Package 'ph2bye'

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Type Package

Title Phase II Clinical Trial Design Using Bayesian Methods

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Description Calculate the Bayesian posterior/predictive probability and
determine the sample size and stopping boundaries for single-arm Phase II design.

License GPL (>= 2)

URL https://allen.shinyapps.io/BayesDesign/

LazyData TRUE

Depends stats, graphics, animation, nleqslv

Imports Rcpp, VGAM

Suggests clinfun, gsDesign, survival

LinkingTo Rcpp

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NeedsCompilation yes

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ph2bye-package   *ph2bye: A package for Phase II single-arm Bayesian design.*

Description

The ph2bye package provides three categories of important functions: PostP.design, PredP.design and MultPostP.design.

Posterior probability criterion functions

The posterior probability criterion functions include PostP and PostP.design functions.

Predictive probability criterion functions

The predictive probability criterion functions include PredP and PredP.design functions.

Posterior probability criterion function for multiple outcomes

The posterior probability criterion functions include MultPostP and MultPostP.design functions.

Whole design function with double thresholds showing futility and efficacy boundary together

The criterion function DT.design.

Prior calculation function

The function prior calculating Beta prior parameters accourding different prior information.

Author(s)

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bayes.design   *Bayesian design method for sequentially monitoring patients using Beta-Binomial posterior probability based on observing data*

Description

Make animation plots to present sequential monitor stopping rule using Beta-Binomial Bayesian model

Usage

```
bayes.design(a,b,r=0, stop.rule="futility", add.size=5, alpha=0.05,
p0 ,delta=0.2,tau1=0.9,tau2=0.9,tau3=0.9,tau4=0.9, time.interval =1)
```

Arguments

a	the hyperparameter (shape1) of the Beta prior for the experimental drug.
b	the hyperparameter (shape2) of the Beta prior for the experimental drug.
r	the maximum number of patients treated by the experimental drug.
stop.rule	the hyperparameter (shape1) of the Beta prior for the experimental drug.
add.size	a single integer value, random number generator (RNG) state for random number generation.
alpha	the siginificant level to determine the credible interval, set 0.05 by default.
p0	the prespecified reseponse rate.
delta	the minimally acceptable increment of the response rate.
tau1	threshold for stopping rule 1.
tau2	threshold for stopping rule 2.
tau3	threshold for stopping rule 3.
tau4	threshold for stopping rule 4.
time.interval	a positive number to set the time interval of the animation (unit in seconds); default to be 1.

Value

animation plot of determination of stopping boundaries.

References

Yin, G. (2012). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
# Using Multiple Myeloma (MM) data example
MM.r = rep(0,6); MM.mean = 0.1; MM.var = 0.0225
a <- MM.mean^2*(1-MM.mean)/MM.var - MM.mean; b <- MM.mean*(1-MM.mean)^2/MM.var - (1-MM.mean)
bayes.design(a=a,b=b,r=MM.r,stop.rule="futility",p0=0.1)

# Using Acute Promyelocytic Leukaemia (APL) data example
APL.r <- c(0,1,0,0,1,1); APL.mean = 0.3; APL.var = 0.0191
a <- APL.mean^2*(1-APL.mean)/APL.var - APL.mean; b <- APL.mean*(1-APL.mean)^2/APL.var - (1-APL.mean)
bayes.design(a=a,b=b,r=APL.r,stop.rule="efficacy",p0=0.1)
```

BB.aniplot	*Sequentially monitor patients using Beta-Binomial posterior probability*

Description

Make animation plots to present sequential monitor the patients using Beta-Binomial Bayesian model

Usage

```
BB.aniplot(a, b, r, N=1, alpha=0.05, seed=1234, time.interval=1, output=TRUE)
```

Arguments

a	the hyperparameter (shape1) of the Beta prior for the experimental drug.
b	the hyperparameter (shape2) of the Beta prior for the experimental drug.
r	vector of number of response in each cohort, the value of each element should not exceed N
N	the number of patients treated by the experimental drug at a certain stage of the trial.
alpha	the siginificant level to determine the credible interval, set 0.05 by default.
seed	a single integer value, random number generator (RNG) state for random number generation.
time.interval	a positive number to set the time interval of the animation (unit in seconds); default to be 1.
output	a logical value, whether to output the inference results of posterior distribution and mean, observed data and credible interval.

Value

animation plot of updating posterior as prior, and output the inference information of prior and posterior distribution if output=TRUE.

References

Yin, G. (2012). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
# Using APL data
r=rep(0,6)
BB.aniplot(a=1,b=1,r=r, alpha=0.05, seed=1234)
# Simulate binomial data
B <- 10; N=1; p=0.3
```

```
r <- rbinom(n = B,size = N,prob = p)
BB.aniplot(a=1,b=1,r=r,time.interval = 0.2,output = FALSE)
```

DT.design	*The whole design with double thresholds showing futility and efficacy boundary together*

Description

The design function to sequentially monitor sample size and stopping boundary for both futility and efficacy

Usage

```
DT.design(type, a, b, nmin, nmax, p0, p1, theta0, theta1, theta_t, optimize)
```

Arguments

type	type of stopping criterion: "PostP" or "PredP".
a	the hyperparameter (shape1) of the Beta prior for the experimental drug.
b	the hyperparameter (shape2) of the Beta prior for the experimental drug.
nmin	the minimum number of patients treated by the experimental drug.
nmax	the maximum number of patients treated by the experimental drug.
p0	the pre-specified reseponse rate.
p1	the pre-specified reseponse rate.
theta0	the cutoff probability for futility: typically, $\theta_0 = [0.01, 0.1]$.
theta1	the cutoff probability for efficacy: typically, $\theta_1 = [0.9, 0.99]$.
theta_t	the cutoff probability for efficacy including future patients; typically, $\theta_T = [0.85, 0.95]$. Set 0.9 by default.
optimize	logical value, if optimize=TRUE, then only output the minimal sample size for the same number of futility and efficacy boundaries.

Value

boundsets	the boundaries sets: U_n and L_n

References

Thall, P. F., Simon, R. (1994). Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* **50**: 337-349.

Lee, J. J., Liu, D. D. (2008). A predictive probability design for phase II cancer clinical trials. *Clinical Trials* **5**: 93-106.

Yin, G. (2012). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
## Using vague prior Unif(0,1), sequential monitor
DT.design(type = "PostP", a=1, b=1, nmin=20, nmax=60, p0=0.4, p1=0.3, theta0 = 0.05, theta1 = 0.9)
DT.design(type = "PredP", a=1, b=1, nmin=20, nmax=60, p0=0.4, p1=0.3, theta0 = 0.05, theta1 = 0.9,
theta_t = 0.9)
## Or using Jeffery prior with Beta(0.5,0.5), multi-stage monitor when sample size is
## 10, 20, ..., 80
DT.design(type = "PostP", a=0.5, b=0.5, nmin=1, nmax=85, p0=0.3, p1=0.3, theta0 = 0.05,
theta1 = 0.9)[(1:8)*10,]
DT.design(type = "PredP", a=0.5, b=0.5, nmin=1, nmax=85, p0=0.3, p1=0.3, theta0 = 0.05,
theta1 = 0.9, theta_t = 0.9)[(1:8)*10,]
```

MultPostP	*The posterior probability criterion function for Phase II single-arm design*

Description

Thall, Simon and Estey's criterion function for determining the trial decision boundaries for efficacy (futility) and safety (toxicity).

Usage

```
MultPostP(x, n, a.vec, p0)
```

Arguments

x
: the value of observed data. It can be $x_E = y_{ET} + y_{ET^C}$ i.e. number of responses for efficacy among n patients treated by the experimental drug, or $x_T = y_{ET} + y_{E^CT}$ i.e. number of responses for toxicity among n patients treated by the experimental drug, where $y = (y_{ET}, y_{E^CT}, y_{ET^C}, y_{E^CT^C})$, that is, among n patients treated by the experimental drug, y_{ET} of them have experienced both toxicity and efficacy, y_{E^CT} have experienced toxicity only, y_{ET^C} have experienced efficacy only, $y_{E^CT^C}$ have neither experienced toxicity nor efficacy.

n
: the number of patients treated by the experimental drug at a certain stage of the trial.

a.vec
: the hyperparameter vector of the Dirichlet prior for the experimental drug.

p0
: the prespecified reseponse rate for efficacy, futility or toxicity.

Value

prob
: the posterior probability: $Pr(p_E > p_0 | X = x_E)$ or $Pr(p_T > p_0 | X = x_T)$

References

Berry, S. M., Carlin, B. P., Lee, J. J., & Muller, P. (2010). *Bayesian adaptive methods for clinical trials.* CRC press.

Thall, Peter F., Richard M. Simon, and Elihu H. Estey. (1995). *Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in medicine* **14.4**: 357-379.

Yin, G. (2013). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
n <- 30; x.eff <- 5; x.tox <- 8; param <- c(1,1,1,1); p0.eff <- 0.9; p0.tox <- 0.95
MultPostP(x=x.eff, n=n, a.vec=param, p0=p0.eff)
MultPostP(x=x.tox, n=n, a.vec=param, p0=p0.tox)
```

MultPostP.design	*The stopping boundaries based on the multiple outcomes criterion*

Description

The design function to sequentially monitor sample size and boundary based on Thall, Simon and Estey's criterion.

Usage

```
MultPostP.design(type, nmax, a.vec, p0, theta, optimize)
```

Arguments

type	type of boundaries: "efficacy" or "futility" or "toxicity".
nmax	the maximum number of patients treated by the experimental drug.
a.vec	the hyperparameter vector of the Dirichlet prior for the experimental drug.
p0	the prespecified reseponse rate for efficacy or toxicity.
theta	the cutoff probability: typically, $\theta = [0.9, 0.99]$ for efficacy, $\theta = [0.01, 0.1]$ for futility, and $\theta = [0.95, 1]$ for toxicity.
optimize	logical value, if optimize=TRUE, then only output the minimal sample size for the same number of futility boundaries and maximal sample size for the same number efficacy boundaries

Value

boundset	the boundaries set: U_n or L_n for the experimental drug efficacy or futility; T_n for the experimental drug toxicity.

References

Thall, Peter F., Richard M. Simon, and Elihu H. Estey. (1995). *Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in medicine* **14.4**: 357-379.

Yin, G. (2012). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
## Using vague prior Unif(0,1)
MultPostP.design(type="futility",nmax = 30,a.vec = c(1,1,1,1),p0 = 0.15, theta = 0.05)
MultPostP.design(type="efficacy",nmax = 30,a.vec = c(1,1,1,1),p0 = 0.15, theta = 0.9)
MultPostP.design(type="toxicity",nmax = 30,a.vec = c(1,1,1,1),p0 = 0.15, theta = 0.95)
```

PostP	*The posterior probability criterion function for Phase II single-arm design*

Description

Thall and Simon's criterion function for determining the trial decision boundaries based on the posterior probability.

Usage

```
PostP(x, n, a, b, p0)
```

Arguments

x	the number of responses among n patients treated by the experimental drug.
n	the number of patients treated by the experimental drug.
a	the hyperparameter (shape1) of the Beta prior for the experimental drug.
b	the hyperparameter (shape2) of the Beta prior for the experimental drug.
p0	the prespecified reseponse rate.

Value

prob	the posterior probability: $Pr(p > p_0 \mid X = x)$

References

Berry, S. M., Carlin, B. P., Lee, J. J., & Muller, P. (2010). *Bayesian adaptive methods for clinical trials.* CRC press.

Thall, P. F., Simon, R. (1994). Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* **50**: 337-349.

Yin, G. (2013). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
PostP(8,15,1,1,0.8)
```

`PostP.design`	*The stopping boundaries based on the posterior probability criterion*

Description

The design function to sequentially monitor sample size and boundary based on Thall and Simon's criterion.

Usage

```
PostP.design(type, nmax, a, b, p0, theta, optimize)
```

Arguments

`type`	type of boundaries: "efficacy" or "futility".
`nmax`	the maximum number of patients treated by the experimental drug.
`a`	the hyperparameter (shape1) of the Beta prior for the experimental drug.
`b`	the hyperparameter (shape2) of the Beta prior for the experimental drug.
`p0`	the pre-specified reseponse rate.
`theta`	the cutoff probability: typically, $\theta = [0.9, 0.99]$ for efficacy, $\theta = [0.01, 0.1]$ for futility.
`optimize`	logical value, if optimize=TRUE, then only output the minimal sample size for the same number of futility and efficacy boundaries.

Value

`boundset`	the boundaries set: U_n or L_n

References

Thall, P. F., Simon, R. (1994). Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* **50**: 337-349.

Yin, G. (2012). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
## Using vague prior Unif(0,1)
PostP.design(type = "futility", nmax=100, a=1, b=1, p0=0.3, theta=0.05)
PostP.design(type = "efficacy", nmax=100, a=1, b=1, p0=0.3, theta=0.9)
## Or using Jeffery prior with Beta(0.5,0.5)
PostP.design(type = "futility", nmax=100, a=0.5, b=0.5, p0=0.3, theta=0.05)
PostP.design(type = "efficacy", nmax=100, a=0.5, b=0.5, p0=0.3, theta=0.9)
```

PredP	*The predictive probability criterion function for Phase II single-arm design*

Description

Lee and Liu's criterion function for determining the trial decision cutoffs based on the predictive probability.

Usage

```
PredP(x, n, nmax, a, b, p0, theta_t)
```

Arguments

x	the number of responses among n patients treated by the experimental drug at a certain stage of the trial.
n	the number of patients treated by the experimental drug at a certain stage of the trial.
nmax	the maximum number of patients treated by the experimental drug.
a	the hyperparameter (shape1) of the Beta prior for the experimental drug.
b	the hyperparameter (shape2) of the Beta prior for the experimental drug.
p0	the the response rate for the standard drug.
theta_t	the cutoff probability for efficacy including future patients; typically, $\theta_T = [0.85, 0.95]$. Set 0.9 by default.

Value

prob	the predictive probability: $PP = \sum\limits_{y=0}^{n_{max}-n} Pr(Y = y|x)I(\Pr(p > p_0|Y = y, x) \geq \theta_T)$

References

Lee, J. J., Liu, D. D. (2008). A predictive probability design for phase II cancer clinical trials. *Clinical Trials* **5**: 93-106.

Yin, G. (2012). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
# Using vague prior Uniform(0,1), i.e. Beta(1,1)
PredP(16, 23, 40, 1, 1, 0.5, 0.9)
```

PredP.design   *The stopping boundaries based on the predictive probability criterion*

Description

The design function to sequentially monitor sample size and boundary based on Lee and Liu's criterion.

Usage

```
PredP.design(type, nmax, a, b, p0, theta_t, theta, optimize)
```

Arguments

type	type of boundaries: "efficacy" or "futility".
nmax	the maximum number of patients treated by the experimental drug.
a	the hyperparameter (shape1) of the Beta prior for the experimental drug.
b	the hyperparameter (shape2) of the Beta prior for the experimental drug.
p0	the the response rate for the standard drug.
theta_t	the cutoff probability for efficacy including future patients; typically, $\theta_T = [0.85, 0.95]$. Set 0.9 by default.
theta	the cutoff probability: typically, $\theta = [0.9, 0.99]$ for efficacy, $\theta = [0.01, 0.1]$ for futility.
optimize	logical value, if optimize=TRUE, then only output the minimal sample size for the same number of futility and efficacy boundaries.

Value

boundset	the boundaries set: U_n or L_n

References

Lee, J. J., Liu, D. D. (2008). A predictive probability design for phase II cancer clinical trials. *Clinical Trials* **5**: 93-106.

Yin, G. (2012). *Clinical Trial Design: Bayesian and Frequentist Adaptive Methods.* New York: Wiley.

Examples

```
PredP.design(type = "futility", nmax=40, a=1, b=1, p0=0.3, theta=0.05)
PredP.design(type = "efficacy", nmax=40, a=1, b=1, p0=0.3, theta=0.9)
```

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prior   *Beta priors determination based on different prior information*

Description

The prior function to calculate the Beta prior parameters

Usage

```
prior(type, mu, v, N, W, init)
```

Arguments

type	type of prior information: "MeanVar" uses mean and variance, "Optimist" uses (ORR) mean, "ORRN" uses ORR and smaple size, "ORRW" uses ORR and CI width.
mu	prior(ORR) mean.
v	prior variance
N	prior sample size.
W	prior confidence interval width.
init	initial value to solve the nonlinear equations for "ORRW" type.

Value

parameters	the vector of Beta parameters: a and b

References

Thall, P. F., Simon, R. (1994). Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* **50**: 337-349.

Mayo, M. S., & Gajewski, B. J. (2004). Bayesian sample size calculations in phase II clinical trials using informative conjugate priors. *Controlled clinical trials* **25**(2): 157-167.

Tan, S. B., & Machin, D. (2002). Bayesian two-stage designs for phase II clinical trials. *Statistics in medicine* **21**(14): 1991-2012. New York: Wiley.

Examples

```
prior(type = "MeanVar", mu=0.2, v=0.025)
prior(type = "Optimist", mu = 0.2)
prior(type = "ORRN", mu = 0.2, N = 10)
prior(type = "ORRW", mu = 0.2, W = 0.5)
```

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