

References

Leifer, E.S., Troendle, J.F., Kolecki, A., Follmann, D. Joint testing of overall and simple effect for the two-by-two factorial design. (2020). Submitted.

Lin, D-Y., Gong, J., Gallo, P., et al. Simultaneous inference on treatment effects in survival studies with factorial designs. Biometrics. 2016; 72: 1078-1085.

Slud, E.V. Analysis of factorial survival experiments. Biometrics. 1994; 50: 25-38.

See Also

`crit2x2`, `eventProb`, `lgrkPower`, `strLgrkPower`

Examples

```
# Corresponds to scenario 4 in Table 2 from Leifer, Troendle, et al. (2020).
rateC <- 0.0445  # one-year C group event rate
hrA <- 0.80
hrB <- 0.80
hrAB <- 0.72
mincens <- 4.0
maxcens <- 8.4
evtprob <- eventProb(rateC, hrA, hrB, hrAB, mincens, maxcens)
avgprob <- evtprob$avgprob
```

```
 probAB_C <- evtprob$probAB_C
 dig <- 2
 alpha <- 0.05
 corAa  <- 1/sqrt(2)
 corAab <- 1/sqrt(2)
 coraab <- 1/2
 critvals <- crit2x2(corAa, corAab, coraab, dig, alpha)
 critPA2A <- critvals$critPA2A
 critPA2ab <- critvals$critPA2ab
 n <- 4600
 powerPA2(n, hrA, hrB, hrAB, avgprob, probAB_C,
           critPA2A, critPA2ab, dig)
# $powerPA2overallA
# [1] 0.6582819

# $powerPA2simpleAB
# [1] 0.9197286
```

`roundDown` *Round down a negative number*

Description

Rounds a negative number to the nearest, more negative number to a specified decimal place.

Usage

```
roundDown(x, dig)
```

Arguments

`x`	number to be rounded
`dig`	number of decimal places to be rounded

Details

`roundDown` is used to round a negative Z-statistic critical value, which has (infinitely) many significant digits, to the nearest `dig` decimal place which is more extreme than the critical value itself. This is done to preserve the desired type I error level.

Examples

```
roundDown(-1.95456, 2)
# [1] -1.96
```

`simdat` *Simulated 2x2 factorial trial data*

Description

A dataset mimicking data that might be obtained from a two-by-two factorial clinical trial. It is the first 100 rows of the data set `simdata`.

Usage

```
data(simdat)
```

Format

A data frame with 100 rows and 10 variables

Details

- `subjno` subject ID
- `time` time to event or censoring
- `event` event indicator (1=event, 0=censoring)
- `indA` indicator of receiving treatment A (1=yes, 0=no)
- `indB` indicator of receiving treatment B (1=yes, 0=no)
- `cvd` history of cardiovascular disease (1=yes, 0=no)
- `fac2-fac5` indicator variables for the 5 level factor variable

`simdata` *Simulated 2x2 factorial trial data*

Description

A dataset mimicking data that might be obtained from a two-by-two factorial clinical trial.

Usage

```
data(simdata)
```

Format

A data frame with 4600 rows and 10 variables

Details

- `subjno` subject ID
- `time` time to event or censoring
- `event` event indicator (1=event, 0=censoring)
- `indA` indicator of receiving treatment A (1=yes, 0=no)
- `indB` indicator of receiving treatment B (1=yes, 0=no)
- `cvd` history of cardiovascular disease (1=yes, 0=no)
- `fac2-fac5` indicator variables for the 5 level factor variable

`simdataSub` *Simulated 2x2 factorial trial data*

Description

A dataset mimicking data that might be obtained from a two-by-two factorial clinical trial. It is the first 100 rows of the data set `simdata`.

Usage

```
data(simdataSub)
```

Format

A data frame with 100 rows and 10 variables

Details

- `subjno` subject ID
- `time` time to event or censoring
- `event` event indicator (1=event, 0=censoring)
- `indA` indicator of receiving treatment A (1=yes, 0=no)
- `indB` indicator of receiving treatment B (1=yes, 0=no)
- `cvd` history of cardiovascular disease (1=yes, 0=no)
- `fac2-fac5` indicator variables for the 5 level factor variable

`strLgrkPower` *Stratified (overall) logrank power*

Description

Computes the power for the overall treatment A effect based on the stratified logrank test based on Slud (1994).

Usage

```
strLgrkPower(n, hrA, hrB, hrAB, avgprob, dig = 2, alpha = 0.05)
```

Arguments

`n`	total subjects with n/4 subjects in the C, A, B, and AB groups
`hrA`	group A to group C hazard ratio
`hrB`	group B to group C hazard ratio
`hrAB`	group AB to group C hazard ratio
`avgprob`	average event probability across the four groups as calculated by the function eventProb
`dig`	number of decimal places to which we `roundDown` the critical value corresponding to `alpha`
`alpha`	two-sided significance level

Details

The `roundDown` function is used in conjunction with the `dig` argument to insure that any rounding of the (negative) critical values will be done conservatively to control the familywise type I error at the desired level.

Value

`mean`	logrank mean value
`power`	logrank power
`nevent`	expected number of events

Author(s)

Eric Leifer, James Troendle

References

Leifer, E.S., Troendle, J.F., Kolecki, A., Follmann, D. Joint testing of overall and simple effect for the two-by-two factorial design. (2019). Submitted.

Slud, E.V. Analysis of factorial survival experiments. Biometrics. 1994; 50: 25-38.

See Also

`roundDown`, `eventProb`

Examples

```
rateC <- 0.0445
hrA <- 0.80
hrB <- 0.80
hrAB <- 0.72
mincens <- 4.0
maxcens <- 8.4
avgprob <- eventProb(rateC, hrA, hrB, hrAB, mincens, maxcens)$avgprob
n <- 4600
strLgrkPower(n, hrA, hrB, hrAB, avgprob, dig = 2, alpha = 0.05)
# $mean
# [1] -2.537779

# $power
# [1] 0.7182932

# $nevent
# [1] 954.8738
```

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