Package 'BayesianPlatformDesignTimeTrend'

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Title Simulate and Analyse Bayesian Platform Trial with Time Trend

Version 1.1.0

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Description Simulating the multi-arm multi-stage or platform trial with Bayesian approach using the 'rstan' package, which provides the R interface for the Stan.
This package supports fixed ratio and Bayesian adaptive randomization approaches for randomization.
Additionally, it allows for the study of time trend problems in platform trials.
There are demos available for a multi-arm multi-
stage trial with two different null scenarios, as well as for Bayesian trial cutoff screening.
The Bayesian adaptive randomisation approaches are described in:
Trippa et al. (2012) <doi:10.1200/JCO.2011.39.8420> and
Wathen et al. (2017) <doi:10.1177/1740774517692302>.
The randomisation algorithm is described in:
Zhao W <doi:10.1016/j.cct.2015.06.008>.
The analysis methods of time trend effect in platform trial are described in:
Saville et al. (2022) <doi:10.1177/17407745221112013> and
Bofill Roig et al. (2022) <doi:10.1186/s12874-022-01683-w>.

URL https://github.com/ZXW834/PlatFormDesignTime

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Biarch true

Depends R (>= 4.0.0), rstan (>= 2.18.1)

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R topics documented:

`BayesianPlatformDesignTimeTrend-package`
The 'BayesianPlatformDesignTimeTrend' package.

Description

This package simulates the multi-arm multi-stage or platform trial with bayesian approach using the 'rstan' package, which provides the R interface for to the stan. The package uses Thall's and Trippa's randomisation approach for Bayesian adaptive randomisation. In addition, the time trend problem of platform trial can be studied in this package. There is a demo for multi-arm multi-stage trial for two different null scenario in this package.

References

Stan Development Team (2020). RStan: the R interface to Stan. R package version 2.21.2. https://mc-stan.org

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`AdaptiveRandomisation` *AdaptiveRandomisation*

Description

This is a function doing the randomisation process. This Function generates the Sequence for patient allocation to each arm, patient outcomes.

Usage

```
AdaptiveRandomisation(
  Fixratio,
  rand.algo,
  K,
  n.new,
  randomprob,
  treatmentindex,
  groupwise.response.probs,
  group,
  armleft,
```

```
  max.deviation,
  trend_add_or_multip,
  trend.function,
  trend.effect,
  ns,
  Fixratiocontrol
)
```

Arguments

`Fixratio`	A indicator TRUE/FALSE
`rand.algo`	Randomisation algorithm: "Coin": Biased coin; "Urn": Urn method
`K`	Total number of arms at the beginning
`n.new`	The cohort size
`randomprob`	A named vector of randomisation probability to each arm
`treatmentindex`	The vector of treatment arm index excluding the control arm whose index is 0
`groupwise.response.probs`	A matrix of response probability of each arm
`group`	The current stage
`armleft`	The number of treatment left in the platform (>2)
`max.deviation`	Tuning parameter of using urn randomisation method.
`trend_add_or_multip`	How time trend affects the true response probability: "add" or "mult"
`trend.function`	The function returns time trend effect regarding to different time trend pattern
`trend.effect`	The strength of time trend effect as a parameter in trend.function()
`ns`	A vector of accumulated number of patient at each stage
`Fixratiocontrol`	A numeric value indicating the weight of control in randomisation. Eg. 1 means equal randomisation, 2 means thw number of patients allocated to control is twice as large as other treatment arm.

Value

A list of patient allocation and patient outcome nstage: A vector of the number of patients allocated to each arm ystage: A vector of the patients outcome after treating with each arm znew: A vector of treatment index assigned to each patient in the current cohort ynew: A vector of outcome index record for each patient after treatment in the current cohort

Author(s)

Ziyan Wang

References

Mass weighted urn design—a new randomization algorithm for unequal allocations. Zhao, Wenle. Contemporary clinical trials 43 (2015): 209-216.

Examples

```
AdaptiveRandomisation(
Fixratio = FALSE,
rand.algo = "Urn",
K = 2,
n.new = 30,
randomprob = matrix(c(0.5, 0.5), ncol = 2, dimnames = list(c(),c("1","2"))),
treatmentindex = 1,
groupwise.response.probs = matrix(rep(c(0.4, 0.4), 5), byrow = TRUE, ncol = 2, nrow = 5),
group = 1,
armleft = 2,
max.deviation = 3,
trend_add_or_multip = "mult",
trend.function = function(ns, group, i, trend.effect) {delta = 0; return(delta)},
trend.effect = c(0, 0),
ns = c(30, 60, 90, 120, 150),
Fixratiocontrol = NA)
```

`alphaspending` *alphaspending*

Description

This function estimates the mean error rate spent at each interim analysis for a trial Example usage:

1. sapply(res = result, fun = alphaspending) will generate list of the proportion of trial replicates are stopped at each stage for all scenarios in result where result is a list containing output data for different scenario
2. sapply(sapply(result,FUN = alphaspending),sum) will generate the type I error rate or power for all scenario on the result list
3. alpha(result) generate the proportion of trial replicates are stopped at each stage where result is the output data for one specific scenario
4. sum(alpha(result)) will generate the type I error rate or power for a specific scenario

Usage

```
alphaspending(res)
```

Arguments

`res`	A list of output matrix of a number of trial replicates

Value

The error rate at each interim analysis

Author(s)

Ziyan Wang

Examples

```
## Not run: alphaspending(res)
```

`ARmethod` *ARmethod*

Description

This function adjusts the posterior randomisation probability for each arm using many approaches. Currently Thall's approach and Trippa's approach are used. Double biased coin and other method will be added in the next version.

Usage

```
ARmethod(
  Fixratio,
  BARmethod,
  group,
  stats,
  post.prob.btcontrol,
  K,
  n,
  tuningparameter,
  c,
  post.prob.best,
  max.ar,
  armleft,
  treatmentindex
)
```

Arguments

`Fixratio`	A indicator TRUE/FALSE
`BARmethod`	The indicator of which adaptive randomisation method is used
`group`	The current stage
`stats`	The output matrix
`post.prob.btcontrol`	The vector of posterior probability of each active treatment arm better than control
`K`	Total number of arms at the beginning
`n`	The vector of sample size for each arm

`tuningparameter`
: The tuning parameter indicator for Thall's approach

`c`
: The tuning parameter for Thall's approach

`post.prob.best`
: Posterior probability of each arm to be the best

`max.ar`
: The upper boundary for randomisation ratio for each arm

`armleft`
: The number of treatment left in the platform (>2)

`treatmentindex`
: The vector of treatment arm index excluding the control arm whose index is 0

Value

randomprob: The vector of adjusted randomisation probability to each arm

Author(s)

Ziyan Wang

References

Bayesian adaptive randomized trial design for patients with recurrent glioblastoma. Trippa, Lorenzo, Eudocia Q. Lee, Patrick Y. Wen, Tracy T. Batchelor, Timothy Cloughesy, Giovanni Parmigiani, and Brian M. Alexander. Journal of Clinical Oncology 30, no. 26 (2012): 3258. A simulation study of outcome adaptive randomization in multi-arm clinical trials. Wathen, J. Kyle, and Peter F. Thall. Clinical Trials 14, no. 5 (2017): 432-440.

Examples

```
ARmethod(Fixratio = FALSE,
BARmethod = "Thall",
group = 1,
stats = matrix(rep(NA, 40), ncol = 8, nrow = 5),
post.prob.btcontrol = 0.5,
K = 2,
n = c(30, 30),
tuningparameter = "fixed",
c = 1,
post.prob.best = c(0.5, 0.5),
max.ar = 0.75,
armleft = 2,
treatmentindex = 1)
```

Boundaryconstruction *Boundaryconstruction*

Description

This function constructs the stopping boundary based on input information

Usage

```
Boundaryconstruction(Stopbound.inf = Stopbound.inf, ns = ns)
```

Arguments

Stopbound.inf	The list of stop boundary information for more see Stopboundinf
ns	A vector of accumulated number of patient at each stage

Value

A list of the futility boundary and the efficacy boundary

Author(s)

Ziyan Wang

Examples

```
Stopbound.inf=list(Stop.type="Early-Pocock",Boundary.type="Symmetric",cutoff=c(0.9928,0.0072))
ns=c(60,120,180,240,300)
Boundaryconstruction(Stopbound.inf, ns)
```

dataloginformd *Cutoff screening example: the details of grid*

Description

Details of grid including famliy wise error rate of a cutoff value, the cutoff value and the square of cutoff value for modelling and prediction

Usage

```
dataloginformd
```

Format

A data frame with 24 rows and 3 variables:

`tpIE` FWER

`cutoff` Cutoff value

`cutoff2` Square of cutoff value

`demo_Cutoffscreening` *demo_Cutoffscreening*

Description

This function does a cutoff screening for trial simulation.

Usage

```
demo_Cutoffscreening(
  ntrials = 1000,
  trial.fun = simulatetrial,
  grid.inf = list(start = c(0.9, 0.95, 1), extendlength = 15),
 input.info = list(response.probs = c(0.4, 0.4), ns = c(30, 60, 90, 120, 150), max.ar =
  0.75, rand.algo = "Urn", max.deviation = 3, model.inf = list(model = "tlr", ibb.inf =
  list(pi.star = 0.5, pess = 2, betabinomialmodel = ibetabinomial.post), tlr.inf =
    list(beta0_prior_mu = 0, beta1_prior_mu = 0, beta0_prior_sigma = 2.5,
  beta1_prior_sigma = 2.5, beta0_df = 7, beta1_df = 7, reg.inf = "main", variable.inf =
  "Fixeffect")), Stop.type = "Early-Pocock", Boundary.type = "Symmetric", Random.inf =
    list(Fixratio = FALSE,
     Fixratiocontrol = NA, BARmethod = "Thall",
   Thall.tuning.inf = list(tuningparameter = "Fixed", fixvalue = 1)), trend.inf =
  list(trend.type = "step", trend.effect = c(0, 0), trend_add_or_multip = "mult")),
  cl = 2
)
```

Arguments

`ntrials`	A numeric variable indicating how many trial replicates you want to run
`trial.fun`	The function of trial simulation, related to MainFunction.R
`grid.inf`	A list of grid information to create start grid and extend grid for cutoff screening.
`input.info`	A list of input information including all information required for trial simulation.
`cl`	A numeric variable indicating how many cores you want to use in parallel programming.

Value

A vector of recommended cutoff. The final value is the latest recommended value. A plot for all tested cutoff and error rate

Author(s)

Ziyan Wang

Examples

```
demo_Cutoffscreening(ntrials = 2, cl = 2,
    grid.inf = list(start = c(0.9, 0.95, 1), extendlength = 2))
```

---

demo_Cutoffscreening.GP

A demo for cutoff screening using Bayesian optimisation

Description

This function does a cutoff screening for trial simulation using Bayesian optimisation.

Usage

```
demo_Cutoffscreening.GP(
  ntrials = 1000,
  trial.fun = simulatetrial,
 grid.inf = list(start.length = 10, grid.min = NULL, grid.max = NULL, confidence.level =
   0.95, grid.length = 5000, change.scale = FALSE, noise = TRUE, errorrate = 0.1,
    simulationerror = 0.01, iter.max = 15, plotornot = FALSE),
 input.info = list(response.probs = c(0.15, 0.15, 0.15, 0.15), ns = c(120, 240, 360,
    480, 600), max.ar = 0.85, rand.algo = "Urn", max.deviation = 3, model.inf =
   list(model = "tlr", ibb.inf = list(pi.star = 0.5, pess = 2, betabinomialmodel =
    ibetabinomial.post), tlr.inf = list(beta0_prior_mu = 0, beta1_prior_mu = 0,
  beta0_prior_sigma = 2.5, beta1_prior_sigma = 2.5, beta0_df = 7, beta1_df = 7, reg.inf
  = "main", variable.inf = "Fixeffect")), Stop.type = "Early-OBF", Boundary.type =
    "Symmetric", Random.inf = list(Fixratio = FALSE,
     Fixratiocontrol = NA,
  BARmethod = "Thall", Thall.tuning.inf = list(tuningparameter = "Unfixed", fixvalue =
    1)), trend.inf = list(trend.type = "step", trend.effect = c(0, 0, 0, 0),
    trend_add_or_multip = "mult")),
  cl = 2
)
```

Arguments

ntrials	A numeric variable indicating how many trial replicates you want to run
trial.fun	The function of trial simulation, related to MainFunction.R
grid.inf	A list of grid information to create start grid and extend grid for cutoff screening. 'start.length' is the size of start grid. Default is 10. 'grid.min' is the lower bound for screening grid. 'grid.max' is the upper bound for screening grid. 'errorrate' refers to the target of type I error rate or family-wise error

rate. 'confidence.level' is a numeric value indicating the confidence level of estimate. Default is 0.95. 'grid.length' is the accuracy of grid. Default is 5000. 'change.scale' is a logic value indicating whether we want to change scale when doing Gaussian process. Default is FALSE. 'noise' is a logic value indicating whether the input x is noisy. Default is TRUE. 'simulationerror' is a numeric value indicating the tolerable error for simulated type I error rate. Default is 0.01, 'iter.max' is a numeric value indicating the maximum number of evaluations. Default is 15. 'plotornot' is a logic value indicating whether the errorrate vs grid plot needed to be generated at each iteration. Default is FALSE.

`input.info` A list of input information including all information required for trial simulation.

`cl` A numeric variable indicating how many cores you want to use in parallel programming.

Value

A vector of recommended cutoff. The final value is the latest recommended value. A plot for all tested cutoff and error rate

Author(s)

Ziyan Wang

Examples

```
demo_Cutoffscreening.GP(ntrials = 2, cl = 2,
    grid.inf = list(
    start.length = 10,
    confidence.level = 0.95,
    grid.length = 5000,
    change.scale = FALSE,
    noise = TRUE,
    errorrate = 0.1,
    simulationerror = 0.01,
    iter.max = 15,
    plotornot = FALSE))
```

---

demo_multscenario *demo_multscenario*

Description

This is a demo function simulating multi-arm multi-stage design with two different null scenarios where the response probability of control is 0.15 and 0.4, respectively. The clinically meaningful increment on probability scale is 0.2. The stopping boundary is the OBF. The cutoff vector in the demo is tuned to keep Type I error rate to be 0.05. The output data can be saved as .RData file

Usage

```
demo_multscenario(ntrials = 1000, cl = 2, save_data = FALSE)
```

Arguments

ntrials	A numeric value. The number of total trail replicates for each scenario.
cl	A numeric variable indicating how many cores you want to use in parallel programming.
save_data	An indicator of whether the output data need to be saved. Default is FALSE.

Value

A list of data for plotting. One is results of trial replicates for all scenarios. The other one is a data frame containing all summarised evaluation metrics for all scenarios

Author(s)

Ziyan Wang

Examples

```
demo_multscenario(ntrials = 2, cl = 2, save_data = FALSE)
```

FWER_disconjunctivepowerfunc *FWER_disconjunctivepowerfunc*

Description

This function reads in the output matrix of a number of trial replicates to calculate the Family wise error rate or disconjunctive power

Usage

```
FWER_disconjunctivepowerfunc(res)
```

Arguments

res	A list of output matrix of a number of trial replicates

Value

Family wise error rate or disconjunctive power

Examples

```
## Not run: FWER_disconjunctivepowerfunc(res)
```

GP.optim *GP.optim: optimiser to give the next cutoff for evaluation*

Description

A function to predict the next cutoff value for evaluation.

Usage

```
GP.optim(
  x,
  y,
  errorrate = 0.05,
  confidence.level = 0.95,
  grid.length = 5000,
  change.scale = FALSE,
  noise = T,
  grid.min,
  grid.max
)
```

Arguments

x	A numeric vector of cutoff data
y	A numeric vector of error rate data
errorrate	A numeric value. The error rate we want to achieve. Error rate here means type I error rate or family-wise error rate. Default is 0.05.
confidence.level	A numeric value indicating the confidence level of estimate. Default is 0.95
grid.length	A numeric value indicating the grid resolution. Default is 5000.
change.scale	A logic value indicating whether we want to change scale when doing Gaussian process. Default is FALSE.
noise	A logic value indicating whether the input x is noisy. Default is TRUE.
grid.min	A numeric value indicating the lower bound of the grid for screening.
grid.max	A numeric value indicating the upper bound of the grid for screening.

Value

A list including the next cutoff value for evaluation `next.cutoff` and a list of predictions for screening grid.

Author(s)

Ziyan Wang

References

Surrogates: Gaussian process modeling, design, and optimization for the applied sciences. CRC press. Gramacy, R.B., 2020. Bayesian optimization for adaptive experimental design: A review. IEEE access, 8, 13937-13948. Greenhill, S., Rana, S., Gupta, S., Vellanki, P., & Venkatesh, S. (2020).

Examples

```
x = c(7.123968, 6.449631, 1.984406,
3.507463, 4.972510, 2.925768,
5.816682, 4.367796,
7.349160, 1.113648)
y = c(0.0396, 0.0450,
0.5116, 0.2172,
0.1040, 0.3058,
0.0592, 0.1384,
0.0296, 0.7936)
grid.min=1
grid.max=8
GP.res=GP.optim(x=x, y=y, errorrate = 0.1, grid.min = grid.min, grid.max = grid.max)
GP.res$next.cutoff
```

---

ibetabinomial.post *ibetabinomial.post*

Description

This function calculates the posterior probability of each active treatment arm better than control using betabinomial model

Usage

```
ibetabinomial.post(n, y, pi.star = 0.5, pess = 2)
```

Arguments

n	A vector of treated patients for each arm (The first element is for control)
y	A vector of treated patient outcomes for each arm (The first element is for control)
pi.star	The prior response probability. The default is 0.5
pess	The effective sample size of beta prior. The default is 2

Value

A vector posterior probability of each active treatment arm better than control

Author(s)

Ziyan Wang

Examples

```
n <- c(20,20,20,20)
y <- c(12,12,12,6)
ibetabinomial.post(n, y, pi.star = 0.5, pess = 2)
#[1] 0.5000000 0.5000000 0.0308018
```

Initializetrialparameter

Initializetrialparameter

Description

This function initialises the inner parameter used in simulate.trial function

Usage

```
Initializetrialparameter(response.probs, ns)
```

Arguments

response.probs	A vector of response probability of each arm
ns	A vector of accumulated number of patient at each stage

Value

A list of initialised parameters including the number of arms for this trial 'K', the number of arm active 'armleft', the index of treatment arm 'treatmentindex', the vector of total number of patients allocated to each arm 'n' the number of total number of patients survived for each arm 'y1', the matrix for true response probability of each arm at each stage 'groupwise.response.probs' which is required for the time trend study, the vector of randomisation probability for each arm 'randomprob', the array of arm assignment for each patient 'z', the array of outcome for each patient 'y', the array of the stage index for each patient 'group_indicator', the matrix of the probability of each arm to be the best at each stage 'post.prob.best.mat'.

Author(s)

Ziyan Wang

Examples

```
Initializetrialparameter(response.probs = c(0.4,0.6), ns = c(15,30,45,60,75,90))

#$K
#[1] 2

#$armleft
#[1] 2

#$treatmentindex
#[1] 1

#$n
#[1] 0 0

#$y1
#[1] 0 0

#$groupwise.response.probs
#     [,1] [,2]
#[1,]  0.4  0.6
#[2,]  0.4  0.6
#[3,]  0.4  0.6
#[4,]  0.4  0.6
#[5,]  0.4  0.6
#[6,]  0.4  0.6

#$randomprob
#     1   2
#[1,] 0.5 0.5

#$z
#numeric(0)

#$y
#numeric(0)

#$group_indicator
#numeric(0)

#$post.prob.best.mat
#     0 1
#[1,] 0 0
#[2,] 0 0
#[3,] 0 0
#[4,] 0 0
#[5,] 0 0
#[6,] 0 0
```

intbias *intbias*

Description

This function estimates the mean bias of treatment - stage interaction effect

Usage

```
intbias(res)
```

Arguments

res	A list of output matrix of a number of trial replicates

Value

A matrix of mean treatment - stage interaction effect bias

Examples

```
## Not run: intbias(res)
```

Meanfunc *Meanfunc*

Description

This function reads in the output matrix of a number of trial replicates to calculate mean treatment effect estimate.

Usage

```
Meanfunc(res)
```

Arguments

res	A list of output matrix of a number of trial replicates

Value

Mean treatment effect estimates of each treatment arm

Examples

```
## Not run: Meanfunc(res)
```

modelinf.fun *modelinf.fun*

Description

This function summarize the input parameters describing the model for analysis and transfer them into a list

Usage

```
modelinf.fun(
  model = "tlr",
  ibb.inf = list(pi.star = 0.5, pess = 2, betabinomialmodel = ibetabinomial.post),
  tlr.inf = list(beta0_prior_mu = 0, beta1_prior_mu = 0, beta0_prior_sigma = 2.5,
   beta1_prior_sigma = 2.5, beta0_df = 7, beta1_df = 7, reg.inf = "main", variable.inf =
    "Fixeffect")
)
```

Arguments

model	The statistical model. ibb: betabinomial model / tlr: logistic model
ibb.inf	The list of information for betabinomial model including: betabinomialmodel: The betabinomial model, pi.star: prior response rate, pess: prior effective sample size
tlr.inf	The list of information for logistic model including: The mean (mu), variance (sigma), degree of freedom (df) of the intercept and the main effect of the linear terms in logistic model. reg.inf: The type of linear function in logistic model. variable.inf: Fixeffect/Mixeffect. Indicating whether a mix effect model is used (for time trend effect modelling)

Value

A list of model information including model, ibb.inf and tlr.inf

Author(s)

Ziyan Wang

Examples

```
modelinf.fun(model = "tlr",
  ibb.inf = list(pi.star = 0.5,
                 pess = 2,
                 betabinomialmodel = ibetabinomial.post),
  tlr.inf = list(beta0_prior_mu = 0,
                 beta1_prior_mu = 0,
                 beta0_prior_sigma = 2.5,
                 beta1_prior_sigma = 2.5,
```

```
beta0_df = 7,
beta1_df = 7,
reg.inf =  "main",
variable.inf = "Fixeffect"
))
```

Nfunc *Nfunc*

Description

This function reads in the output matrix of a number of trial replicates to calculate mean estimate of total number of patients allocated to each arm

This function reads in the output matrix of a number of trial replicates to calculate mean estimate of total number of patients allocated to each arm

Usage

```
Nfunc(res)
```

```
Nfunc(res)
```

Arguments

res	A list of output matrix of a number of trial replicates

Value

The mean estimate of total number of patients allocated to each arm

The mean estimate of total number of patients allocated to each arm

Examples

```
## Not run: Nfunc(res)
## Not run: Nfunc(res)
```

OPC_alt *Operation characteristic table for alternative scenario*

Description

Operation characteristic table for alternative scenario using main + continuousstage model. The time trend pattern is step. The strength of time trend is 0.1 equally for all arm. The effect of time trend on true response probability is multiplicative.

Usage

```
OPC_alt
```

Format

A data frame with 3 rows and 16 variables:

`Type.I.Error.or.Power` Power

`Bias.1` Treatment effect bias for treatment 1

`Bias.2` Treatment effect bias for treatment 2

`Bias.3` Treatment effect bias for treatment 3

`rMSE.1` Rooted mean squared error for treatment 1

`rMSE.2` Rooted mean squared error for treatment 2

`rMSE.3` Rooted mean squared error for treatment 3

`N.per.arm.1` Mean total number of patient allocated to control

`N.per.arm.2` Mean total number of patient allocated to treatment 1

`N.per.arm.3` Mean total number of patient allocated to treatment 2

`N.per.arm.4` Mean total number of patient allocated to treatment 3

`Survive.per.arm.1` Mean total number of patient allocated to control

`Survive.per.arm.2` Mean total number of patient survived when using treatment 1

`Survive.per.arm.3` Mean total number of patient survived when usin treatment 2

`Survive.per.arm.4` Mean total number of patient survived when usin treatment 3

`N` Mean total number of patient in a trial

OPC_null *Operation characteristic table for null scenario*

Description

Operation characteristic table for null scenario using main and main + continuousstage model. The main effect model was run for a null scenario with and without time trend. The time trend pattern is step. The strength of time trend is 0.1 equally for all arm. The effect of time trend on true response probability is multiplicative.

Usage

```
OPC_null
```

Format

A data frame with 3 rows and 16 variables:

`Type.I.Error.or.Power` Family wise error rate

`Bias.1` Treatment effect bias for treatment 1

`Bias.2` Treatment effect bias for treatment 2

`Bias.3` Treatment effect bias for treatment 3

`rMSE.1` Rooted mean squared error for treatment 1

`rMSE.2` Rooted mean squared error for treatment 2

`rMSE.3` Rooted mean squared error for treatment 3

`N.per.arm.1` Mean total number of patient allocated to control

`N.per.arm.2` Mean total number of patient allocated to treatment 1

`N.per.arm.3` Mean total number of patient allocated to treatment 2

`N.per.arm.4` Mean total number of patient allocated to treatment 3

`Survive.per.arm.1` Mean total number of patient allocated to control

`Survive.per.arm.2` Mean total number of patient survived when using treatment 1

`Survive.per.arm.3` Mean total number of patient survived when usin treatment 2

`Survive.per.arm.4` Mean total number of patient survived when usin treatment 3

`N` Mean total number of patient in a trial

OPC_Trial.simulation *Operation characteristic table for Trial.simulation() null scenario*

Description

Operation characteristic table for null scenario using main model.

Usage

```
OPC_Trial.simulation
```

Format

A data frame with 1 rows and 8 variables:

`Type.I.Error.or.Power` Power

`Bias` Treatment effect bias for treatment 1

`rMSE` Rooted mean squared error for treatment effect 1

`N.per.arm.1` Mean total number of patient allocated to control

`N.per.arm.2` Mean total number of patient allocated to treatment 1

`Survive.per.arm.1` Mean total number of patient allocated to control

`Survive.per.arm.2` Mean total number of patient survived when using treatment 1

`N` Mean total number of patient in a trial

optimdata *A list of data from Gaussian process for cutoff screening.*

Description

A list of data from Gaussian process for cutoff screening.

Usage

```
optimdata
```

Format

A list with two element:

`next.cutoff` The cutoff value for the next evaluation

`prediction` A list of values from Gaussian process model

`tpIE` A vector of type I error rate data

`cutoff` A vector of cutoff data

OutputStats.initialising
OutputStats.initialising

Description

This function initializes the output matrix including all evaluation metrics based on input information

Usage

```
OutputStats.initialising(variable.inf, reg.inf, ns, K)
```

Arguments

variable.inf	The parameter information in the model
reg.inf	The model information. For the fixed effect model, the input of reg.inf can be main, main + stage_continuous, main * stage_continuous, main + stage_discrete, main * stage_discrete. For the mixed effect model, the reg.inf is invalid.
ns	A vector of accumulated number of patient at each stage
K	Total number of arm including control

Value

The empty output matrix including different evaluation metrics.

Author(s)

Ziyan Wang

Examples

```
OutputStats.initialising(
    variable.inf = "Fixeffect",
    reg.inf = "main",
    ns = c(15, 30, 45, 60, 75),
    K = 2)
```

perHtypeIerror_powerfunc *perHtypeIerror_powerfunc*

Description

This function reads in the output matrix of a number of trial replicates to calculate the error rate

Usage

```
perHtypeIerror_powerfunc(res)
```

Arguments

res	A list of output matrix of a number of trial replicates

Value

Type I error rate or power of each treatment - control comparison

Author(s)

Ziyan Wang

Examples

```
## Not run: perHtypeIerror_powerfunc(res)
```

predictedtpIEinformd *Cutoff screening example: the predicted value from quadratic model*

Description

The predicted value from quadratic model for famliy wise error rate vs cutoff value plotting

Usage

```
predictedtpIEinformd
```

Format

A data frame with 1001 rows and 1 variables:

predictedtpIEinformd The predicted FWER value of a large grid

Randomisation.inf *Randomisation.inf*

Description

This function checks the validity of the randomisation information input

Usage

```
Randomisation.inf(
  Random.inf = list(Fixratio = FALSE, Fixratiocontrol = NA, BARmethod = "Thall",
    Thall.tuning.inf = list(tuningparameter = "Fixed", fixvalue = 1))
)
```

Arguments

Random.inf	A list of adaptive randomisation information. 'Fixratio' a indicator of whether the randomisation process uses fix ratio. Default is FALSE. 'Fixratiocontrol' the numerical value indicating the randomisation weight of the control arm compared to the treatment arms. Default is NA for Fixratio = FALSE. 'BARmethod' the Bayesian adaptive randomisation type. Default is "Thall" indicating the use of Thall's approach in the randomisation process. The other value is 'Trippa'. 'Thall.tuning.inf' the list of tuning parameter for Thall's approach including 'tuningparameter' (Default is "Fixed" indicating that the tuning paramter is fixed for all stages) and 'fixvalue' (Default is 1).

Value

A list of input randomisation information

Author(s)

Ziyan Wang

Examples

```
Randomisation.inf(Random.inf = list(
Fixratio = FALSE,
Fixratiocontrol = NA,
BARmethod = "Thall",
Thall.tuning.inf = list(tuningparameter = "Fixed",  fixvalue = 1)
))
```

recommandloginformd *Cutoff screening example: the recommended grid value at each time point*

Description

he recommended grid value at each time point. There are 20 cutoff value explored

Usage

```
recommandloginformd
```

Format

A data frame with 20 rows and 1 variables:

`recommandloginformd` The cutoff value at each time point

resultrtostats *resultrtostats*

Description

This is an inner function of the function `resultstantoRfunc`

Usage

```
resultrtostats(
  trteff = NA,
  treatmentindex = NA,
  armleft,
  K,
  group,
  reg.inf,
  fit,
  ns
)
```

Arguments

`trteff`	Stan posterior samples of treatment effect sample distribution
`treatmentindex`	A vector of treatment index at the beginning of a trial
`armleft`	The number of treatment left in the platform (>2)
`K`	Total number of arms at the beginning
`group`	The current stage

reg.inf	The information of how much accumulated information will be used
fit	The stan output
ns	A vector of accumulated number of patient at each stage

Value

A list of stan result inference stats1: A vector of posterior probability for all treatment arms including dropped and active treatment arm stats4: The mean treatment effect estimate of each treatment compared to control stats5: The variance of treatment effect estimate of each treatment compared to control post.prob.btcontrol: a vector including Posterior probability of each active treatment arm better than control

Author(s)

Ziyan Wang

Examples

```
## Not run: resultrtostats(trteff = NA, treatmentindex = NA, armleft, K, group, reg.inf, fit, ns)
```

---

resultrtostats.rand *resultrtostats.rand*

Description

The inner function of function resultstantoRfunc.rand

Usage

```
resultrtostats.rand(
  trteff = NA,
  treatmentindex = NA,
  armleft,
  K,
  group,
  fit,
  ns
)
```

Arguments

trteff	Stan posterior samples of treatment effect sample distribution
treatmentindex	A vector of treatment index at the beginning of a trial
armleft	The number of treatment left in the platform (>2)
K	Total number of arms at the beginning
group	The current stage
fit	The stan output
ns	A vector of accumulated number of patient at each stage

Value

A list of stan result inference stats1: A vector of posterior probability for all treatment arms including dropped and active treatment arm stats4: The mean treatment effect estimate of each treatment compared to control stats5: The variance of treatment effect estimate of each treatment compared to control post.prob.btcontrol: a vector including Posterior probability of each active treatment arm better than control

Author(s)

Ziyan Wang

Examples

```
## Not run: resultrtostats.rand(trteff = NA, treatmentindex = NA, armleft, K, group, fit, ns)
```

`resultstantoRfunc` *resultstantoRfunc*

Description

This function summarise the fix effect stan output data to and transform them to be readable.

Usage

```
resultstantoRfunc(
  group,
  reg.inf,
  variable.inf,
  fit,
  armleft,
  treatmentindex,
  K,
  ns
)
```

Arguments

`group`	The current stage
`reg.inf`	The information of how much accumulated information will be used
`variable.inf`	The information of whether to use random effect model or fix effect model.
`fit`	The stan output
`armleft`	The number of treatment left in the platform (>2)
`treatmentindex`	A vector of treatment index at the beginning of a trial
`K`	Total number of arms at the beginning
`ns`	A vector of accumulated number of patient at each stage

Value

A list of stan result inference stats1: A vector of posterior probability for all treatment arms including dropped and active treatment arm stats4: The mean treatment effect estimate of each treatment compared to control stats5: The variance of treatment effect estimate of each treatment compared to control post.prob.btcontrol: a vector including Posterior probability of each active treatment arm better than control stats6: A vector of mean stage (time trend) effect estimate stats7: A vector of mean treatment - stage (time trend) interaction effect estimate sampefftotal: The posterior samples of response probability of each active arm on logit scale. This can be transformed to probit scale by using inv.logit() function.

Author(s)

Ziyan Wang

Examples

```
## Not run: resultstantoRfunc(group, reg.inf, fit, armleft, treatmentindex, K, ns)
```

`resultstantoRfunc.rand` *resultstantoRfunc.rand*

Description

This function summarise the mix effect stan output data to and transform them to be readable.

Usage

```
resultstantoRfunc.rand(group, fit, armleft, treatmentindex, K, ns)
```

Arguments

`group`	The current stage
`fit`	The stan output
`armleft`	The number of treatment left in the platform (>2)
`treatmentindex`	A vector of treatment index at the beginning of a trial
`K`	Total number of arms at the beginning
`ns`	A vector of accumulated number of patient at each stage

Value

A list of stan result inference stats1: A vector of posterior probability for all treatment arms including dropped and active treatment arm stats4: The mean treatment effect estimate of each treatment compared to control stats5: The variance of treatment effect estimate of each treatment compared to control post.prob.btcontrol: a vector including Posterior probability of each active treatment arm better than control stats6: A vector of mean stage (time trend) effect estimate stats7: A vector of mean treatment - stage (time trend) interaction effect estimate sampefftotal: The posterior samples of response probability of each active arm on logit scale. This can be transformed to probit scale by using inv.logit() function.

Author(s)

Ziyan Wang

Examples

```
## Not run: resultstantoRfunc.rand(group, fit, armleft, treatmentindex, K, ns)
```

`Save.resulttoRDatafile`

Save.resulttoRDatafile

Description

This function generates the name of file for output table and dataset

Usage

```
Save.resulttoRDatafile(
 input.info = list(response.probs = c(0.4, 0.4), ns = c(30, 60, 90, 120, 150), max.ar =
  0.75, rand.type = "Urn", max.deviation = 3, model.inf = list(model = "tlr", ibb.inf =
  list(pi.star = 0.5, pess = 2, betabinomialmodel = ibetabinomial.post), tlr.inf =
   list(beta0_prior_mu = 0, beta1_prior_mu = 0, beta0_prior_sigma = 2.5,
  beta1_prior_sigma = 2.5, beta0_df = 7, beta1_df = 7, reg.inf = "main", variable.inf =
  "Fixeffect")), Stopbound.inf = Stopboundinf(Stop.type = "Early-Pocock", Boundary.type
   = "Symmetric", cutoff = c(0.99,
    0.01)), Random.inf = list(Fixratio = FALSE,
  Fixratiocontrol = NA, BARmethod = "Thall", Thall.tuning.inf = list(tuningparameter =
  "Fixed", fixvalue = 1)), trend.inf = list(trend.type = "step", trend.effect = c(0,
   0), trend_add_or_multip = "mult"))
)
```

Arguments

`input.info`	A list of input information require for trial simulation

Value

A list of name for table and dataset

Author(s)

Ziyan Wang

Examples

```
Save.resulttoRDatafile(
input.info = list(
  response.probs = c(0.4, 0.4),
  ns = c(30, 60, 90, 120, 150),
  max.ar = 0.75,
  rand.type = "Urn",
  max.deviation = 3,
  model.inf = list(
    model = "tlr",
    ibb.inf = list(
      pi.star = 0.5,
      pess = 2,
      betabinomialmodel = ibetabinomial.post
    ),
    tlr.inf = list(
      beta0_prior_mu = 0,
      beta1_prior_mu = 0,
      beta0_prior_sigma = 2.5,
      beta1_prior_sigma = 2.5,
      beta0_df = 7,
      beta1_df = 7,
      reg.inf =  "main",
      variable.inf = "Fixeffect"
    )
  ),
  Stop.type = "Early-Pocock",
  Boundary.type = "Symmetric",
  Random.inf = list(
    Fixratio = FALSE,
    Fixratiocontrol = NA,
    BARmethod = "Thall",
    Thall.tuning.inf = list(tuningparameter = "Fixed",  fixvalue = 1)
  ),
  trend.inf = list(
    trend.type = "step",
    trend.effect = c(0, 0),
    trend_add_or_multip = "mult"
  )
))
```

simulatetrial *simulatetrial*

Description

This function simulates a MAMS trial applying adaptive methods where the time trend effect can be studied.

Usage

```
simulatetrial(
  ii,
  response.probs = c(0.4, 0.4),
  ns = c(30, 60, 90, 120, 150),
  max.ar = 0.75,
  rand.algo = "Urn",
  max.deviation = 3,
  model.inf = list(model = "tlr", ibb.inf = list(pi.star = 0.5, pess = 2,
    betabinomialmodel = ibetabinomial.post), tlr.inf = list(beta0_prior_mu = 0,
   beta1_prior_mu = 0, beta0_prior_sigma = 2.5, beta1_prior_sigma = 2.5, beta0_df = 7,
    beta1_df = 7, reg.inf = "main", variable.inf = "Fixeffect")),
  Stopbound.inf = Stopbound.inf,
  Random.inf = Random.inf,
  trend.inf = trend.inf
)
```

Arguments

ii	Meaning less parameter but required for foreach function in doParallel package
response.probs	A vector of true response probability for each arm. Default response.probs = c(0.4, 0.4).
ns	A vector of accumulated number of patient at each stage. Default is ns = c(30, 60, 90, 120, 150).
max.ar	The upper boundary for randomisation ratio for each arm. Default is 0.75 for a two arm trial. The minimum value depends on K where 1 - max.ar <= 1/K
rand.algo	The method of applying patient allocation with a given randomisation probability vector. Default is "Urn".
max.deviation	The tuning parameter for Urn randomisation method. Default is 3.
model.inf	The list of interim data analysis model information for more see modelinf.fun
Stopbound.inf	The list of stop boundary information for more see Stopboundinf
Random.inf	The list of Adaptive randomisation information for more see Randomisation.inf
trend.inf	The list of time trend information

Value

A matrix including all evaluation metrics

Author(s)

Ziyan Wang

Examples

```
set.seed(1)
simulatetrial(response.probs = c(0.4, 0.4),
              ns = c(30, 60, 90, 120, 150),
              max.ar = 0.75,
              rand.algo = "Urn",
              max.deviation = 3,
              model.inf = list(
              model = "tlr",
              ibb.inf = list(
              pi.star = 0.5,
              pess = 2,
              betabinomialmodel = ibetabinomial.post
              ),
              tlr.inf = list(
              beta0_prior_mu = 0,
              beta1_prior_mu = 0,
              beta0_prior_sigma = 2.5,
              beta1_prior_sigma = 2.5,
              beta0_df = 7,
              beta1_df = 7,
              reg.inf =  "main",
              variable.inf = "Fixeffect"
              )
              ),
              Stopbound.inf = Stopboundinf(
              Stop.type = "Early-Pocock",
              Boundary.type = "Symmetric",
              cutoff = c(0.99,0.01)
              ),
              Random.inf = list(
              Fixratio = FALSE,
              Fixratiocontrol = NA,
              BARmethod = "Thall",
              Thall.tuning.inf = list(tuningparameter = "Fixed",  fixvalue = 1)
              ),
              trend.inf = list(
              trend.type = "step",
              trend.effect = c(0, 0),
              trend_add_or_multip = "mult"
              ))
```

Sperarmfunc *Sperarmfunc*

Description

This function reads in the output matrix of a number of trial replicates to calculate mean total number of survived patients of each arm

This function reads in the output matrix of a number of trial replicates to calculate mean total number of survived patients of each arm

Usage

```
Sperarmfunc(res)

Sperarmfunc(res)
```

Arguments

res	A list of output matrix of a number of trial replicates

Value

The mean total number of survived patients of each arm

The mean total number of survived patients of each arm

Examples

```
## Not run: Sperarmfunc(res)
## Not run: Sperarmfunc(res)
```

stan.logisticmodeltrans *stan.logisticmodeltrans*

Description

This function transform the data in trial simulation to the data required for stan modelling

Usage

```
stan.logisticmodeltrans(
  z,
  y,
  randomprob,
  group_indicator,
  armleft,
  group,
  variable.inf,
  reg.inf
)
```

Arguments

z	A vector of all treatment index data from the beginning of a trial
y	A vector of all outcome data from the beginning of a trial
randomprob	A named vector of randomisation probability to each arm
group_indicator	A vector for the stage at which each patient was treated
armleft	The number of treatment left in the platform (>2)
group	The current stage
variable.inf	Fixeffect/Mixeffect for logistic model parameter
reg.inf	The information of how much accumulated information will be used

Value

A list of information require for the stan model including: zdropped: The vector of treatment index for each patient whose treatment arm is active at current stage. ydropped: The vector of outcome index for each patient whose treatment arm is active at current stage. Ndropped: The total number of patients that are treated with active treatment arms at current stage. group_indicator_dropped: The vector of stage index for each patient whose treatment arm is active at current stage. zlevel: The active treatment arm index at current stage xdummy: A design matrix transformed from zdropped and group_indicator_dropped for modelling

Author(s)

Ziyan Wang

Examples

```
stan.logisticmodeltrans(
z = c(1,2,1,2,2,1,2,1),
y = c(0,0,0,0,1,1,1,1),
randomprob = matrix(c( 0.5, 0.5), ncol = 2, dimnames = list(c("Stage1"), c("1", "2"))),
group_indicator = c(1,1,1,1,1,1,1,1),
armleft = 2,
group = 1,
```

```
variable.inf = "Fixeffect",
reg.inf = "main")
```

`Stopboundinf` *Stopboundinf*

Description

This function summaries and checks stopping boundary information.

Usage

```
Stopboundinf(
  Stop.type = "Early-Pocock",
  Boundary.type = "Symmetric",
  cutoff = c(0.9928, 0.0072)
)
```

Arguments

`Stop.type`	The type of stopping boundary should be "Early-Pocock", "Early-OBF" and "Noearly". Default is "Early-Pocock" which is the Pocock boundary with early stopping.
`Boundary.type`	Whether the futility boundary and the efficacy boundary are the same conservative. Default is "Symmetric" which means they are as conservative as each other. Boundary.type = "Asymmetric" means that the efficacy boundary and the futility boundary are not as conservative as each other
`cutoff`	= c(cutoff1, cutoff2). A numerical vector of cutoff value for each boundary. The first element is the efficacy boundary cutoff. The second element is the futility boundary cutoff Pr(theta_1 > theta_0|D_n) > cutoff1. Should input the cutoff1 for efficacy boundary as the first element Pr(theta_1 < theta_0|D_n) < cutoff2. Should input the cutoff2 for futility boundary as the first element

Value

The list of information required for boundary construction function 'Stopbound.inf'

Author(s)

Ziyan Wang

Examples

```
Stop.type = "Early-Pocock" #(Pocock boundarty is a flat boundary across time)
Boundary.type = "Symmetric"
cutoff = c(0.9928, 0.0072)

Stopbound.inf = Stopboundinf(Stop.type, Boundary.type, cutoff)
#Stopbound.inf
#$Stop.type
# [1] "Early-Pocock"
#$Boundary.type
#[1] "Symmetric"
#$cutoff
# [1] 0.9928 0.0072
```

`Timetrend.fun` *Timetrend.fun*

Description

This function generate the time trend function based on trend information. This function also check the validity of the input time trend information.

Usage

```
Timetrend.fun(trend.inf)
```

Arguments

`trend.inf`	The list of information for time trend effect including 'trend.type', 'trend.effect', 'trend_add_or_multip'. 'trend.type' is the shape of time trend. Default is "step". Other types are "linear", "inverse.U.linear", "plateau". "trend.effect" the vector of the strength of time trend for each arm. The first element is for the control arm. "trend_add_or_multip" the pattern of time trend affecting the true response probability. Default is "mult".

Value

A list containing the time trend function according to input trend.type variable, and a indicator of whether there is a time trend in data generation based on input trend information

Author(s)

Ziyan Wang

Examples

```
Timetrend.fun(trend.inf = list(
               trend.type = "step",
               trend.effect = c(0, 0),
               trend_add_or_multip = "mult"
               ))
```

`Trial.simulation` *Trial simulation*

Description

This function simulates and does final analysis of a trial with one scenario. The time cost of this function depend on the cpu cores of the user's cpmputer.

Usage

```
Trial.simulation(
  ntrials = 5000,
  trial.fun = simulatetrial,
 input.info = list(response.probs = c(0.4, 0.4), ns = c(30, 60, 90, 120, 150), max.ar =
  0.75, rand.algo = "Urn", max.deviation = 3, model.inf = list(model = "tlr", ibb.inf =
  list(pi.star = 0.5, pess = 2, betabinomialmodel = ibetabinomial.post), tlr.inf =
    list(beta0_prior_mu = 0, beta1_prior_mu = 0, beta0_prior_sigma = 2.5,
  beta1_prior_sigma = 2.5, beta0_df = 7, beta1_df = 7, reg.inf = "main", variable.inf =
  "Fixeffect")), Stopbound.inf = Stopboundinf(Stop.type = "Early-Pocock", Boundary.type
    = "Symmetric", cutoff = c(0.99,
      0.01)), Random.inf = list(Fixratio = FALSE,
  Fixratiocontrol = NA, BARmethod = "Thall", Thall.tuning.inf = list(tuningparameter =
  "Fixed", fixvalue = 1)), trend.inf = list(trend.type = "step", trend.effect = c(0,
    0), trend_add_or_multip = "mult")),
  cl = 2
)
```

Arguments

`ntrials`	A numeric variable indicating how many trial replicates you want to run. Default is 5000.
`trial.fun`	The function of trial simulation for more see `simulatetrial`
`input.info`	A list of input information including all information required for trial simulation.
`cl`	A numeric variable indicating how many cores you want to use in parallel programming.

Value

A list of output including the final output of each trial replicates called 'result' The analysis result table of the specific trial called 'OPC' and the file name for saving these output on the computer

Author(s)

Ziyan Wang

Examples

```
set.seed(1)
Trial.simulation(ntrials = 2, cl = 2)
```

---

trtbias *trtbias*

Description

This function estimates the mean bias of treatment effect

Usage

```
trtbias(res, trueeffect)
```

Arguments

res	A list of output matrix of a number of trial replicates
trueeffect	A vector of true treatment effect in each scenario

Value

A matrix of mean treatment effect bias

Examples

```
## Not run: trtbias(res, trueeffect)
```

---

trteffect *trteffect*

Description

This function estimates the mean treatment effect bias and its rooted mean squared error

Usage

```
trteffect(res, trueeff)
```

Arguments

res	A list of output matrix of a number of trial replicates
trueeff	A vector of true treatment effect in each scenario

Value

A vector of mean treatment effect bias and its rooted mean squared error

Examples

```
## Not run: trteffect(res, trueeff)
```

`varfunc` *varfunc*

Description

This function reads in the output matrix of a number of trial replicates to calculate the variance of treatment effect estimate.

Usage

```
varfunc(res)
```

Arguments

`res`	A list of output matrix of a number of trial replicates

Value

The variance of Treatment effect estimates of each treatment arm

Examples

```
## Not run: varfunc(res)
```

Index