Package 'VNM'

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Type Package

Title Finding Multiple-Objective Optimal Designs for the 4-Parameter Logistic Model

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Imports graphics, Rcpp

LinkingTo Rcpp

Depends methods

Description Provide tools for finding multiple-objective optimal designs for estimating the shape of dose-response, the ED50 (the dose producing an effect midway between the expected responses at the extreme doses) and the MED (the minimum effective dose level) for the 2,3,4-parameter logistic models and for evaluating its efficiencies for the three objectives. The acronym VNM stands for V-algorithm using Newton Raphson method to search multiple-objective optimal design.

Collate 'AllClasses.R' 'summary-methods.R' 'plot-methods.R' 'MOPT.R' 'ceff1.R' 'ceff2.R' 'Deff.R' 'S.Weight.R' 'ff.R' 'RcppExports.R'

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`VNM-package` *Tools for constructing 3-objective optimal designs*

Description

The package contains several functions useful for finding 3-objective optimal designs to estimate the shape of dose-response, the ED50 and the MED for the 4PL model. The package also can be used for the 2PL or the 3PL models.

Below is the 4PL model used in this package:

4-parameter logistic(4PL) model

$$Y = \frac{\theta_1}{1 + e^{\theta_2 x + \theta_3}} + \theta_4 + \varepsilon, \varepsilon \sim N(0, \sigma^2)$$

Here x is the dose in log scale, θ_1 is the Emax, θ_2 is the negative of the Hill's coefficient in the Hill's model that controls the rate of change in the response, θ_3 is $-\theta_2$ log(ED50) and θ_4 is the lower limit of the response when $\theta_1 > 0, \theta_2 \neq 0$, and $-\infty <$ ED50 $< \infty$. The 4PL model becomes the 2PL model when $\theta_1 = 1$ and $\theta_4 = 0$ or the 3PL model when $\theta_4 = 0$.

Details

Package:	VNM
Type:	Package
Version:	1.0
Date:	2014-05-15
License:	GPL-2

The main functions are:

MOPT: Finds and verifies that the generated design is the multiple-objective optimal design.

Deff: Computes D-efficiency of the generated design for estimating the model parameters.

ceff1: Computes c-efficiency of the generated design for estimating the ED50.

ceff2: Computes c-efficiency of the generated design for estimating the MED.

S.Weight: Computes the optimal weights for the fixed design points.

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

References

Hyun, S.W., Wong, W.K, Yang, Y. VNM: An R Package for Finding Multiple-Objective Optimal Designs for the 4-Parameter Logistic Model. (*Journal of Statistical Software*, 83, 1-19, 2018, doi: 10.18637/jss.v083.i05.)

Hyun, S. W., Wong, W.K. Multiple-Objective Optimal Designs for Studying the Dose Response Function and Interesting Dose Levels. (*International Journal of Biostatistics*, 11, 253-271, 2015)

Examples

```
##Find the 3-objective optimal design for the 4PL model
result=MOPT(LB=log(.001), UB=log(1000), P=c(0.137,1.563,.00895,-1.790),lambda=c(1/3,1/3),
delta=-1)

##Generated the 3-objective optimal design
Res.D=summary(result)

##Verification plot of the generated design
plot(result)

dose=Res.D[1,]
weight=Res.D[2,]

##Check D-efficiency of the generated design
Deff(weight, P=c(0.137,1.563,.00895,-1.790), dose, LB=log(.001), UB=log(1000))

##Check c-efficiency of the generated design for estimating the ED50
#ceff1(weight, P=c(0.137,1.563,.00895,-1.790), dose, LB=log(.001), UB=log(1000))

##Check c-efficency of the generated design for estimating the MED
#ceff2(weight, P=c(0.137,1.563,.00895,-1.790), dose, LB=log(.001), UB=log(1000), delta=-1, r=30)
```

---

ceff1 *Checking c-efficiency for estimating the ED50.*

Description

Obtaining c-efficiency for estimating the ED50 for a given design under the 4-parameter logistic model. This also can be used to compute the c-efficiency for the ED50 under the 2 or 3-parameter logistic models by setting the parameters values differently.

Usage

```
ceff1(weight,P,dose,LB,UB,r,grid,epsilon,epsilon_w)
```

Arguments

`weight`	A numeric vector. Weights for a given design. The weights represent the proportional allocations of subjects to the dose levels in a given design.
`P`	A numeric vector. Solicited information on nominal values for the vector. P=(p1, p2, p3, p4), where p1 is the lower limit of the response (θ_4), p2 is Emax (θ_1), p3 is the ED50 (exp (-$\frac{\theta_3}{\theta_2}$)) and p4 is the slope at the ED50 (-θ_2). For the 4-parameter logistic model, a user needs to specify all 4 nominal values in P: P = (p1, p2, p3, p4). For the 3-parameter logistic model, a user needs to specify only the 3 nominal values, Emax, the ED50, and the slope: P = (p2, p3, p4). For the 2-parameter logistic model, a user needs to specify only the 2 nominal values, the ED50 and the slope: P = (p3, p4).
`dose`	A vector. Dose levels for a given design.
`LB`	Numeric. Predetermined lower bound of the dose range for the log dose.
`UB`	Numeric. Predetermined upper bound of the dose range for the log dose.
`r`	Numeric. The number of iterations to select the initial design to search c-optimal design for estimating the ED50. Default is 10 and needed to be increased (for example, r = 30 or 50) if the searched c-optimal design is not a true optimal.
`grid`	Numeric. The grid density to discretize the predetermined dose interval. Default is 0.01.
`epsilon`	Numeric. Stopping criterion for the algorithm to search c-optimal design for the ED50. Default is 0.001.
`epsilon_w`	Numeric. Stopping criterion for the Newton Raphson method inside of the algorithm. Default is 10^-6.

Value

An object of class OPT.

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

References

Hyun, S.W., Wong, W.K, Yang, Y. VNM: An R Package for Finding Multiple-Objective Optimal Designs for the 4-Parameter Logistic Model. (*Journal of Statistical Software*, 83, 1-19, 2018, doi: 10.18637/jss.v083.i05.)

Hyun, S. W., Wong, W.K. Multiple-Objective Optimal Designs for Studying the Dose Response Function and Interesting Dose Levels. (*International Journal of Biostatistics*, 11, 253-271, 2015)

Examples

```
##The given design
dose=c(-6.91,-4.89,-4.18,6.91)
weight=c(.344,.323,.162,.171)
```

```
##Model parameter values for the 4PL
par.4PL=c(0.137,1.563,.00895,-1.790)

##Check c-efficiency of the given design for estimating the ED50 and its verification plot
Res.c1=ceff1(weight, P=par.4PL, dose, LB=log(.001), UB=log(1000))
summary(Res.c1)
plot(Res.c1)
```

---

ceff2 *Checking c-efficiency for estimating the MED.*

Description

Obtaining c-efficiency for estimating the minimum effective dose MED for a given design under the 4-parameter logistic model. MED is the dose that produces a mean response of δ unites better than the minimum dose. This also can be used to compute the c-efficiency for MED under the 2 or 3-parameter logistic models by setting the parameter values differently.

Usage

```
ceff2(weight,P,dose,LB,UB,delta,r,grid,epsilon,epsilon_w)
```

Arguments

weight	A numeric vector. Weights for a given design. The weights represent the proportional allocations of subjects to the dose levels in a given design.
P	A numeric vector. Solicited information on nominal values for the vector. P = (p1, p2, p3, p4), where p1 is the lower limit of the response (θ_4), p2 is Emax (θ_1), p3 is the ED50 (exp(-$\frac{\theta_3}{\theta_2}$)) and p4 is the slope at the ED50 (-θ_2). For the 4-parameter logistic model, a user needs to specify all 4 nominal values in P: P = (p1, p2, p3, p4). For the 3-parameter logistic model, a user needs to specify only the 3 nominal values, Emax, the ED50, and the slope: P = (p2, p3, p4). For the 2-parameter logistic model, a user needs to specify only the 2 nominal values, the ED50 and the slope: P = (p3, p4).
dose	A vector. Dose levels for a given design.
LB	Numeric. Predetermined lower bound of the dose range for the log dose.
UB	Numeric. Predetermined upper bound of the dose range for the log dose.
delta	Numeric. Predetermined clinically significant effect to define the MED. The MED is the dose producing the mean response of delta units better than the minimum dose.
r	Numeric. The number of iteritions to select the initial design to search c-optimal design for estimating the MED. Default is 10 and needed to be increased (for example, r = 30 or 50) if the searched c-optimal design is not a true optimal.
grid	Numeric. The grid density to discretize the predetermined dose interval. Default is 0.01.

`epsilon` Numeric. Stopping criterion for the algorithm to search c-optimal design for the MED. Default is 0.001.

`epsilon_w` Numeric. Stopping criterion for the Newton Raphson method inside of the algorithm. Default is 10^-6.

Value

An object of class OPT.

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

References

Hyun, S.W., Wong, W.K, Yang, Y. VNM: An R Package for Finding Multiple-Objective Optimal Designs for the 4-Parameter Logistic Model. (*Journal of Statistical Software*, 83, 1-19, 2018, doi: 10.18637/jss.v083.i05.)

Hyun, S. W., Wong, W.K. Multiple-Objective Optimal Designs for Studying the Dose Response Function and Interesting Dose Levels. (*International Journal of Biostatistics*, 11, 253-271, 2015)

Examples

```
##The given design
dose=c(-6.91,-4.89,-4.18,6.91)
weight=c(.344,.323,.162,.171)

##Model parameter values for the 4PL
par.4PL=c(0.137,1.563,.00895,-1.790)

##delta to define MED
delta=-1

##Check c-efficiency of the given design for estimating the MED and its verification plot
Res.c2=ceff2(weight, P=par.4PL, dose, LB=log(.001), UB=log(1000), delta, r=30)
summary(Res.c2)
plot(Res.c2)
```

`Deff` *Checking D-efficiency for estimating model parameters.*

Description

Obtaining D-efficiency for estimating model parameters for a given design under the 4-parameter logistic model. This also can be used to compute the D-efficiency under the 2 or 3-parameter logistic models by setting the parameter values differently.

Usage

```
Deff(weight,P,dose,LB,UB,r,grid,epsilon,epsilon_w)
```

Arguments

`weight`	A numeric vector. Weights for a given design. The weights represent the proportional allocations of subjects to the dose levels in a given design.
`P`	A numeric vector. Solicited information on nominal values for the vector. P = (p1, p2, p3, p4), where p1 is the lower limit of the response (θ_4), p2 is Emax (θ_1), p3 is the ED50 (exp(-$\frac{\theta_3}{\theta_2}$)) and p4 is the slope at the ED50 (-θ_2). For the 4-parameter logistic model, a user needs to specify all 4 nominal values in P: P = (p1, p2, p3, p4). For the 3-parameter logistic model, a user needs to specify only the 3 nominal values, Emax, the ED50, and the slope: P = (p2, p3, p4). For the 2-parameter logistic model, a user needs to specify only the 2 nominal values, the ED50 and the slope: P = (p3, p4).
`dose`	A vector. Dose levels for a given design.
`LB`	Numeric. Predetermined lower bound of the dose range for the log dose.
`UB`	Numeric. Predetermined upper bound of the dose range for the log dose.
`r`	Numeric. The number of iterations to select the initial design to search D-optimal design for estimating model parameters. Default is 10 and needed to be increased (for example, r = 30 or 50) if the searched D-optimal design is not a true optimal.
`grid`	Numeric. The grid density to discretize the predetermined dose interval. Default is 0.01.
`epsilon`	Numeric. Stopping criterion for the algorithm to search D-optimal design. Default is 0.001.
`epsilon_w`	Numeric. Stopping criterion for the Newton Raphson method inside of the algorithm. Default is 10^-6.

Value

An object of class OPT.

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

References

Hyun, S.W., Wong, W.K, Yang, Y. VNM: An R Package for Finding Multiple-Objective Optimal Designs for the 4-Parameter Logistic Model. (*Journal of Statistical Software*, 83, 1-19, 2018, doi: 10.18637/jss.v083.i05.)

Hyun, S. W., Wong, W.K. Multiple-Objective Optimal Designs for Studying the Dose Response Function and Interesting Dose Levels. (*International Journal of Biostatistics*, 11, 253-271, 2015)

Examples

```
##The given design
dose=c(-6.91,-4.89,-4.18,6.91)
weight=c(.344,.323,.162,.171)

##Model parameter values for the 4PL
par.4PL=c(0.137,1.563,.00895,-1.790)

##Check D-efficiency of the given design and its verification plot
Res.D=Deff(weight, P=par.4PL, dose, LB=log(.001), UB=log(1000))
summary(Res.D)
plot(Res.D)
```

`MOPT` *Search the 3-objective optimal designs for estimating model parameters, ED50, and MED.*

Description

Search the 3-objective optimal designs that maximizes a weighted average of efficiencies for estimating model parameters, the ED50, and the MED under the 4PL model and verifies the optimality of the generated design using the General Equivalence Theorem. This also can be used to search the 3-objective optimal designs under the 2 or 3-parameter logistic models by setting the parameter values differently.

Usage

```
MOPT(LB, UB, P, lambda, delta, r, grid, epsilon, epsilon_w, verbose)
```

Arguments

`LB` Numeric. Predetermined lower bound of the dose range for the log dose.

`UB` Numeric. Predetermined upper bound of the dose range for the log dose.

`P` A numeric vector. Solicited information on nominal values for the vector. P = (p1, p2, p3, p4), where p1 is the lower limit of the response (θ_4), p2 is Emax (θ_1), p3 is the ED50 (exp(-$\frac{\theta_3}{\theta_2}$)) and p4 is the slope at the ED50 (-θ_2). For the 4-parameter logistic model, a user needs to specify all 4 nominal values in P: P = (p1, p2, p3, p4). For the 3-parameter logistic model, a user needs to specify only the 3 nominal values, Emax, the ED50, and the slope: P = (p2, p3, p4). For the 2-parameter logistic model, a user needs to specify only the 2 nominal values, the ED50 and the slope: P = (p3, p4).

`lambda` A numeric vector. User-selected weights for the first two objectives. lambda = c(q1, q2), where q1, q2 represent weights for estimating model parameter and estimating the ED50 respectively. They are non-negative and q1 + q2 <= 1.

`delta` Numeric. Predetermined clinically significant effect to define the MED. The MED is the dose producing the mean response of delta units better than the minimum dose.

`r` Numeric. The number of iteritions to select the initial design to search the 3-objective optimal design. Default is 10 and needed to be increased (for example, r = 30 or 50) if the searched optimal design is not a true optimal.

`grid` Numeric. The grid density to discretize the predetermined dose interval. Default is 0.01.

`epsilon` Numeric. Stopping criterion for the algorithm to search the multiple-objective optimal design. Default is 0.001.

`epsilon_w` Numeric. Stopping criterion for the Newton Raphson method inside of the algorithm. Default is 10^-6.

`verbose` Set to TRUE if you want more evidence of progress while data is being processed. Set to FALSE if you want your CPU cycles to be used on analysis and not printing messages. Default is FALSE.

Value

An object of class OPT.

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

References

Atkinson, A.C., Donev, A.N. Tobias RD Optimal Experimental Designs with SAS. (*Oxford University Press, Oxford*, 2007)

Hyun, S.W., Wong, W.K, Yang, Y. VNM: An R Package for Finding Multiple-Objective Optimal Designs for the 4-Parameter Logistic Model. (*Journal of Statistical Software*, 83, 1-19, 2018, doi: 10.18637/jss.v083.i05.)

Hyun, S. W., Wong, W.K. Multiple-Objective Optimal Designs for Studying the Dose Response Function and Interesting Dose Levels. (*International Journal of Biostatistics*, 11, 253-271, 2015)

Examples

```
##Model parameter values for the 4PL
par.4PL=c(0.137,1.563,.00895,-1.790)

##Find the 3-objective optimal design for the 4PL model
Res.M=MOPT(LB=log(.001), UB=log(1000), par.4PL, lambda=c(1/3,1/3), delta=-1, r=30)

##Generated the 3-objective optimal design
summary(Res.M)

##Verification plot of the generated design
plot(Res.M)
```

OPT *Class to contain the results from function MOPT, ceff1, ceff2, and Deff.*

Description

The function MOPT, ceff1, ceff2, Deff return object of class OPT that contains the variables for the verification plot, the optimal matrix, and the efficiency.

Objects from the Class

new("OPT",Par="PAR",OPT=new("matrix"),Eff=new("numeric"))

Slots

`Par`: An object of class PAR containing the variables for the verification plot.

`Opt`: A numeric matrix showing the multiple-objective optimal design for estimating model parameters, the ED50, and the MED (for function MOPT), or c-optimal design for ED50 (for function ceff1), or c-optimal design for MED (for function ceff2), or D-optimal design (for function Deff).

`Eff`: A numeric number showing the c-efficiency for ED50 (for function ceff1), or c-efficiency for MED (for function ceff2), or D-efficiency (for function Deff).

Methods

plot `signature(x = "OPT")`: ...

summary `signature(object = "OPT")`: ...

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

Examples

```
showClass("OPT")
```

PAR *Class to contain the variables for the verification plots from function MOPT, ceff1, ceff2, and Deff.*

Description

For function MOPT, ceff1, ceff2, and Deff, the plot of the sensitivity function over the given dose interval can be used to verify the optimality of the obtained design. Class PAR is used to contain the variables for the plot.

Objects from the Class

new("PAR",fid="character",LB="numeric",UB="numeric",grid="numeric",ds="vector")

Slots

`fid`: A character showing the name of the function from where the four arguments are.

`LB`: A numeric number showing the predetermined lower bound of the dose range for the log dose.

`UB`: A numeric number showing the predetermined upper bound of the dose range for the log dose.

`grid`: A numeric number showing the grid density to discretize the predetermined dose interval.

`ds`: A numeric vector represents the values of criterion (an absolute value of the difference between the sensitivity function and 1) computed at each iteration.

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

Examples

```
showClass("PAR")
```

---

plot-methods — *Methods to plot the verification plot of the obtained optimal design.*

Description

Function MOPT, ceff1, ceff2, and Deff return objects of class OPT. The plot-methods plot the verification plot of the multiple-objective optimal design (from function MOPT), the D-optimal design (from function Deff), the c-optimal design for estimating the ED50 (from function ceff1), and the c-optimal design for estimating the MED (from function ceff2).

Methods

```
signature(x = "OPT")
```

S.Weight *Identify optimal weights for given dose levels.*

Description

Find optimal proportions of subjectives at the given dose levels to estimate the model parameters, the ED50 and the MED simultaneously under the 4-parameter logistiv model. This also can be used to find the optimal weights at the given dose under the 2 or 3-parameter logistic models by setting the parameter values differently.

Usage

```
S.Weight(X,P,lambda,delta,epsilon_w)
```

Arguments

X	A numeric vector. Given dose levels to search the optimal weights.
P	A numeric vector. Solicited information on nominal values for the vector. P=(p1, p2, p3, p4), where p1 is the lower limit of the response (θ_4), p2 is Emax (θ_1), p3 is the ED50 (exp(-$\frac{\theta_3}{\theta_2}$)) and p4 is the slope at the ED50 (-θ_2). For the 4-parameter logistiv model, a user needs to specify all 4 nominal values in P: P = (p1, p2, p3, p4). For the 3-parameter logistic model, a user needs to specify only the 3 nominal values, Emax, the ED50, and the slope: P = (p2, p3, p4). For the 2-parameter logistic model, a user needs to specify only the 2 nominal values, the ED50 and the slope: P = (p3, p4).
lambda	A numeric vector. User-selected weights for the first two objectives. lambda = c(q1, q2), where q1,q2 represent weights for estimating model parameter and estimating the ED50 respectively. They are non-negative and q1 + q2 <= 1.
delta	Numeric. Predetermined clinically significant effect to define the MED. The MED is the dose producing the mean response of dt units better than the minimum dose.
epsilon_w	Numeric. Stopping criterion for the Newton Raphson method to search the optimal weights for the given dose levels. Default is 10^-6.

Value

An object of class SW.

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

References

Hyun, S.W., Wong, W.K, Yang, Y. VNM: An R Package for Finding Multiple-Objective Optimal Designs for the 4-Parameter Logistic Model. (*Journal of Statistical Software*, 83, 1-19, 2018, doi: 10.18637/jss.v083.i05.)

Hyun, S. W., Wong, W.K. Multiple-Objective Optimal Designs for Studying the Dose Response Function and Interesting Dose Levels. (*International Journal of Biostatistics*, 11, 253-271, 2015)

Examples

```
##The given dose levels
dose=c(-6.91,-4.89,-4.18,6.91)

##Model parameter values for the 4PL
par.4PL=c(0.137,1.563,.00895,-1.790)

##Find the optimal weights for the given dose levels
Res.W=S.Weight(dose, par.4PL, lambda=c(1/3,1/3), delta=-1)

##Print the obtained optimal weights, and its verification
    summary(Res.W)
```

---

summary-methods — *Methods to print SW objects or the optimal design and the efficiency from OPT objects.*

Description

Function MOPT, ceff1, ceff2, and Deff return objects of class OPT. Function S.Weight returns objects of class SW. The summary-methods print the multiple-objective optimal design (from function MOPT); the c-optimal design and c-efficiency for estimating the ED50 (from function ceff1); the c-optimal design and c-efficiency for estimating the MED (from function ceff2); the D-optimal design and D-efficiency (from function Deff); the matrix of the optimal weights and the first and second derivative of the optimality criterion w.r.t weights (from function S.Weight).

Methods

`signature(object = "OPT")`

`signature(object = "SW")`

SW *Class to contain the results from function S. Weight.*

Description

The function S.Weight returns an object of class SW that contains the optimal weights and the first and second derivatives of the criterion.

Objects from the Class

new("SW",Opt.W=new("matrix"),First.C=new("vector"),Second.C=new("vector"))

Slots

`Opt.W`: A numeric matrix showing the optimal weights.

`First.C`: A numeric vector showing the first derivative of the criterion.

`Second.C`: A numeric vector showing the second derivative of the criterion.

Methods

summary `signature(object = "SW")`: ...

Author(s)

Seung Won Hyun, Weng Kee Wong, and Yarong Yang

Examples

```
showClass("SW")
```

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