Package: visit (via r-universe)

August 27, 2024

Title Vaccine Phase I Design with Simultaneous Evaluation of Immunogenicity and Toxicity

Version 2.2

Author Zilu Wang [aut, cre] Chenguang Wang [aut, cre] Gary L Rosner [aut] Richard BS Roden [aut] Trustees of Columbia University [cph] (tools/make_cpp.R, R/stanmodels.R)

Maintainer Chenguang Wang <cwang68@jhmi.edu>

Description Phase I clinical trials are the first step in drug development to test a new drug or drug combination on humans. Typical designs of Phase I trials use toxicity as the primary endpoint and aim to find the maximum tolerable dosage. However, these designs are poorly applicable for the development of cancer therapeutic vaccines because the expected safety concerns for these vaccines are not as much as cytotoxic agents. The primary objectives of a cancer therapeutic vaccine phase I trial thus often include determining whether the vaccine shows biologic activity and the minimum dose necessary to achieve a full immune or even clinical response. This package implements a Bayesian Phase I cancer vaccine trial design that allows simultaneous evaluation of safety and immunogenicity outcomes. See Wang et al. (2019) <DOI:10.1002/sim.8021> for further details.

Depends methods, R (>= 3.5.0), rstan (>= 2.19.2), Rcpp (>= 1.0.2)

License GPL (>= 3)

LinkingTo BH (>= 1.69.0-1), Rcpp (>= 1.0.2), rstan (>= 2.14), RcppEigen (>= 0.3.3.5.0), StanHeaders (>= 2.18.1-10), RcppParallel (>= 5.0.2)

Imports sqldf (>= 0.4), parallel (>= 3.2), rstantools (>= 2.1.1), RcppParallel (>= 5.0.2)

Encoding UTF-8

RoxygenNote 7.2.3

SystemRequirements GNU make

NeedsCompilation yes

Suggests knitr, shiny, rmarkdown, pander, xtable

VignetteBuilder knitr

Repository CRAN

Date/Publication 2023-08-09 10:30:02 UTC

Contents

`visit-package` *cancer Vaccine phase I design with Simultaneous evaluation of Immunogenecity and Toxicity*

Description

This package contains the functions for implementing the **visit** design for Phase I cancer vaccine trials.

Background

Phase I clinical trials are the first step in drug development to apply a new drug or drug combination on humans. Typical designs of Phase I trials use toxicity as the primary endpoint and aim to find the maximum tolerable dosage. However, these designs are generally inapplicable for the development of cancer vaccines because the primary objectives of a cancer vaccine Phase I trial often include determining whether the vaccine shows biologic activity.

The **visit** design allows dose escalation to simultaneously account for immunogenicity and toxicity. It uses lower dose levels as the reference for determining if the current dose level is optimal in terms of immune response. It also ensures subject safety by capping the toxicity rate with a given upper bound. These two criteria are simultaneously evaluated using an intuitive decision region that avoids complicated safety and immunogenicity trade-off elicitation from physicians.

There are several considerations that are clinically necessary for developing the design algorithm. First, we assume that there is a non-decreasing relationship that exists between toxicity and dosage, i.e., the toxicity risk does not decrease as dose level increases. Second, the immune response rate may reach a plateau or even start to decline as the dose level increases.

Notation

For subject s, let $D_s = l$ ($l = 1, \ldots, L$) denote the received dose level, $T_s = 1$ if any DLT event is observed from the subject and 0 otherwise, $R_s = 1$ if immune response is achieved for the subject and 0 otherwise.

Let $\theta_{ij}^{(l)} = P(T = i, R = j | D = l)$ for $i, j = 0, 1$, $\theta^{(l)} = \{\theta_{ij}^{(l)} : i, j = 0, 1\}$ and $\Theta = \{\theta^{(l)} : l = 1, \ldots, L\}$. Furthermore, for dose level l, let $p^{(l)} = P(T = 1 | D = l) = \theta_{10}^{(l)} + \theta_{11}^{(l)}$ be the DLT risk, $q^{(l)} = P(R = 1 | D = l) = \theta_{01}^{(l)} + \theta_{11}^{(l)}$ be the immune response probability, and $r^{(l)} = \theta_{00}^{(l)}\theta_{11}^{(l)} / \theta_{01}^{(l)}\theta_{10}^{(l)}$ be the odds ratio. Let $n_{ij}^{(l)}$ be the observed number of subjects with $T = i$ and $R = j$ at dose level l, $n^{(l)} = \{n_{ij}^{(l)} : i, j = 0, 1\}$ and H denote all the data observed by the time the current analysis is conducted.

Dose escalation algorithm

The dose escalation algorithm is based on the posterior probability distribution of $\pi(p^{(l)}, q^{(l)} | H)$, where $p^{(l)}$ and $q^{(l)}$ represent the DLT risk and immune response rate, respectively, of the current dose level l, and H denotes the cumulative data at the time of interim analysis.

Let p_l denote the lower boundary of DLT risk below which the dose is considered absolutely safe, p_u denote the upper boundary of DLT risk above which the dose is considered toxic. **visit** implements a sequential identification approach based on conditional probabilities derived from $\pi(p^{(l)}, q^{(l)} | H)$. Let C_1, C_2, C_3 be fixed cut-off values in $[0, 1]$. The steps are as follows:

Step 1. If $Prob(p^{(l)} > p_U | H) > C_1$, then the current dose level is considered to be **too toxic**. The trial should be stopped and the next lower dose level should be reported as the recommended dose.

Step 2. $Prob(q^{(l)} \leq q_L | p^{(l)} \leq p_U, H) > C_2$, then the current dose level is considered to be **no more effective than its lower dose** levels. The trial should be stopped and the next lower dose level should be reported as the recommended dose.

Step 3. If $Prob(p^{(l)} \leq p_L | p^{(l)} \leq p_U, q^{(l)} > q_L, H) > C_3$, then the current dose level is considered to be **safe and effective**. The trial will escalate to dose level $l + 1$.

Step 4. The current dose level is considered to be **uncertain**. The trial should continue to treat more patients at dose level l.

The values of should be chosen C_1, C_2, C_3 prior to study initiation and reflect the considerations of the investigators and patients. These thresholds should also give reasonable overall study operating characteristics.

We can see that, based on the posterior distribution of $\pi(p^{(l)}, q^{(l)}|H)$, the currently dose level is in one of the four regions: **1: too toxic**, **2: no more effective than its lower dose**, **3: safe and effective**, and **4: uncertain**. These regions are termed as a `Decision Map`.

Probability models

visit provides several options for the probability models that can be considered for Bayesian inference. The models are non-decreasing with respect to the dose-toxicity relationship and avoid monotonic assumptions for the dose-immune response curve.

Non-parametric model: As one of the simplest models, we posit no assumptions on the dose-toxicity or dose-immune response relationships and assume the outcome data $n_{00}, n_{01}, n_{10}, n_{11}$ follow a multinomial distribution.

Non-parametric+ model: This is the simplified **non-parametric** model with the odds ratios $r = 1$.

Partially parametric model: Compared to non-parametric models, a parametric model may allow the incorporation of dose-toxicity, dose-efficacy, and toxicity-efficacy relationships in dose escalation. In the context of evaluating cancer vaccines, however, it is difficult to posit assumptions on the dose-efficacy relationship, since the immune response rate may even decrease as the dose level increases. On the other hand, it remains reasonable to assume that the dose-toxicity curve is non-decreasing. Therefore, we propose a partially parametric model that only makes assumptions about dose-toxicities but leaves the dose-immune response relationship unspecified.

Specifically, we construct the dose-toxicity model as:

$$\log p^{(l)} = e^{\alpha} \log \tau^{(l)}.$$

The $\tau^{(l)}$'s are deterministic design parameters reflecting the expectation of the DLT risk at dose level l with $\tau^{(l)} > \tau^{(l')}$ for $l > l'$.

For the immune response and the odds ratio, we assume $q^{(l)}$ and $r^{(l)}$ at different dose levels are independent a priori.

Partially parametric+ model: This is the simplified **partially parametric** model with the odds ratios $r = 1$.

Graphical user interface

This package provides a web-based graphical user interface developed using R Shiny. See `vtShiny` for details.

References

Wang, C., Rosner, G. L., & Roden, R. B. (2019). A Bayesian design for phase I cancer therapeutic vaccine trials. Statistics in medicine, 38(7), 1170-1189.

parameters *Parameters*

Description

Parameters that are shared by multiple functions

Arguments

obs.y	Observed data matrix with l rows and 4 columns. Row k in the matrix represents the observed data from dose level k. The columns are • column 1: number of patient with no DLT, no immune response • column 2: number of patient with no DLT, immune response • column 3: number of patient with DLT, no immune response • column 4: number of patient with DLT, immune response
prob.mdl	Option of the probability models: • NONPARA: non-parametric+ model • NONPARA+: non-parametric model • PARA: partially parametric model • PARA+: partially parametric+ model Default value is NONPARA. See visit for details.
priors	A class VTPRIOR object created by vtPriorPar for PARA and PARA+ model.
etas	Vector of length 2 representing (p_L, p_U). p_L: lower bound of DLT risk, below which the current dose is considered absolutely safe; p_U: upper bound of DLT risk above which the current dose is considered too toxic
prev.res	Response rate from the next lower dose level, say, $l-1$. This can be a scalar representing the mean of the response rate $E(q^{(l-1)})$, or a vector of posterior samples of the response rate $q^{(l-1)}$. For $l=1$, this value is set to 0.
dec.cut	Thresholds C_1, C_2, C_3. If the vector length is shorter than 3, it is repeated to have 3 elements. See visit for details.
digits	Digits for print
seed	Random seed
...	Reserved parameters

plot.VTDEC *Plot decision map*

Description

Plot a decision map based on a class VTDEC object that contains the current posterior analysis results

Usage

```
## S3 method for class 'VTDEC'
plot(x, margin = 0.003, nms = c("TT", "NME", "SE",
  "UN"), col.reg = "pink", col.prob = "blue", cex.prob = 0.9,
  cex.nms = 1, ...)
```

Arguments

x	A class VTDEC list generated by vtDecMap
margin	Margin between regions in the decision map
nms	Labels of the regions on a decision map. Defaults are: • TT:Too Toxic • NME:No More Effective • SE:Safe and Effective • UN:Uncertain
col.reg	Background color of the selected region
col.prob	Text color of the selected region.
cex.prob	Text size of the probabilities
cex.nms	Text size of the region labels
...	Optional arguments for plot.

Examples

```
etas       <- c(0.1, 0.3)
dec.cut    <- c(0.6,0.6,0.6)
cur.obs.y  <- c(3, 2, 1, 1)
prev.obs.y <- c(5, 2, 0, 0)
rst.inter  <- vtInterim(cur.obs.y,  prev.obs.y = prev.obs.y,
                        prob.mdl = "NONPARA", etas = etas, dec.cut = dec.cut,
                        nsmp = 2000);
plot(rst.inter)
```

`plot.VTTRUEPS` *Plot true parameters*

Description

Plot true DLT risk rates and response rates.

Usage

```
## S3 method for class 'VTTRUEPS'
plot(x, draw.levels = NULL, draw.curves = 1:6,
  legends = NULL, ltys = c(1, 1, 2, 2, 2, 2), pch = 19:24,
  ylim = c(0, 1), cols = c("red", "blue", "brown", "black", "gray",
  "green"), add.legend = TRUE, ...)
```

Arguments

`x`	A class `VTTRUEPS` matrix generated by `vtScenario`
`draw.levels`	Select dose levels to draw. Default `NULL` draws all levels.
`draw.curves`	Indicate which curves to plot. The options are • 1:p: DLT risk rate • 2:q: Response rate • 3:θ_{00} • 4:θ_{01} • 5:θ_{10} • 6:θ_{11} See `visit` for details.
`legends`	Line legends
`ltys`	Line types
`pch`	Line PCH
`ylim`	Y limits
`cols`	Line colors
`add.legend`	Include legends (TRUE) or not (FALSE)
`...`	optional arguments for plot

Examples

```
rst.sce <- vtScenario(tox = c(0.05, 0.05, 0.08),
                      res = c(0.2, 0.3, 0.5),
                      rho = 1)
plot(rst.sce, draw.levels = 1:2, draw.curves=1:6)
```

summary.VTSIMU *Summarize simulation results*

Description

Summarize the simulation results with numerous statistical measures

Usage

```
## S3 method for class 'VTSIMU'
summary(object, ...)
```

Arguments

object	A class VTSIMU list generated by vtSimu
...	Reserved parameters

Value

A list containing

- dose: Frequency for each dose level being selected as the optimal dose level
- npat: Average number of patients for each cohort and each dose level
- samples: Average number of DLT risks and responses for each cohort on each dose level
- decision: Frequency each region in the decision map is selected for each cohort on each dose level
- prob: Average conditional probabilities corresponding to each region in the decision map for each cohort on each dose level
- ptox: Mean and credible interval of DLT risk rates for each cohort on each dose level
- pres: Mean and credible interval of immune response rates for each cohort on each dose level

Examples

```
rst.sce <- vtScenario(tox = c(0.05, 0.05, 0.08),
                      res = c(0.2, 0.3, 0.5),
                      rho = 1)
rst.simu  <- vtSimu(n.rep = 50, n.cors = 2, trueps = rst.sce,
                    size.cohort=3, size.level=12,
                    prob.mdl="NONPARA");
sum.simu <- summary(rst.simu)
```

summary.VTTRUEPS *Print true probabilities*

Description

Print the true probabilities, with probabilities of toxicity and resistance, and ρ.

Usage

```
## S3 method for class 'VTTRUEPS'
summary(object, digits = 2, ...)
```

Arguments

object	A class VTTRUEPS matrix generated by vtScenario
digits	Digits for print
...	Reserved parameters

Value

A table showing the summary of the VTTRUEPS object. The first four columns are individual probability, fifth and sixth are probability for toxicity and resistance, and seventh is rho, the correlation.

Examples

```
rst.sce <- vtScenario(tox = c(0.05, 0.05, 0.08),
                      res = c(0.2, 0.3, 0.5),
                      rho = 1)
summary(rst.sce)
```

summary2 *S3 Summary function*

Description

S3 Summary function

Usage

```
summary2(x, ...)
```

Arguments

x	object
...	reserved parameters

summary2.VTSIMU *Summarize simulation results*

Description

Summarize simulation results to get the frequency of a dose level is identified as the optimal dose level and the number of DLT's and responses

Usage

```
## S3 method for class 'VTSIMU'
summary2(x, ...)
```

Arguments

x	A class VTSIMU list generated by vtSimu
...	Reserved parameters

Value

A numeric array that shows 1: number of times each level is selected, 2. total number of times any level is selected, 3. frequency each level is selected, 4. frequency any level is selected, 5. average number of DLT's and responders for each level, 6. average total number of DLT's and responders

Examples

```
rst.sce <- vtScenario(tox = c(0.05, 0.05, 0.08),
                      res = c(0.2, 0.3, 0.5),
                      rho = 1)
rst.simu  <- vtSimu(n.rep = 20, n.cors = 2, trueps = rst.sce,
                    size.cohort=3, size.level=12,
                    prob.mdl="NONPARA");
sum.simu <- summary2(rst.simu)
```

summary2.VTTRUEPS *Print true probabilities in latex format*

Description

Print the true probabilities, with probabilities of toxicity and resistance, and ρ, in latex format

Usage

```
## S3 method for class 'VTTRUEPS'
summary2(x, rp2d = -1, digits = 2, ...)
```

Arguments

x	A class VTTRUEPS matrix generated by vtScenario
rp2d	Columns to be in bold font
digits	Digits for print
...	Reserved parameters

Value

A summary of the true probabilities in latex format.

Examples

```
rst.sce <- vtScenario(tox = c(0.05, 0.05, 0.08),
                      res = c(0.2, 0.3, 0.5),
                      rho = 1)
ltx.ps <- summary2(rst.sce)
```

---

vtDecMap *Obtain decision map information*

Description

Summarize the posterior distribution of $\theta_{00}^{(l)}, \theta_{01}^{(l)}, \theta_{10}^{(l)}, \theta_{11}^{(l)}$ and get information for making dose escalation decisions

Usage

```
vtDecMap(thetas, etas, prev.res = 0, dec.cut = 0.6)
```

Arguments

thetas	Posterior samples of θ, a class VTPOST matrix generated by vtPost
etas	Vector of length 2 representing (p_L, p_U). p_L: lower bound of DLT risk, below which the current dose is considered absolutely safe; p_U: upper bound of DLT risk above which the current dose is considered too toxic
prev.res	Response rate from the next lower dose level, say, $l-1$. This can be a scalar representing the mean of the response rate $E(q^{(l-1)})$, or a vector of posterior samples of the response rate $q^{(l-1)}$. For $l=1$, this value is set to 0.
dec.cut	Thresholds C_1, C_2, C_3. If the vector length is shorter than 3, it is repeated to have 3 elements. See visit for details.

Details

This function summarizes the posterior distribution of the $\theta_{00}^{(l)}, \theta_{01}^{(l)}, \theta_{10}^{(l)}, \theta_{11}^{(l)}$ and sequentially get the conditional probabilities of each decision map region. See `visit` for details of the decision map regions.

Value

A class `VTDEC` list. See the return value from `vtInterim` for details.

Examples

```
etas     <- c(0.1, 0.3)
dec.cut  <- c(0.6,0.6,0.6)
obs.y    <- rbind(c(5, 2, 0, 0))
rst.post <- vtPost(obs.y,  prob.mdl = "NONPARA", nsmp = 2000)
dec.map  <- vtDecMap(rst.post, etas = etas, dec.cut = dec.cut)
```

`vtInterim` *Conduct interim analysis*

Description

Conduct an interim analysis for determining dose escalation actions

Usage

```
vtInterim(cur.obs.y, prev.obs.y = NULL, prev.res = NULL,
  etas = c(0.1, 0.3), dec.cut = 0.65, priors = NULL,
  prob.mdl = c("NONPARA", "NONPARA+", "PARA", "PARA+"), seed = NULL,
  ...)
```

Arguments

`cur.obs.y`	Observed data from the current level, which is a vector of length 4. The numbers correspond to `obs.y` in `vtPost`.
`prev.obs.y`	Observed data from previous levels, which has the same structure as `obs.y` in `vtPost`.
`prev.res`	Response rate from the next lower dose level, say, $l-1$. This can be a scalar representing the mean of the response rate $E(q^{(l-1)})$, or a vector of posterior samples of the response rate $q^{(l-1)}$. For $l=1$, this value is set to 0.
`etas`	Vector of length 2 representing (p_L, p_U). p_L: lower bound of DLT risk, below which the current dose is considered absolutely safe; p_U: upper bound of DLT risk above which the current dose is considered too toxic
`dec.cut`	Thresholds C_1, C_2, C_3. If the vector length is shorter than 3, it is repeated to have 3 elements. See `visit` for details.

priors	A class VTPRIOR object created by vtPriorPar for PARA and PARA+ model.
prob.mdl	Option of the probability models: • NONPARA: non-parametric+ model • NONPARA+: non-parametric model • PARA: partially parametric model • PARA+: partially parametric+ model Default value is NONPARA. See visit for details.
seed	Random seed
...	Additional arguments for vtPost

Details

Using data from previous levels and the current level to conduct Bayesian analysis, get the decision map information and make decision about dose escalation actions. The actions include stop the trial, escalate to the next higher dose level, or enroll more patients in the current level. See visit for details.

Value

A class VTDEC list containing

- prob: Probabilities of each decision map region
- region: The region selected based on the sequential procedure described in visit
- ptox: Mean risk of DLT, $E(p^{(l)})$
- pres: Mean immune response rate, $E(q^{(l)})$
- con.prob: Conditional probabilities of each decision map region
- prev.res: Function parameter
- etas: Function parameter
- dec.cut: Function parameter

Examples

```
etas       <- c(0.1, 0.3)
dec.cut    <- c(0.6,0.6,0.6)
cur.obs.y  <- c(3, 2, 1, 1)
prev.obs.y <- c(5, 2, 0, 0)
rst.inter  <- vtInterim(cur.obs.y,  prev.obs.y = prev.obs.y,
                        prob.mdl = "NONPARA", etas = etas,
                        dec.cut = dec.cut,
                        nsmp = 2000);
```

vtPost *Postetrior sampling for given observed samples*

Description

Call STAN to draw posterior samples of the joint distribution of immunogenicity rate and toxicity risk

Usage

```
vtPost(obs.y, prob.mdl = c("NONPARA", "NONPARA+", "PARA", "PARA+"),
  priors = NULL, ..., nsmp = 4000, prior.const = 0.5)
```

Arguments

obs.y	Observed data matrix with l rows and 4 columns. Row k in the matrix represents the observed data from dose level k. The columns are • column 1: number of patient with no DLT, no immune response • column 2: number of patient with no DLT, immune response • column 3: number of patient with DLT, no immune response • column 4: number of patient with DLT, immune response
prob.mdl	Option of the probability models: • NONPARA: non-parametric+ model • NONPARA+: non-parametric model • PARA: partially parametric model • PARA+: partially parametric+ model Default value is NONPARA. See visit for details.
priors	A class VTPRIOR object created by vtPriorPar for PARA and PARA+ model.
...	additional parameters for package rstan's sampling method. These options include warmup, thin, algorithm. See rstan::sampling for details.
nsmp	number of iterations
prior.const	Specify α for a Beta(α, α) prior. The Beta prior is used for NONPARA and NONPARA+ models. Default value 0.5.

Value

A class VTPOST matrix of posterior samples with nsmp rows and 4 columns. Columns 1-4 correspond to$\theta_{00}^{(l)}, \theta_{01}^{(l)}, \theta_{10}^{(l)}, \theta_{11}^{(l)}$. See visit for details about θ's.

Examples

```
obs.y    <- rbind(c(5, 2, 0, 0), c(3, 4, 0, 0), c(1, 6, 0, 0))
prior <- vtPriorPar(prior.y = NULL, tau = c(0.1, 0.3, 0.6), sdalpha=10, sdrho=10, vtheta=NULL)
rst.post <- vtPost(obs.y, priors = prior, warmup = 100, prob.mdl = "PARA", nsmp = 200)
```

vtPriorPar *Get prior distribution parameters*

Description

Get prior distribution parameters for partially parametric or partially parametric+ models

Usage

```
vtPriorPar(prior.y = NULL, tau = NULL, sdalpha = 10, sdrho = 10,
  vtheta = NULL)
```

Arguments

prior.y	Historical data for generating prior parameters. It has the same structure as obs.y in vtPost.
tau	Vector of τ values. See visit for details. Can not be NULL if prior.y is NULL.
sdalpha	σ_α. See visit for details.
sdrho	σ_ρ.
vtheta	Additional variance term for eliciting prior parameters from prior.y

Details

The priors are specified as $q^{(l)} \sim Beta(a_q^{(l)}, b_q^{(l)})$, and $\log \rho^{(l)} \sim N(0, \sigma_\rho^2)$.

Value

A VTPRIOR list with

- TAU:vector of τ's for each level
- ABCD:A matrix of 4 columns: a_q, b_q, a_ρ, σ_ρ. Each row represents a dose level.

Examples

```
par.prior <- vtPriorPar(tau = c(0.2, 0.4, 0.6), sdalpha = 10);
```

vtScenario *Set simulation scenario*

Description

Simulation function. Get true θ's using marginal probabilities and odds ratio ρ for all dose levels.

Usage

```
vtScenario(tox = c(0.05, 0.05, 0.08), res = c(0.2, 0.3, 0.5),
  rho = 1)
```

Arguments

tox	Vector of marginal DLT risk rates for all levels
res	Vector of marginal immune response rates for all levels
rho	Vector of odds ratio for all levels. If length of rho is shorter than the length of tox or res, vector rho is repeated to have the same length as tox and res.

Details

The calculation is as following. If $\rho = 1$, then $\theta_{11} = pq$, $\theta_{01} = (1-p)q$, $\theta_{10} = p(1-q)$, and $\theta_{00} = (1-p)(1-q)$. Otherwise, $\theta_{11} = -(\sqrt{A+B}$, $\theta_{01} = q-\theta_{11}$, $\theta_{10} = p-\theta_{11}$, and $\theta_{00} = \theta_{01}\theta_{10}\rho/\theta_{11}$, where $A = (p+q-p\rho-q\rho-1)^2 - 4(\rho-1)pq\rho)$ and $B = (p+q-p\rho-q\rho-1))/2/(\rho-1)$.

Value

a VTTRUEPS object containing all θ's in a matrix with its number of rows equaling the number of dose levels and its number of columns being 4.

Examples

```
rst.sce <- vtScenario(tox=c(0.05, 0.05, 0.08), res=c(0.2, 0.3, 0.5), rho=1)
```

vtShiny *Run Web-Based* visit *application*

Description

Call Shiny to run visit as a web-based application.

Usage

```
vtShiny()
```

Details

A web browser will be brought up for users to access the GUI of visit.

Examples

```
## Not run:
vtShiny()
## End(Not run)
```

---

vtSimu *Conduct simulation study*

Description

Simulate clinical trials with given settings for multiple times to evaluate the study operating characteristics.

Usage

```
vtSimu(n.rep = 100, seed = NULL, ..., n.cores = 1,
  update.progress = NULL)
```

Arguments

n.rep	Number of repetitions
seed	Seed
...	Optional parameters for vtSingleTrial
n.cores	Number of cores for parallel computations
update.progress	Reserved parameter for Shiny GUI

Value

A class VTSIMU list with length n.rep of results. Each item is a list return from vtSingleTrial.

Examples

```
rst.sce <- vtScenario(tox = c(0.05, 0.05, 0.08),
                      res = c(0.2, 0.3, 0.5),
                      rho = 1)

rst.simu  <- vtSimu(n.rep = 100, n.cors = 2, trueps = rst.sce,
                    size.cohort=3, size.level=12, prob.mdl="NONPARA");
```

`vtSingleTrial` *Simulate a single trial*

Description

Simulation function for simulating a single trial

Usage

```
vtSingleTrial(trueps, size.cohort = 3, size.level = NULL,
  etas = c(0.1, 0.3), dec.cut = 0.65, prob.mdl = c("NONPARA",
  "NONPARA+", "PARA", "PARA+"), priors = NULL, ...)
```

Arguments

`trueps`	True θ's. A `VTTRUEPS` object made from `vtScenario`
`size.cohort`	Size of each cohort
`size.level`	Maximum number of patients for each dose level
`etas`	Vector of length 2 representing (p_L, p_U). p_L: lower bound of DLT risk, below which the current dose is considered absolutely safe; p_U: upper bound of DLT risk above which the current dose is considered too toxic
`dec.cut`	Thresholds C_1, C_2, C_3. If the vector length is shorter than 3, it is repeated to have 3 elements. See `visit` for details.
`prob.mdl`	Option of the probability models: • NONPARA: non-parametric+ model • NONPARA+: non-parametric model • PARA: partially parametric model • PARA+: partially parametric+ model Default value is `NONPARA`. See `visit` for details.
`priors`	A class `VTPRIOR` object created by `vtPriorPar` for `PARA` and `PARA+` model.
`...`	Optional arguments for `vtPost`

Value

- `dose`: Optimal dose level
- `n.patients`: Number of patients for each dose level and each cohort
- `ptox`: Posterior mean of DLT risk rate after each interim analysis
- `pres`: Posterior mean of immune response rate after each interim analysis
- `region`: Identified region in the decision map after each interim analysis
- `prob`: Posterior mean of θ's after each interim analysis
- `smps`: Observed data after each cohort

Examples

```
rst.sce <- vtScenario(tox = c(0.05, 0.05, 0.08),
                      res = c(0.2, 0.3, 0.5),
                      rho = 1)
rst.simu  <- vtSingleTrial(trueps = rst.sce, size.cohort=3, size.level=12,
                           prob.mdl="NONPARA");
```

---

vtStan *Call STAN models for MCMC sampling*

Description

Call STAN to draw posterior samples of the joint distribution of immunogenicity rate and toxicity risk for parametric and parametric+ model

Usage

```
vtStan(obs.y, priors, model = 0, iter = 4000, chains = 4,
  warmup = 2000, ...)
```

Arguments

obs.y	Observed data matrix with l rows and 4 columns. Row k in the matrix represents the observed data from dose level k. The columns are • column 1: number of patient with no DLT, no immune response • column 2: number of patient with no DLT, immune response • column 3: number of patient with DLT, no immune response • column 4: number of patient with DLT, immune response
priors	A class VTPRIOR object created by vtPriorPar for PARA and PARA+ model.
model	option of the probability models: **0:** parametric model **1:** parametric+ model See visit for details.
iter	STAN option: number of iterations
chains	STAN option: number of chains
warmup	STAN option: number of warmup
...	additional parameters for package rstan's sampling method. These options include iter, warmup, thin, algorithm. See rstan::sampling for details.

Value

A rstan object that contains the posterior sampling results

vtTrack *Plot the track plot of dose escalation*

Description

Generate a plot representing the observed data and dose escalation decisions.

Usage

```
vtTrack(obs.all, cex.txt = 0.9, decision = 1, max.level = NULL,
  letters = c("E", "C", "S"), colors = c("green", "yellow", "red"),
  height = 0.5, end.width = 2, end.height = height,
  cex.roman = 0.9, cex.end = 0.9, ...)
```

Arguments

obs.all	All observations collected in a matrix with 5 columns. Column 1 is the index of interim analysis starting from 1. Columns 2-5 correspond to columns 1-4 in obs.y for vtPost.
cex.txt	Text size of numbers in the plot
decision	Dose escalation decision. The options are • 1: Escalate • 2: Continue at the same level • 3: Stop the trial
max.level	Maximum number of dose levels shown in the plot
letters	Labels for dose escalation actions 1-3. Default values are "E", "C", "S"
colors	Possible colors in the last action box
height	Height of each individual box
end.width	Width of the last action box
end.height	Height of the last action box
cex.roman	Text size of the roman numerals
cex.end	Text size of the letter in the last action box
...	Optional arguments for plot.

Examples

```
obs.all  <- rbind(c(1, 5, 2, 0, 0),
                  c(2, 3, 4, 0, 0),
                  c(3, 1, 6, 0, 0));
vtTrack(obs.all, end.width = 0.8, max.level = 3, decision = 3);
```

Index