

Package ‘factorial2x2’

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Type Package

Title Design and Analysis of a 2x2 Factorial Trial

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Author Eric Leifer and James Troendle

Maintainer Eric Leifer <Eric.Leifer@gmail.com>

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) correlation 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
```

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 <code>roundDown</code> 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 <code>pmvnorm</code> function call
abseps	abseps setting in the <code>pmvnorm</code> function call
tol	tol setting in the <code>uniroot</code> 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

<code>critEA3</code>	Equal Allocation 3 procedure's critical value for all three test statistics
<code>sigEA3</code>	two-sided nominal significance level corresponding to <code>critEA3</code>
<code>critPA2A</code>	Proportional Allocation 2 procedure's critical value for the overall A statistic
<code>sigPA2A</code>	two-sided nominal significance level corresponding to <code>critPA2A</code>
<code>critPA2ab</code>	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 independent 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 probability of the A and C groups
probAB_C	average event probability 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	<i>Significance testing for the Proportional Allocation 2, Equal Allocation 3, Equal Allocation 2 procedures</i>
---------------	--

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 <code>roundDown</code> the critical value
niter	number of iterations passed to <code>crit2x2</code> 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	<i>Power for the Equal Allocation 3, Proportional Allocation 2, and Equal Allocation 2 procedures.</i>
--------------	--

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

# $powerEA3simpleAB
# [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
```

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 <code>roundDown</code> 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 <code>pmvnorm</code> to average out its randomness
abseps	abseps setting in the <code>pmvnorm</code> 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 Dunnett-corrected `critEA3` critical value. As described in Leifer, Troendle, et al. (2019), the `critEA3 = -2.32` critical value corresponds to controlling the familywise 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 test 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	<i>Round down a negative number</i>
-----------	-------------------------------------

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	<i>Simulated 2x2 factorial trial data</i>
--------	---

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	<i>Simulated 2x2 factorial trial data</i>
------------	---

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	<i>Stratified (overall) logrank power</i>
--------------	---

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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