Package ‘bpp’

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Tools for Computation of Bayesian Predictive Power for a Normally Distributed Endpoint with Known Variance

Description

Implements functions to update Bayesian Predictive Power Computations after not stopping a clinical trial at an interim analysis, whether blinded or unblinded, for a Normally distributed endpoint with known variance, with a prominent example being the hazard ratio.

Details

| Package:   | bpp            |
| Type:      | Package        |
| Version:   | 1.0.4          |
| Date:      | 2022-01-13     |
| License:   | GPL (>=2)      |
| LazyLoad:  | yes            |

Author(s)

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References


Examples

# type ?bpp_interim for code of all the computations in Rufibach et al (2016a).

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**basicPlot**

*Basic plot functions to illustrate prior and posterior densities when considering a time-to-event endpoint*

**Description**

Basic plot function, labels are specific to the hazard ratio, i.e. when looking at a time-to-event endpoint.

**Usage**

```r
basicPlot(leg = TRUE, IntEffBoundary = NA, IntFutBoundary = NA, successmean = NA, priormean = NA)
```

**Arguments**

- `leg` logical, display legend?
- `IntEffBoundary` Interim efficacy boundary.
- `IntFutBoundary` Interim futility boundary.
- `successmean` The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- `priormean` Mean of the prior.

**Value**

Empty generic plot.

**Author(s)**

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**References**

Examples

# type ?bpp.linterim for code of all the computations in Rufibach et al (2016a).

bpp  

Bayesian Predictive Power (BPP) for Normally Distributed Endpoint

Description

Compute BPP for a Normally distributed endpoint, e.g. log(hazard ratio).

Usage

bpp(prior = c("normal", "flat"), successmean, finalSE, priormean, ...)

Arguments

prior  

Prior density on effect sizes.

successmean  
The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.

finalSE  

(Known) standard error at which the final analysis of the study under consideration takes place.

priormean  

Prior mean.

...  

Further arguments specific to the chosen prior (see bpp for examples).

Value

A real number, the bpp.

Author(s)

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References


Examples

# type bpp_interim for code of all the computations in Rufibach et al (2016a).

## bpp_interim

**Bayesian Predictive Power (BPP) for Normally Distributed Endpoint**

### Description

Compute BPP and posterior density for a Normally distributed endpoint, e.g. log(hazard ratio), assuming either an unblinded or blinded interim result.

### Usage

```r
bpp_interim(prior = c("normal", "flat"), interimSE, finalSE, successmean, IntEffBoundary, IntFutBoundary, IntFix, priormean, propA = 0.5, thetas, ...)
```

### Arguments

- **prior**: Prior density on effect sizes.
- **interimSE**: (Known) standard error of estimate at interim analysis.
- **finalSE**: (Known) standard error at which the final analysis of the study under consideration takes place.
- **successmean**: The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- **IntEffBoundary**: Efficacy boundary at the interim analysis.
- **IntFutBoundary**: Futility boundary at the interim analysis.
- **IntFix**: Effect sizes observed at the interim analysis, to compute BPP for an unblinded interim analysis.
- **priormean**: Prior mean.
- **propA**: Proportion of subjects randomized to arm A.
- **thetas**: Grid to compute posterior density on.
- **...**: Further arguments specific to the chosen prior (see bpp_interim for examples).
Value

A list containing the following elements:

- initial BPP: BPP based on the prior.
- conditional power interval: Conditional power, updating power at design stage with interval knowledge, i.e. corresponding to IntEffBoundary and IntFutBoundary.
- BPP after not stopping at interim interval: BPP after not stopping at a blinded interim, provides the results corresponding to IntEffBoundary and IntFutBoundary.
- BPP after not stopping at interim exact: BPP after not stopping at an unblinded interim, provides the results corresponding to IntFix.
- posterior density exact: The posterior density, exact knowledge of interim result, i.e. corresponding to IntFix.
- posterior density interval: The posterior density, interval knowledge, i.e. corresponding to IntEffBoundary and IntFutBoundary.

Author(s)

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References


Examples

```r
# Reproduce all the computations in Rufibach et al (2016a) for a Normal prior.
#------------------------------------------------------------------------------------------
# set all parameters:
#------------------------------------------------------------------------------------------
# prior mean / sd
hr0 <- 0.85
sd0 <- 0.11
priormean <- log(hr0)
```
# specifications for pivotal study
propA <- 0.5  # proportion of patients randomized to arm A
fac <- (propA * (1 - propA)) ^ (-1)
nevents <- c(0.5, 1) * 1600
finalSE <- sqrt(fac / nevents[2])
alphas <- c(0.001, 0.049)
za <- qnorm(1 - alphas / 2)
hrMDD <- exp(- za * sqrt(fac / nevents))
successmean <- log(hrMDD[2])

# efficacy and futility interim boundary
effi <- log(hrMDD[1])
futi <- log(1.025)

# grid to compute densities on
thetas <- seq(-0.65, 0.3, by = 0.01)

# compare Normal and flat prior density
# ------------------------------------------
par(las = 1, mar = c(9, 5, 2, 1), mfrow = c(1, 2))
plot(0, 0, type = "n", xlim = c(-0.6, 0.3), ylim = c(-0.1, 5), xlab = "", ylab = "density",
     main = "")

title(expression("Normal and flat prior density for "*theta), line = 0.7)

basicPlot(lg = FALSE, IntEffBoundary = effi, IntFutBoundary = futi, successmean = successmean,
          priormean = priormean)
lines(thetas, dnorm(thetas, mean = log(hr0), sd = sd0), col = 2, lwd = 2)

# flat prior:
hr0flat <- 0.866
width1 <- 0.21
height1 <- 2.48

lines(thetas, dUniformNormalTails(thetas, mu = log(hr0flat), width = width1, height = height1),
      lwd = 2, col = 3)

# computations for Normal prior
# ------------------------------------------

# prior probabilities to be below 0.7 or above 1:
lims <- c(0.7, 1)

pnorm1 <- plnorm(lims[1], meanlog = log(hr0), sdlog = sd0, lower.tail = TRUE, log.p = FALSE)
# pnorm(log(lims[1]), mean = log(hr0), sd = sd0)

pnorm2 <- plnorm(lims[2], meanlog = log(hr0), sdlog = sd0, lower.tail = FALSE, log.p = FALSE)
# 1 - pnorm(log(lims[2]), mean = log(hr0), sd = sd0)

# initial bpp
bpp0 <- bpp(prior = "normal", successmean = successmean, finalSE = finalSE,
            priormean = log(hr0), priorsigma = sd0)

# update prior with first external study
hr1 <- 0.396
sd1 <- 0.837
up1 <- NormalNormalPosterior(datamean = log(hr1), sigma = sd1, n = 1, 
nu = log(hr0), tau = sd0)
bpp1 <- bpp(prior = "normal", successmean = successmean, finalSE = finalSE, 
priormean = up1$postmean, priorsigma = up1$postsigma)

# update prior with second external study (result derived from pooled analysis: 
# Cox regression on patient level, stratified by study):
hr2 <- 0.287
sd2 <- 0.658
up2 <- NormalNormalPosterior(datamean = log(hr2), sigma = sd2, n = 1, nu = log(hr0), tau = sd0)
bpp2 <- bpp(prior = "normal", successmean = successmean, finalSE = finalSE, 
priormean = up2$postmean, priorsigma = up2$postsigma)

# compute bpp after not stopping at interim:
# assuming both boundaries:
bpp3.tmp <- bpp_1interim(prior = "normal", interimSE = sqrt(fac / nevents[1]), 
finalSE = finalSE, successmean = successmean, 
IntEffBoundary = effi, IntFutBoundary = futi, IntFix = log(1), 
priormean = up2$postmean, propA = 0.5, thetas, 
priorsigma = up2$postsigma)
bpp3 <- bpp3.tmp$"BPP after not stopping at interim interval"
post3 <- bpp3.tmp$"posterior density interval"

# assuming only efficacy boundary:
bpp3_effi_only <- bpp_1interim(prior = "normal", interimSE = sqrt(fac / nevents[1]), 
finalSE = finalSE, successmean = successmean, 
IntEffBoundary = effi, IntFutBoundary = log(Inf), IntFix = log(1), 
priormean = up2$postmean, propA = 0.5, thetas, 
priorsigma = up2$postsigma)$"BPP after not stopping at interim interval"

# assuming only futility boundary:
bpp3_futi_only <- bpp_1interim(prior = "normal", interimSE = sqrt(fac / nevents[1]), 
finalSE = finalSE, successmean = successmean, 
IntEffBoundary = log(0), IntFutBoundary = futi, IntFix = log(1), 
priormean = up2$postmean, propA = 0.5, thetas, 
priorsigma = up2$postsigma)$"BPP after not stopping at interim interval"

# assuming interim efficacy boundary:
bpp4.tmp <- bpp_1interim(prior = "normal", interimSE = sqrt(fac / nevents[1]), 
finalSE = finalSE, successmean = successmean, 
IntEffBoundary = effi, IntFutBoundary = Inf, IntFix = c(effi, futi), priormean = up2$postmean, 
propA = 0.5, thetas, priorsigma = up2$postsigma)
bpp4 <- bpp4.tmp$"BPP after not stopping at interim exact"[2, 1]
post4 <- bpp4.tmp$"posterior density exact"[, 1]

# assuming interim futility boundary:
bpp5.tmp <- bpp_1interim(prior = "normal", interimSE = sqrt(fac / nevents[1]), 
finalSE = finalSE, successmean = successmean, 
IntEffBoundary = effi, IntFutBoundary = Inf, IntFix = c(effi, futi), priormean = up2$postmean, 
propA = 0.5, thetas, priorsigma = up2$postsigma)
bpp5 <- bpp5.tmp$"BPP after not stopping at interim exact"[2, 1]
post5 <- bpp5.tmp$"posterior density exact"  # same as post4[, 2]

# ------------------------------------------
# reproduce plots in paper
# ------------------------------------------

# first two updates
par(las = 1, mar = c(9, 5, 2, 1), mfrow = c(1, 2))
plot(0, 0, type = "n", xlim = c(-0.6, 0.3), ylim = c(-0.1, 5), xlab = "", ylab = "density",
     main = "")
title(expression("Normal prior density and corresponding posteriors for "*theta"), line = 0.7)
basicPlot(leg = FALSE, IntEffBoundary = effi, IntFutBoundary = futi, successmean = successmean,
          priormean = priormean)
lines(thetas, dnorm(thetas, mean = log(hr0), sd = sd0), col = 2, lwd = 2)
lines(thetas, dnorm(thetas, mean = up1$postmean, sd = up1$postsigma), col = 3, lwd = 2)
lines(thetas, dnorm(thetas, mean = up2$postmean, sd = up2$postsigma), col = 4, lwd = 2)
lines(thetas, post3, col = 1, lwd = 2)
legend(-0.64, 5.2, c("prior", "posterior after Sub1", "posterior after Sub1 & Sub2",
                    "posterior after Sub1 & Sub2 and not stopping at interim"),
       lty = 1, col = c(2:4, 1), bty = "n", lwd = 2)

# posterior densities for interval knowledge and thetahat equal to boundaries:
plot(0, 0, type = "n", xlim = c(-0.6, 0.3), ylim = c(-0.1, 8), xlab = "", ylab = "density",
     main = "")
title(expression("Posteriors for "*theta" after not stopping at interim, for Normal prior"),
      line = 0.7)
basicPlot(leg = FALSE, IntEffBoundary = effi, IntFutBoundary = futi, successmean = successmean,
          priormean = priormean)
lines(thetas, post3, col = 1, lwd = 2)
lines(thetas, post4, col = 2, lwd = 2)
lines(thetas, post5, col = 3, lwd = 2)

leg2 <- c("interval knowledge",
          expression(hat(theta) = efficacy boundary"),
          expression(hat(theta) = futility boundary")
)
legend(-0.62, 8.2, leg2, lty = 1, col = 1:3, lwd = 2, bty = "n",
       title = "posterior after not stopping at interim")

# ------------------------------------------
# Reproduce all the computations in Rufibach et al (2016a) for flat prior.
# ------------------------------------------

# set all parameters first:
# ------------------------------------------

# parameters of flat prior:
priormean <- log(hr0flat)
# computations for flat prior
# ------------------------------------------

# prior probabilities to be below 0.7 or above 1:
lims <- c(0.7, 1)
flat1 <- pUniformNormalTails(x = log(lims[1]), mu = priormean, width = width1, height = height1)
flat2 <- 1 - pUniformNormalTails(x = log(lims[2]), mu = priormean, width = width1, height = height1)

# prior
bpp0_1 <- bpp(prior = "flat", successmean = successmean, finalSE = finalSE, 
                priormean = priormean, width = width1, height = height1)

# update with first external study
hr1 <- 0.396
sd1 <- 0.837
bpp1_1 <- integrate(FlatNormalPosterior, lower = -Inf, upper = Inf, successmean = successmean, 
                     finalSE = finalSE, interimmean = log(hr1), interimSE = sd1, 
                     priormean = priormean, width = width1, height = height1)$value

# update prior (result derived from pooled analysis: Cox regression on patient level, 
# stratified by study)
hr2 <- 0.287
sd2 <- 0.658
bpp2_1 <- integrate(FlatNormalPosterior, -Inf, Inf, successmean = successmean, 
                     finalSE = finalSE, interimmean = log(hr2), interimSE = sd2, 
                     priormean = priormean, width = width1, height = height1)$value

# update after not stopping at interim
# first compute synthesized prior:
hr0 <- 0.85
sd0 <- 0.11
up2 <- NormalNormalPosterior(datamean = log(hr2), sigma = sd2, n = 1, nu = log(hr0), tau = sd0)

# assuming both boundaries:
bpp3.tmp_1 <- bpp_interim(prior = "flat", interimSE = sqrt(fac / nevents[1]), 
                          finalSE = finalSE, successmean = successmean, 
                          IntEffBoundary = effi, IntFutBoundary = futi, IntFix = log(1), 
                          priormean = up2$postmean, propA = 0.5, thetas, 
                          width = width1, height = height1)
bpp3_1 <- bpp3.tmp_1$"BPP after not stopping at interim interval"
post3_1 <- bpp3.tmp_1$"posterior density interval"

# assuming only efficacy boundary:
bpp3_1_effi_only <- bpp_interim(prior = "flat", interimSE = sqrt(fac / nevents[1]), 
                                finalSE = finalSE, successmean = successmean, 
                                IntEffBoundary = effi, IntFutBoundary = log(Inf), IntFix = log(1), 
                                priormean = up2$postmean, propA = 0.5, thetas = thetas, 
                                width = width1, 
                                height = height1)$"BPP after not stopping at interim interval"

# assuming only futility boundary:
bpp3_l_futi_only <- bpp_linterim(prior = "flat", interimSE = sqrt(fac / nevents[1]), finalSE = finalSE, successmean = successmean, IntEffBoundary = log(0), IntFutBoundary = futi, IntFix = log(1), priormean = up2$postmean, propA = 0.5, thetas = thetas, width = width1, height = height1)$"BPP after not stopping at interim interval"

# assuming interim efficacy boundary:
bpp4_l.tmp <- bpp_linterim(prior = "flat", interimSE = sqrt(fac / nevents[1]), finalSE = finalSE, successmean = successmean, IntEffBoundary = log(0), IntFutBoundary = effi, IntFix = effi, priormean = up2$postmean, propA = 0.5, thetas = thetas, width = width1, height = height1)$"BPP after not stopping at interim exact"[2, 1]
post4_l <- bpp4_l.tmp$"posterior density exact"

# assuming interim futility boundary:
bpp5_l.tmp <- bpp_linterim(prior = "flat", interimSE = sqrt(fac / nevents[1]), finalSE = finalSE, successmean = successmean, IntEffBoundary = log(0), IntFutBoundary = effi, IntFix = effi, priormean = up2$postmean, propA = 0.5, thetas = thetas, width = width1, height = height1)$value

bpp5_l.tmp <- bpp_linterim(prior = "flat", interimSE = sqrt(fac / nevents[1]), finalSE = finalSE, successmean = successmean, IntEffBoundary = log(0), IntFutBoundary = effi, IntFix = effi, priormean = up2$postmean, propA = 0.5, thetas = thetas, width = width1, height = height1)$"BPP after not stopping at interim exact"[2, 1]
post5_l <- bpp5_l.tmp$"posterior density exact"

# ------------------------------------------
# plots for flat prior
# ------------------------------------------

# first two updates with external studies
# compute posteriors
flatpost1 <- rep(NA, length(thetas))
flatpost2 <- flatpost1
for (i in 1:length(thetas)){
  flatpost1[i] <- estimate_posterior(x = thetas[i], prior = "flat", interimmean = log(hr1), interimSE = sd1, priormean = priormean, width = width1, height = height1)
  flatpost2[i] <- estimate_posterior(x = thetas[i], prior = "flat", interimmean = log(hr2), interimSE = sd2, priormean = priormean, width = width1, height = height1)
}

par(las = 1, mar = c(9, 5, 2, 1), mfrow = c(1, 2))
plot(0, 0, type = "n", xlim = c(-0.6, 0.3), ylim = c(-0.10, 5), xlab = "", ylab = "density", main = "")
title(expression("Flat prior density and corresponding posteriors for \("theta\)), line = 0.7)
basicPlot(leg = FALSE, IntEffBoundary = effi, IntFutBoundary = futi, successmean = successmean, 
   priormean = priormean)
lines(thetas, dUniformNormalTails(thetas, mu = priormean, width = width1, height = height1), 
   lwd = 2, col = 2)
lines(thetas, flatpost1, col = 3, lwd = 2)
lines(thetas, flatpost2, col = 4, lwd = 2)
lines(thetas, post3_1, col = 1, lwd = 2)
legend(-0.64, 5.2, c("prior", "posterior after Sub1", "posterior after Sub1 & Sub2", 
   "posterior after Sub1 & Sub2 and not stopping at interim"), lty = 1, 
   col = c(2:4, 1), bty = "n", lwd = 2)

# posterior densities for interval knowledge and thetahat equal to boundaries:
plot(0, 0, type = "n", xlim = c(-0.6, 0.3), ylim = c(-0.10, 8), xlab = "", ylab = "density", 
   main ="")
title(expression("Posteriors for \(\hat{\theta}\) after not stopping at interim, for Flat prior"), 
   line = 0.7)
basicPlot(leg = FALSE, IntEffBoundary = effi, IntFutBoundary = futi, successmean = successmean, 
   priormean = priormean)
lines(thetas, post3_1, col = 1, lwd = 2)
lines(thetas, post4_1, col = 2, lwd = 2)
lines(thetas, post5_1, col = 3, lwd = 2)

leg.flat <- c("interval knowledge", 
   expression(hat(theta)*" = efficacy boundary"), 
   expression(hat(theta)*" = futility boundary")
)

legend(-0.62, 8.2, leg.flat, lty = 1, col = 1:3, lwd = 2, bty = "n", 
   title = "posterior after not stopping at interim,")

# reproduce Table 1 in Rufibach et al (2016a)
# ------------------------------------------
mat <- matrix(NA, ncol = 2, nrow = 10)
mat[, 1] <- c(pnorm1, pnorm2, bpp0, bpp1, bpp2, bpp3, bpp3_futi_only, bpp3_effi_only, 
   bpp4, bpp5)
mat[, 2] <- c(flat1, flat2, bpp0_1, bpp1_1, bpp2_1, bpp3_1, bpp3_1_futi_only, 
   bpp3_1_effi_only, bpp4_1, bpp5_1)
colnames(mat) <- c("Normal prior", "Flat prior")
rownames(mat) <- c(paste("Probability for hazard ratio to be $\leq $ ", lims[1], sep = ""), 
   paste("Probability for hazard ratio to be $\geq $ ", lims[2], sep = ""), 
   "PoS based on prior distribution", "PoS after Sub1", "PoS after Sub1 and Sub2", 
   "PoS after not stopping at interim, assuming $inte{\hat{\theta}}$ in [effi{\theta}, futi{\theta}]$", 
   "PoS after not stopping at interim, assuming $inte{\hat{\theta}}$ in [-infty, futi{\theta}]$", 
   "PoS after not stopping at interim, assuming $inte{\hat{\theta}}$ in [effi{\theta}, infty]$", 
   "PoS after not stopping at interim, assuming $inte{\hat{\theta}}$ in effi{\theta}$", 
   "PoS after not stopping at interim, assuming $inte{\hat{\theta}}$ in futi{\theta}$")
as.data.frame(format(mat, digits = 2))
Bayesian Predictive Power (BPP) for Binary Endpoint

Description
Compute BPP and posterior density for a binary endpoint, e.g. response proportions, assuming either an unblinded or blinded interim result.

Usage
bpp_1interim_binary(prior = c("normal", "flat"), successdelta, pi1, n1, 
pi2, n2, IntEffBoundary, IntFutBoundary, 
IntFix, priormean, propA = 0.5, thetas, ...)

Arguments
prior Prior density on effect sizes.
successdelta The proportion difference that defines success at the final analysis. We assume that higher proportions are better, e.g. as for response in oncology. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
pi1 Assumed response proportion in intervention arm.
n1 2-d vector of sample sizes in intervention arm, at interim and final analysis.
pi2 Assumed response proportion in control arm.
n2 2-d vector of sample sizes in control arm, at interim and final analysis.
IntEffBoundary Efficacy boundary at the interim analysis.
IntFutBoundary Futility boundary at the interim analysis.
IntFix Effect sizes observed at the interim analysis, to compute BPP for an unblinded interim analysis.
priormean Prior mean.
propA Proportion of subjects randomized to arm A.
thetas Grid to compute posterior density on.
... Further arguments specific to the chosen prior (see bpp_1interim_binary for examples).

Value
A list containing the following elements:
initial BPP BPP based on the prior.
BPP after not stopping at interim interval BPP after not stopping at a blinded interim, provides the results corresponding to IntEffBoundary and IntFutBoundary.
BPP after not stopping at interim exact
   BPP after not stopping at an unblinded interim, provides the results corresponding to IntFix.

posterior density interval
   The posterior density, interval knowledge, i.e. corresponding to IntEffBoundary and IntFutBoundary.

posterior power interval
   The posterior power, interval knowledge, i.e. corresponding to IntEffBoundary and IntFutBoundary.

posterior density exact
   The posterior density, exact knowledge of interim result, i.e. corresponding to IntFix.

Author(s)

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References


Examples

```
# simple example with response proportions
pi1 <- 0.6 # proportion in intervention arm
pi2 <- 0.45 # proportion in control arm
n1 <- 174
n2 <- 174

# MDD at final analysis - proportion difference that corresponds to "success"
mdd <- 0.1

n1_int <- 87
n2_int <- 87

# prior if normal
pi20 <- 0.44
pi10 <- 0.64
n0 <- 50
priormean <- pi10 - pi20
sd0 <- sqrt(pi20 * (1 - pi20) / (n0 / 2) + pi10 * (1 - pi10) / (n0 / 2))

# efficacy boundary
```
effi <- 0.2

# futility boundary
futi <- 0

thetas <- seq(-0.65, 0.3, by = 0.01)

bpp_interim_binary(prior = "normal", successdelta = mdd, pi1 = pi1,
                   n1 = c(n1_int, n1), n2 = c(n2_int, n2),
                   pi2 = pi2, IntEffBoundary = effi, IntFutBoundary = futi,
                   IntFix = 1, priormean = priormean, propA = 0.5,
                   thetas = thetas, priorsigma = sd0)[[1]]
propA  Proportion of subjects randomized to arm A.
thetas  Grid to compute posterior density on.
...  Further arguments specific to the chosen prior (see `bpp_interim_continuous` for examples).

Value

A list containing the following elements:

- **initial BPP**: BPP based on the prior.
- **BPP after not stopping at interim interval**
  - BPP after not stopping at a blinded interim, provides the results corresponding to `IntEffBoundary` and `IntFutBoundary`.
- **BPP after not stopping at interim exact**
  - BPP after not stopping at an unblinded interim, provides the results corresponding to `IntFix`.
- **posterior density interval**
  - The posterior density, interval knowledge, i.e. corresponding to `IntEffBoundary` and `IntFutBoundary`.
- **posterior power interval**
  - The posterior power, interval knowledge, i.e. corresponding to `IntEffBoundary` and `IntFutBoundary`.
- **posterior density exact**
  - The posterior density, exact knowledge of interim result, i.e. corresponding to `IntFix`.

Author(s)

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References


Examples

```r
# standard deviation of measurements in one group
stDev <- 24

# number of patients at interim
n1_int <- 46
```
n2_int <- 46

# number of patients at final analysis
n1 <- 92
n2 <- 92

# MDD at final analysis (corresponds to delta = 10 for 80% power)
mdd <- 7.023506

# efficacy boundary
effi <- 15

# futility boundary --> chosen informally
futi <- 0

# prior
priormean <- 12.3
sd0 <- 4.2

# flat prior
width1 <- 25
height1 <- 0.02

thetas <- seq(-0.65, 0.3, by = 0.01)

# Bayesian Predictive Power (BPP) for Time-to-Event Endpoint

Description

Compute BPP and posterior density for a time-to-event endpoint, e.g. hazard ratio, assuming either an unblinded or blinded interim result.

Usage

bpp_interim_t2e(prior = c("normal", "flat"), successHR, d,
               IntEffBoundary, IntFutBoundary, IntFixHR,
               priorHR, propA = 0.5, thetas, ...)

bpp_interim_t2e_continuous(prior = "normal", successmean = mdd, stDev = stDev,
                           n1 = c(n1_int, n1), n2 = c(n2_int, n2),
                           IntEffBoundary = effi, IntFutBoundary = futi, IntFix = 1,
                           priormean = priormean, propA = 0.5, thetas,
                           priorsigma = sd0)[[1]]

bpp_interim_t2e_continuous(prior = "flat", successmean = mdd, stDev = stDev,
                           n1 = c(n1_int, n1), n2 = c(n2_int, n2), IntEffBoundary = effi,
                           IntFutBoundary = futi, IntFix = 1,
                           priormean = 12.3, propA = 0.5, thetas = thetas,
                           width = width1, height = height1)[[1]]
Arguments

prior  Prior density on effect sizes.
successHR  The hazard ratio that defines success at the final analysis. We assume that hazard ratios below 1 are beneficial. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
d  2-d vector with number of events at interim and final analysis. Used to compute standard errors.
IntEffBoundary  Efficacy boundary at the interim analysis, hazard ratio.
IntFutBoundary  Futility boundary at the interim analysis, hazard ratio.
IntFixHR  Effect sizes observed at the interim analysis, to compute BPP for an unblinded interim analysis.
priorHR  Hazard ratio at which prior is centered.
propA  Proportion of subjects randomized to arm A.
thetas  Grid to compute posterior density on.
...  Further arguments specific to the chosen prior (see bpp_interim_t2e for examples).

Value

A list containing the following elements:

initial BPP  BPP based on the prior.
BPP after not stopping at interim interval  BPP after not stopping at a blinded interim, provides the results corresponding to IntEffBoundary and IntFutBoundary.
BPP after not stopping at interim exact  BPP after not stopping at an unblinded interim, provides the results corresponding to IntFix.
posterior density interval  The posterior density, interval knowledge, i.e. corresponding to IntEffBoundary and IntFutBoundary.
posterior power interval  The posterior power, interval knowledge, i.e. corresponding to IntEffBoundary and IntFutBoundary.
posterior density exact  The posterior density, exact knowledge of interim result, i.e. corresponding to IntFix.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>
References


Examples

```r
# number of events
events <- c(191, 381)

# MDD at final analysis
hrMDD <- 0.8172823

# efficacy boundary
hrEff <- 0.6508829

# futility boundary --> chosen informally
hrFuti <- 1

# prior specifications

# Normal prior corresponding to information of 50 events in 1:1 randomized trial
hr0 <- 0.7
sd0 <- sqrt(4 / 50)

# flat prior
width1 <- 0.5
height1 <- 1

# compute bpps
thetas <- seq(0.5, 1.35, by = 0.01)
bpp1b <- bpp_1interim_t2e(prior = "normal", successHR = hrMDD, d = events,
IntEffBoundary = hrEff, IntFutBoundary = hrFuti,
IntFixHR = 1, priorHR = hr0, propA = 0.5, thetas = thetas,
priorsigma = sd0)[[1]]
bpp1_1b <- bpp_1interim_t2e(prior = "flat", successHR = hrMDD, d = events,
IntEffBoundary = hrEff, IntFutBoundary = hrFuti,
IntFixHR = 1, priorHR = hr0, propA = 0.5, thetas = thetas,
width = width1, height = height1)[[1]]
```

Bayesian Predictive Power (BPP) for Normally Distributed Endpoint
Description

Compute BPP and posterior density for a Normally distributed endpoint, e.g. \( \log(\text{hazard ratio}) \), assuming the trial did not stop at two blinded interim analyses.

Usage

```r
bpp_2interim(prior = "normal", interimSE, finalSE, successmean, IntEffBoundary,
             IntFutBoundary, priormean, thetas, ...)
```

Arguments

- **prior**: Prior density on effect sizes. So far, this function only accommodates a Normal prior, as opposed to `bpp_1interim` where also the pessimistic prior introduced in Rufibach et al (2016a) can be specified.
- **interimSE**: (Known) standard error of estimate at interim analysis.
- **finalSE**: (Known) standard error at which the final analysis of the study under consideration takes place.
- **successmean**: The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- **IntEffBoundary**: 2-d vector of efficacy boundaries at the interim analyses.
- **IntFutBoundary**: 2-d vector of futility boundary at the interim analyses.
- **priormean**: Prior mean.
- **thetas**: Grid to compute posterior density on.
- **...**: Further arguments specific to the chosen prior (see `bpp_1interim` for examples).

Value

A list containing the following elements:

- **initial BPP**: BPP based on the prior.
- **BPP after not stopping at interim interval**: BPP after not stopping at a blinded interim.
- **posterior density interval**: The posterior density, interval knowledge.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>
References


Examples

```r
# Illustrate the update after two passed interims using the Gallium clinical trial

# set all parameters:
# ------------------------------------------
# prior mean / sd
hr0 <- 0.9288563
priormean <- log(hr0)
priorsigma <- sqrt(4 / 12)

# specifications for pivotal study
propA <- 0.5 # proportion of patients randomized to arm A
fac <- (propA * (1 - propA)) ^ (-1)
nevents <- c(111, 248, 370)
interimSE <- sqrt(fac / nevents[1:2])
finalSE <- sqrt(fac / nevents[3])
za <- c(3.9285726330559, 2.5028231888636, 1.9936294555664)
alphas <- 2 * (1 - pnorm(za))
hrMDD <- exp(- za * sqrt(fac / nevents))
successmean <- log(hrMDD[3])

# efficacy and futility interim boundary
effi <- log(c(0, hrMDD[2]))
futi <- log(c(1, Inf))

# grid to compute densities on
thetas <- seq(-0.65, 0.3, by = 0.01)

bpp_2interim(prior = "normal", interimSE = interimSE, finalSE = finalSE,
successmean = successmean, IntEffBoundary = effi, IntFutBoundary = futi,
priormean = priormean, thetas = thetas, priorsigma = priorsigma)
```

bpp_binary

Bayesian Predictive Power (BPP) for Binary Endpoint
Description

Compute BPP for a binary endpoint.

Usage

bpp_binary(prior = c("normal", "flat"), successdelta, pi1, n1, pi2, n2, priormean, ...)

Arguments

prior

Prior density on effect sizes.

successdelta

The proportion difference that defines success at the final analysis. We assume that higher proportions are better, e.g. as for response in oncology. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.

pi1

Assumed response proportion in intervention arm. Used to compute standard error at final analysis.

n1

Sample size in intervention arm. Used to compute standard error at final analysis.

pi2

Assumed response proportion in control arm. Used to compute standard error at final analysis.

n2

Sample size in control arm. Used to compute standard error at final analysis.

priormean

Prior mean.

...

Further arguments specific to the chosen prior (see bpp_binary for examples).

Value

A real number, the bpp.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

References


Examples

```r
# simple example with response proportions
pi1 <- 0.6 # proportion in intervention arm
pi2 <- 0.45 # proportion in control arm
n1 <- 174
n2 <- 174

# MDD at final analysis - proportion difference that corresponds to "success"
mdd <- 0.1

# prior if normal
pi20 <- 0.44
pi10 <- 0.64
n0 <- 50
priormean <- pi10 - pi20
sd0 <- sqrt(pi20 * (1 - pi20) / (n0 / 2) + pi10 * (1 - pi10) / (n0 / 2))

bpp0 <- bpp_binary(prior = "normal", successdelta = mdd, pi1 = pi1, n1 = n1,
                   pi2 = pi2, n2 = n2, priormean = priormean, priorsigma = sd0)

# prior if flat
width1 <- 0.5
height1 <- 1.5

bpp0_1 <- bpp_binary(prior = "flat", successdelta = mdd, pi1 = pi1, n1 = n1,
                      pi2 = pi2, n2 = n2, priormean = priormean, priorsigma = sd0,
                      width = width1, height = height1)
```

Description

Compute BPP for a continuous endpoint.

Usage

```r
bpp_continuous(prior = c("normal", "flat"), successmean, stDev,
               n1, n2, priormean, ...)
```

Arguments

- `prior` Prior density on effect sizes.
- `successmean` The mean difference that defines success at the final analysis. We assume that a higher mean is better. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
Standard deviation of measurements in one group. Used to compute standard error at final analysis.

Sample size in intervention arm. Used to compute standard error at final analysis.

Sample size in control arm. Used to compute standard error at final analysis.

Prior mean.

Further arguments specific to the chosen prior (see `bpp_continuous` for examples).

Value

A real number, the bpp.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

References


Examples

```r
# standard deviation of measurements in one group
stDev <- 24

# sample size at final analysis
n1 <- 92
n2 <- 92

# MDD at final analysis (corresponds to delta = 10 for 80% power)
mdd <- 7.023506

# prior
priorMean <- 12.3

# standard error for prior, based on Phase 2 data
sig1 <- 26.1
nlp <- 25
sig2 <- 33.6
n2p <- 25
sd0 <- sqrt(sig1 ^ 2 / nlp + sig2 ^ 2 / n2p)
```
# flat prior
width1 <- 25
height1 <- 0.02

# bpps
bpp_continuous(prior = "normal", successmean = mdd, stDev = stDev,
               n1 = n1, n2 = n2, priormean = priormean, priorsigma = sd0)
bpp_continuous(prior = "flat", successmean = mdd, stDev = stDev,
               n1 = n1, n2 = n2, priormean = priormean,
               width = width1, height = height1)

---

### bpp_t2e

*Bayesian Predictive Power (BPP) for Time-To-Event Endpoint*

**Description**

Compute BPP for a time-to-event endpoint.

**Usage**

```r
bpp_t2e(prior = c("normal", "flat"), successHR, d, propA = 0.5,
        priorHR, ...)
```

**Arguments**

- **prior**: Prior density on effect sizes.
- **successHR**: The hazard ratio that defines success at the final analysis. We assume that a hazard ratio below 1 corresponds to better outcome. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- **d**: Number of events at final analysis.
- **propA**: Proportion of subjects randomized to arm A.
- **priorHR**: Hazard ratio around which the prior is centered.
- **...**: Further arguments specific to the chosen prior (see bpp_t2e for examples).

**Value**

A real number, the bpp.

**Author(s)**

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>
References


Examples

```r
# hazard ratio to beat at final analysis
hrMDD <- 0.8173

# number of events at final analysis
nevents <- 381

# prior
hr0 <- 0.7

# SE for a normal prior corresponding to information of 50 events in 1:1 randomized trial
sd0 <- sqrt(4 / 50)

# parameters of flat prior
width1 <- 0.5
height1 <- 1

# compute bpp
bpp_t2e(prior = "normal", successHR = hrMDD, d = nevents,
       priorHR = hr0, priorsigma = sd0)

bpp_t2e(prior = "flat", successHR = hrMDD, d = nevents,
       priorHR = hr0, width = width1, height = height1)
```

---

**estimate_posterior**

*Posterior density conditional on known interim result*

**Description**

If we update the prior with a known estimate at an interim analysis, we get this density.

**Usage**

```r
estimate_posterior(x, prior = c("normal", "flat"), interimmean, interimSE, priormean, ...)
```
estimate_posterior_nominator

Arguments

x Value at which to evaluate the function.
prior Prior density on effect sizes.
interimmean Mean of the data.
interimSE (Known) standard error of interimmean.
priormean Prior mean.
... Further arguments specific to the chosen prior (see bpp for examples).

Value

Value of the function, a real number.

Author(s)

Kaspar Rufibach (maintainer)
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References


Examples

# type ?bpp_interim for code of all the computations in Rufibach et al (2016a).

Description

If we update the prior with a known estimate at an interim analysis, we get a density that is proportional to the value of this function.

Usage

estimate_posterior_nominator(x, prior = c("normal", "flat"), interimmean, interimSE, priormean, ...)

Posterior density conditional on interim result is proportional to the value of this function
Arguments

- **x**: Value at which to evaluate the function.
- **prior**: Prior density on effect sizes.
- **interimmean**: Mean of the data.
- **interimSE**: (Known) standard error of interimmean.
- **priormean**: Prior mean.
- **...**: Further arguments specific to the chosen prior (see bpp for examples).

Value

Value of the function, a real number.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

References


Examples

# type ?bpp_interim for code of all the computations in Rufibach et al (2016a).

```r

estimate_toIntegrate(x, prior = c("normal", "flat"), successmean, finalSE, interimmean, interimSE, priormean, propA = 0.5, ...)
```

Description

Product of posterior density and conditional power for known interim result, integrate over this function to get BPP.

Usage

```r
estimate_toIntegrate(x, prior = c("normal", "flat"), successmean, finalSE, interimmean, interimSE, priormean, propA = 0.5, ...)
```
Arguments

- **x**: Value at which to evaluate the function.
- **prior**: Prior density on effect sizes.
- **successmean**: The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- **finalSE**: (Known) standard error at which the final analysis of the study under consideration takes place.
- **interimmean**: Mean of the data.
- **interimSE**: (Known) standard error of interimmean.
- **priormean**: Prior mean.
- **propA**: Proportion of subjects randomized to arm A.
- ...: Further arguments specific to the chosen prior (see bpp for examples).

Value

- Value of the function, a real number.

Author(s)

- Kaspar Rufibach (maintainer)
  <kaspar.rufibach@roche.com>

References


Examples

- # type ?bpp_interim for code of all the computations in Rufibach et al (2016a).

---

**FlatNormalPosterior**

*Integrand to compute Bayesian Predictive Power when flat prior has been updated with likelihood*

Description

- Assume we have a flat prior on our effect, update it with a Normal likelihood and then want to compute Bayesian Predictive Power. This function provides the integrand for that computation, i.e. the product of the power function and the posterior.
Usage

FlatNormalPosterior(x, successmean, finalSE, interimmean, interimSE, priormean, width, height)

Arguments

x           Value at which to evaluate the function.
successmean The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
finalSE     (Known) standard error at which the final analysis of the study under consideration takes place.
interimmean Mean of the data.
interimSE   (Known) standard error of interimmean.
priormean   Prior mean.
width       Width of the flat part of the prior.
height      Height of the flat part of the prior.

Value

Value of the function, a real number.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

References


Examples

# type ?bpp_interim for code of all the computations in Rufibach et al (2016a).
interval_posterior_nominator

Posterior density conditional on interim result, only known as interval, is proportional to the value of this function

Description

If we update the prior with the knowledge that the interim estimate was between a futility and efficacy boundary at an interim analysis, we get a density that is proportional to the value of this function.

Usage

```r
interval_posterior_nominator(x, prior = c("normal", "flat"),
                           IntEffBoundary, IntFutBoundary, interimSE, priormean, ...)
```

Arguments

- `x`: Value at which to evaluate the function.
- `prior`: Prior density on effect sizes.
- `IntEffBoundary`: Efficacy boundary at the interim analysis.
- `IntFutBoundary`: Futility boundary at the interim analysis.
- `interimSE`: (Known) standard error of `interimmean`, i.e. at interim analysis.
- `priormean`: Prior mean.
- `...`: Further arguments specific to the chosen prior (see bpp for examples).

Value

Value of the function, a real number.

Author(s)

Kaspar Rufibach (maintainer)
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References


Examples

```r
# type ?bpp_interim for code of all the computations in Rufibach et al (2016a).
```
interval_posterior_nominator2

Posterior density conditional on two interim results, both only known as intervals, is proportional to the value of this function

Description

If we update the prior with the knowledge that two interim estimates were between a futility and efficacy boundary, we get a density that is proportional to the value of this function.

Usage

interval_posterior_nominator2(x, prior = "normal", IntEffBoundary, IntFutBoundary, interimSE, priormean, ...)

Arguments

- x: Value at which to evaluate the function.
- prior: Prior density on effect sizes.
- IntEffBoundary: Efficacy boundary at the interim analysis.
- IntFutBoundary: Futility boundary at the interim analysis.
- interimSE: (Known) standard error of interimmean, i.e. at interim analysis.
- priormean: Prior mean.
- ...: Further arguments specific to the chosen prior (see bpp for examples).

Value

Value of the function, a real number.

Author(s)

Kaspar Rufibach (maintainer)
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References


Examples

# type ?bpp_2interim for code of all the computations in Rufibach et al (2016a).
interval_toIntegrate  

Product of posterior density and conditional power for blinded interim result

Description

Product of posterior density and conditional power for blinded interim result, integrate over this function to get BPP.

Usage

\[
\text{interval_toIntegrate}(x, \text{prior} = \text{c("normal", "flat")}, \text{interimSE}, \text{finalSE}, \text{successmean}, \text{IntEffBoundary}, \text{IntFutBoundary}, \text{priormean}, \ldots)
\]

Arguments

- **x**: Value at which to evaluate the function.
- **prior**: Prior density on effect sizes.
- **interimSE**: (Known) standard error of interimmean, i.e. at interim analysis.
- **finalSE**: (Known) standard error at which the final analysis of the study under consideration takes place.
- **successmean**: The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- **IntEffBoundary**: Efficacy boundary at the interim analysis.
- **IntFutBoundary**: Futility boundary at the interim analysis.
- **priormean**: Prior mean.
- **...**: Further arguments specific to the chosen prior (see bpp for examples).

Value

Value of the function, a real number.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

References

Examples

```r
# type ?bpp_interim for code of all the computations in Rufibach et al (2016a).
```

---

**interval_toIntegrate2**  
*Product of posterior density and conditional power for blinded interim result*

**Description**

Product of posterior density and conditional power for two blinded interim results, integrate over this function to get BPP.

**Usage**

```r
interval_toIntegrate2(x, prior = "normal", interimSE, finalSE, successmean, 
IntEffBoundary, IntFutBoundary, priormean, ...)
```

**Arguments**

- `x`  Value at which to evaluate the function.
- `prior`  Prior density on effect sizes.
- `interimSE`  (Known) standard error of `interimmean`, i.e. at interim analysis.
- `finalSE`  (Known) standard error at which the final analysis of the study under consideration takes place.
- `successmean`  The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- `IntEffBoundary`  Efficacy boundary at the interim analysis.
- `IntFutBoundary`  Futility boundary at the interim analysis.
- `priormean`  Prior mean.
- `...`  Further arguments specific to the chosen prior (see bpp for examples).

**Value**

Value of the function, a real number.

**Author(s)**

Kaspar Rufibach (maintainer)

<kaspar.rufibach@roche.com>
References


Examples

# type ?bpp_2interim for code of all the computations in Rufibach et al (2016a).

### Description

Compute the posterior distribution in a conjugate normal model for known variance: Let $X_1, \ldots, X_n$ be a sample from a $N(\mu, \sigma^2)$ distribution, with $\sigma$ assumed known. We assume a prior distribution on $\mu$, namely $N(\nu, \tau^2)$. The posterior distribution is then $\mu | x \sim N(\mu_p, \sigma_p^2)$ with

$$\mu_p = \frac{1}{(\sigma^2/n + \tau^{-2})^{-1}}(\bar{x}/(\sigma^2/n) + \nu/\tau^2)$$

and

$$\sigma_p = (1/(\sigma^2/n + \tau^{-2})^{-1}.$$

These formulas are available e.g. in Held (2014, p. 182).

### Usage

`NormalNormalPosterior(datamean, sigma, n, nu, tau)`

### Arguments

- `datamean`: Mean of the data.
- `sigma`: (Known) standard deviation of the data.
- `n`: Number of observations.
- `nu`: Prior mean.
- `tau`: Prior standard deviation.

### Value

A list with the entries:

- `postmean`: Posterior mean.
- `postsigma`: Posterior standard deviation.
post_power

Author(s)
Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

References

Examples
```r
## data:
n <- 25
sd0 <- 3
x <- rnorm(n, mean = 2, sd = sd0)

## prior:
nu <- 0
tau <- 2

## posterior:
NormalNormalPosterior(datamean = mean(x), sigma = sd0,
                      n = n, nu = nu, tau = tau)
```

Description
Conditional power conditioning on a blinded interim, i.e. the estimate after the interim is only known to lie in an interval.

Usage
```r
post_power(x, interimSE, finalSE, successmean, IntEffBoundary, IntFutBoundary)
```

Arguments
- `x`: Value at which to evaluate the function.
- `interimSE`: (Known) standard error of interimmean.
- `finalSE`: (Known) standard error at which the final analysis of the study under consideration takes place.
- `successmean`: The mean that defines success at the final analysis. Typically chosen to be the minimal detectable difference, i.e. the critical on the scale of the effect size of interest corresponding to the significance level at the final analysis.
- `IntEffBoundary`: Efficacy boundary at the interim analysis.
- `IntFutBoundary`: Futility boundary at the interim analysis.
UniformNormalTails

Value

Value of the function, a real number.

Author(s)

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

References


Examples

# type ?bpp_interim for code of all the computations in Rufibach et al (2016a).

---

UniformNormalTails Density and CDF for Uniform Distribution with Normal tails

Description

Density function and cumulative distribution function for a Uniform density with Normal tails. Introduced in Rufibach et al (2016a) as pessimistic distribution to compute Bayesian Predictive Power.

Usage

dUniformNormalTails(x, mu, width, height)
pUniformNormalTails(x, mu, width, height)

Arguments

x Vector of quantiles.
mu Mean of the pessimistic prior.
width Width of the flat part of the prior.
height Height of the flat part of the prior.

Value

Density at x.
**Author(s)**

Kaspar Rufibach (maintainer)
<kaspar.rufibach@roche.com>

**References**


**Examples**

# type ?bpp_1interim for code of all the computations in Rufibach et al (2016a).
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