Package ‘DoseFinding’

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Description The DoseFinding package provides functions for the design and analysis of dose-finding experiments (with focus on pharmaceutical Phase II clinical trials). It provides functions for: multiple contrast tests, fitting non-linear dose-response models (using Bayesian and non-Bayesian estimation), calculating optimal designs and an implementation of the MCPMod methodology.

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**Description**

The DoseFinding package provides functions for the design and analysis of dose-finding experiments (for example pharmaceutical Phase II clinical trials). It provides functions for: multiple contrast tests (`MCTtest`), fitting non-linear dose-response models (`fitMod`), a combination of testing and dose-response modelling (`MCPMod`), and calculating optimal designs (`optDesign`), both for normal and general response variable.

**Details**

- **Package:** DoseFinding
- **Type:** Package
- **Version:** 0.9-15
- **Date:** 2016-07-26
- **License:** GPL-3

The main functions are:
- **MCTtest:** Implements a multiple contrast tests
- **powMCT:** Power calculations for multiple contrast tests
- **fitMod:** Fits non-linear dose-response models
- **optDesign:** Calculates optimal designs for dose-response models
- **MCPMod:** Performs MCPMod methodology
- **sampSize:** General function for sample size calculation

**Author(s)**

Bjoern Bornkamp, Jose Pinheiro, Frank Bretz

Maintainer: Bjoern Bornkamp <bbnkmp@gmail.com>
References


Examples

```r
data(ibsCovars)

## perform (model based) multiple contrast test
## define candidate dose-response shapes
models <- Mods(linear = NULL, emax = 0.2, quadratic = -0.17,
               doses = c(0, 1, 2, 3, 4))

## plot models
plot(models)

## perform multiple contrast test
test <- MCTest(dose, resp, ibsCovars, models=models,
               addCovars = ~ gender)

## fit non-linear emax dose-response model
fitemax <- fitMod(dose, resp, data=ibsCovars, model="emax",
                  bnds = c(0.01, 5))

## display fitted dose-effect curve
plot(fitemax, CI=TRUE, plotData="meansCI")

## Calculate optimal designs for target dose (TD) estimation
doses <- c(0, 10, 25, 50, 100, 150)
fmodels <- Mods(linear = NULL, emax = 25, exponential = 85,
               logistic = c(50, exp(8.811)),
               doses = doses, placEff=0, maxEff=0.4)
plot(fmodels, plotTD = TRUE, Delta = 0.2)
weights <- rep(1/4, 4)
destTD <- optDesign(fmodels, weights, Delta=0.2, designCrit="TD")
```
Fit a dose-response model using Bayesian or bootstrap methods.

**Description**

For `type = "Bayes"`, MCMC sampling from the posterior distribution of the dose-response model is done. The function assumes a multivariate normal distribution for `resp` with covariance matrix `S`, and this is taken as likelihood function and combined with the prior distributions specified in prior to form the posterior distribution.

For `type = "bootstrap"`, a multivariate normal distribution for `resp` with covariance matrix `S` is assumed, and a large number of samples is drawn from this distribution. For each draw the `fitMod` function with `type = "general"` is used to fit the draws from the multivariate normal distribution.

**Usage**

```r
bFitMod(dose, resp, model, S, placAdj = FALSE,
        type = c("Bayes", "bootstrap"),
        start = NULL, prior = NULL, nSim = 1000,
        MCMCcontrol = list(), control = NULL, bnds,
        addArgs = NULL)
```

**Arguments**

- `dose` Numeric specifying the dose variable.
- `resp` Numeric specifying the response estimate corresponding to the doses in `dose`
- `S` Covariance matrix associated with the dose-response estimate specified via `resp`
- `model` Dose-response model to fit, possible models are "linlog", "linear", "quadratic", "emax", "exponential", "sigEmax", "betaMod" and "logistic", see `drmodels`
- `placAdj` Whether or not estimates in "placAdj" are placebo-adjusted (note that the linear in log and the logistic model cannot be fitted for placebo-adjusted data)
**type**
Character with allowed values "Bayes" and "bootstrap". Determining whether samples are drawn from the posterior, or the bootstrap distribution.

**start**
Optional starting values for the dose-response parameters in the MCMC algorithm.

**prior**
List containing the information regarding the prior distributions for `type = "Bayes"`. The list needs to have as many entries as there are model parameters. The ordering of the list entries should be the same as in the arguments list of the model see (see `drmodels`). For example for the Emax model the first entry determines the prior for e0, the second to eMax and the third to ed50.

For each list entry the user has the choice to choose from 4 possible distributions:

- **norm**: Vector of length 2 giving mean and standard deviation.
- **t**: Vector of length 3 giving median, scale and degrees of freedom of the t-distribution.
- **lnorm**: Vector of length 2 giving mean and standard deviation on log scale.
- **beta**: Vector of length 4 giving lower and upper bound of the beta prior as well as the alpha and beta parameters of the beta distribution

**nSim**
Desired number of samples to produce with the algorithm

**MCMCcontrol**
List of control parameters for the MCMC algorithm

- **thin**: Thinning rate. Must be a positive integer.
- **w**: Numeric of same length as number of parameters in the model, specifies the width parameters of the slice sampler.
- **adapt**: Logical whether to adapt the w (width) parameter of the slice sampler in a short trial run. The widths are chosen as IQR/1.3 of the trial run.

**control**
Same as the control argument in `fitMod`.

**bnds**
Bounds for non-linear parameters, in case `type = "bootstrap"`. If missing the the default bounds from `defBnds` is used.

**addArgs**
List containing two entries named "scal" and "off" for the "betaMod" and "lin-log" model. When addArgs is NULL the following defaults are used `list(scal = 1.2*max(doses), of = mean(doses))`.

**x, object**
A bFitMod object

**predType, summaryFct, doseSeq, lenSeq**
Arguments for the predict method.

- **predType**: predType determines whether predictions are returned for the dose-response curve or the effect curve (difference to placebo).
- **summaryFct**: If equal to NULL predictions are calculated for each sampled parameter value. Otherwise a summary function is applied to the dose-response predictions for each parameter value. The default is to calculate 0.025, 0.25, 0.5, 0.75, 0.975 quantiles of the predictions for each dose.
- **doseSeq**: Where to calculate predictions. If not specified predictions are calculated on a grid of length `"lenSeq"` between minimum and maximum dose.
- **lenSeq**: Length of the default grid where to calculate predictions.

**plotType, quant, plotData, level, lenDose**
Arguments for plot method.

- **plotType**: Determining whether the dose-response curve or the effect curve should be plotted.
‘quant’: Vector of quantiles to display in plot
‘plotData’: Determines how the original data are plotted: Either as means or
as means with CI or not. The level of the CI is determined by the argument
‘level’.
‘level’: Level for CI, when plotData is equal to ‘meansCI’.
‘lendose’: Number of grid values to use for display.

Additional arguments are ignored.

Details
Componentwise univariate slice samplers are implemented (see Neal, 2003) to sample from the
posterior distribution.

Value
An object of class bFitMod, which is a list containing the matrix of posterior simulations plus some
additional information on the fitted model.

Author(s)
Bjoern Bornkamp

References

See Also
fitMod

Examples

```r
data(biom)
## produce first stage fit (using dose as factor)
anMod <- lm(resp~factor(dose)-1, data=biom)
drfit <- coef(anMod)
S <- vcov(anMod)
dose <- sort(unique(biom$dose))
## define prior list
## normal prior for E0 (mean=0 and sdev=10)
## normal prior for Emax (mean=0 and sdev=100)
## beta prior for ED50: bounds: [0,1.5] parameters shape1=0.45, shape2=1.7
prior <- list(norm = c(0, 10), norm = c(0,100), beta=c(0,1.5,0.45,1.7))
## now fit an emax model
gsample <- bfitMod(dose, drfit, S, model = "emax",
                  start = c(0, 1, 0.1), nSim = 1000, prior = prior)
## summary information
gsample
## samples are stored in
head(gsample$samples)
## predict 0.025, 0.25, 0.5, 0.75, 0.975 Quantile at 0, 0.5 and 1
```
predict(gsample, doseSeq = c(0, 0.5, 1))
## simple plot function
plot(gsample)

## now look at bootstrap distribution
gsample <- bFitMod(dose, drFit, S, model = "emax", type = "bootstrap",
                   nSim = 100, bnds = defBnds(1)$emax)
plot(gsample)

## now fit linear interpolation
prior <- list(norm = c(0,1000), norm = c(0,1000),
              norm = c(0,1000), norm = c(0,1000))
gsample <- bFitMod(dose, drFit, S, model = "linInt",
                   start = rep(1,5), nSim = 1000, prior = prior)
gsample <- bFitMod(dose, drFit, S, model = "linInt", type = "bootstrap",
                   nSim = 100)

## data fitted on placebo adjusted scale
data(IBScovars)
anovaMod <- lm(resp~factor(dose)+gender, data=IBScovars)
drFit <- coef(anovaMod)[2:5] # placebo adjusted estimates at doses
drvcoV <- vcov(anovaMod)[2:5,2:5]
dose <- sort(unique(IBScovars$dose))[-1]
prior <- list(norm = c(0,100), beta=c(0,6,0.45,1.7))
## Bayes fit
gsample <- bFitMod(dose, drFit, drvcoV, model = "emax", placAdj=TRUE,
                   start = c(1, 0.1), nSim = 1000, prior = prior)
## bootstrap fit
gsample <- bFitMod(dose, drFit, drvcoV, model = "emax", placAdj=TRUE,
                   type = "bootstrap", start = c(1, 0.1),
                   nSim = 100, prior = prior, bnds = c(0.01,6))

## calculate target dose estimate
TD(gsample, Delta = 0.2)
## now fit linear interpolation
prior <- list(norm = c(0,1000), norm = c(0,1000), norm = c(0,1000), norm = c(0,1000))
gsample <- bFitMod(dose, drFit, drvcoV, model = "linInt", placAdj=TRUE,
                   start = rep(1,4), nSim = 1000, prior = prior)
gsample <- bFitMod(dose, drFit, drvcoV, model = "linInt", type = "bootstrap",
                   placAdj = TRUE, nSim = 100)

---

### Description

An example data set for dose response studies. This data set was used in Bretz et al. (2005) to illustrate the MCPMod methodology.

### Usage

```r
data(biom)
```
**defBnds**

A data frame with 100 observations on the following 2 variables.

resp a numeric vector containing the response values
dose a numeric vector containing the dose values

**Source**


---

**defBnds**

*Calculates default bounds for non-linear parameters in dose-response models*

---

**Description**

Calculates reasonable bounds for non-linear parameters for the built-in non-linear regression model based on the dose range under investigation.

For the logistic model the first row corresponds to the ED50 parameter and the second row to the delta parameter. For the sigmoid Emax model the first row corresponds to the ED50 parameter and the second row to the h parameter, while for the beta model first and second row correspond to the delta1 and delta2 parameters. See logistic, sigEmax and betaMod for details.

**Usage**

```r
defBnds(mD, emaxL exponentialL logisticL sigemaxL betamod) values for the nonlinear parameters for these model-functions
```

**Arguments**

- mD: Maximum dose in the study.
- emax, exponential, logistic, sigEmax, betaMod: values for the nonlinear parameters for these model-functions

**Value**

List containing bounds for the model parameters.

**Author(s)**

Bjoern Bornkamp
DR-Models

See Also
fitmod

Examples

defBnds(nD = 1)
defBnds(nD = 200)

Built-in dose-response models in DoseFinding

Description

Dose-response model functions and gradients.
Below are the definitions of the model functions:

Emax model

\[ f(d, \theta) = E_0 + E_{max} \frac{d}{ED_{50} + d} \]

Sigmoid Emax Model

\[ f(d, \theta) = E_0 + E_{max} \frac{d^h}{ED_{50}^h + d^h} \]

Exponential Model

\[ f(d, \theta) = E_0 + E_1 (\exp(d/\delta) - 1) \]

Beta model

\[ f(d, \theta) = E_0 + E_{max} B(\delta_1, \delta_2)(d/scal)^{\delta_1}(1 - d/scal)^{\delta_2} \]

here
\[ B(\delta_1, \delta_2) = (\delta_1 + \delta_2)^{\delta_1+\delta_2}/(\delta_1^{\delta_1} \delta_2^{\delta_2}) \]

and scal is a fixed dose scaling parameter.

Linear Model

\[ f(d, \theta) = E_0 + \delta d \]

Linear in log Model

\[ f(d, \theta) = E_0 + \delta \log(d + off) \]

here off is a fixed offset parameter.

Logistic Model

\[ f(d, \theta) = E_0 + E_{max}/ \{1 + \exp(ED_{50} - d)/\delta)\} \]

Quadratic Model

\[ f(d, \theta) = E_0 + \beta_1 d + \beta_2 d^2 \]

Linear Interpolation model

The linInt model provides linear interpolation at the values defined by the nodes vector. In virtually all situations the nodes vector is equal to the doses used in the analysis. For example the Mods and the fitMod function automatically use the doses that are used in the context of the function call as nodes. The guesses specified in the Mods function need to be the treatment effects at the active doses standardized to the interval [0,1] (see the examples in the Mods function).
Usage

emax(dose, e0, eMax, ed50)
emaxGrad(dose, eMax, ed50, ...)

sigEmax(dose, e0, eMax, ed50, h)
sigEmaxGrad(dose, eMax, ed50, h, ...)

exponential(dose, e0, e1, delta)
exponentialGrad(dose, e1, delta, ...)

quadratic(dose, e0, b1, b2)
quadraticGrad(dose, ...)

betaMod(dose, e0, eMax, delta1, delta2, scal)
betaModGrad(dose, eMax, delta1, delta2, scal, ...)

linear(dose, e0, delta)
linearGrad(dose, ...)

linlog(dose, e0, delta, off = 1)
linlogGrad(dose, off, ...)

logistic(dose, e0, eMax, ed50, delta)
logisticGrad(dose, eMax, ed50, delta, ...)

linInt(dose, resp, nodes)
linIntGrad(dose, resp, nodes, ...)

Arguments

dose  Dose variable

e0  For most models placebo effect. For logistic model left-asymptote parameter, corresponding to a basal effect level (not the placebo effect)

eMax  Beta Model: Maximum effect within dose-range
            Emax, sigmoid Emax, logistic Model: Asymptotic maximum effect

ed50  Dose giving half of the asymptotic maximum effect

h  Hill parameter, determining the steepness of the model at the ED50

e1  Slope parameter for exponential model

delta  Exponential model: Parameter, controlling the convexity of the model.
            Linear and linlog model: Slope parameter
            Logistic model: Parameter controlling determining the steepness of the curve

delta1  delta1 parameter for beta model

delta2  delta2 parameter for beta model

b1  first parameter of quadratic model

b2  second parameter of quadratic model (controls, whether model is convex or concave)
Response values at the nodes for the linInt model

Offset value to avoid problems with dose=0 (treated as a fixed value, not estimated)

Scale parameter (treated as a fixed value, not estimated)

Interpolation nodes for the linear interpolation for the linInt model (treated as a fixed value, not estimated)

Just included for convenience in the gradient functions, so that for example quadratic(dose, e0=0, b1=1, b2=3) will not throw an error (although the gradient of the quadratic model is independent of e0, b1 and b2).

Details

The **Emax model** is used to represent monotone, concave dose-response shapes. To distinguish it from the more general sigmoid emax model it is sometimes also called hyperbolic emax model.

The **sigmoid Emax** model is an extension of the (hyperbolic) Emax model by introducing an additional parameter \( h \), that determines the steepness of the curve at the ed50 value. The sigmoid Emax model describes monotonic, sigmoid dose-response relationships.

The **quadratic** model is intended to capture a possible non-monotonic dose-response relationship.

The **exponential model** is intended to capture a possible sub-linear or a convex dose-response relationship.

The **beta model** is intended to capture non-monotone dose-response relationships and is more flexible than the quadratic model. The kernel of the beta model function consists of the kernel of the density function of a beta distribution on the interval \([0, \text{scal}]\). The parameter \( \text{scal} \) is not estimated but needs to be set to a value larger than the maximum dose. It can be set in most functions (‘fitMod’, ‘Mods’) via the ‘addArgs’ argument, when omitted a value of ‘1.2*(maximum dose)’ is used as default, where the maximum dose is inferred from other input to the respective function.

The **linear in log-dose** model is intended to capture concave shapes. The parameter \( \text{off} \) is not estimated in the code but set to a pre-specified value. It can be set in most functions (‘fitMod’, ‘Mods’) via the ‘addArgs’ argument, when omitted a value of ‘0.01*(maximum dose)’ is used as default, where the maximum dose is inferred from other input to the respective function.

The **logistic model** is intended to capture general monotone, sigmoid dose-response relationships. The logistic model and the sigmoid Emax model are closely related: The sigmoid Emax model is a logistic model in log(dose).

The **linInt model** provides linear interpolation of the means at the doses. This can be used as a "nonparametric" estimate of the dose-response curve, but is probably most interesting for specifying a "nonparametric" truth during planning and assess how well parametric models work under a nonparametric truth. For the function ‘Mods’ and ‘fitMod’ the interpolation ‘nodes’ are selected equal to the dose-levels specified.

Value

Response value for model functions or matrix containing the gradient evaluations.
References


See Also

fitMod

Examples

## some quadratic example shapes
quadModList <- Mods(quadratic = c(-0.5, -0.75, -0.85, -1), doses = c(0,1))
plot(quadModList)

## some emax example shapes
emaxModList <- Mods(emax = c(0.02, 0.1, 0.5, 1), doses = c(0,1))
plot(emaxModList)

## example for gradient
emaxGrad(dose = (0:4)/4, eMax = 1, ed50 = 0.5)

## some sigmoid emax example shapes
sigEmaxModList <- Mods(sigEmax = rbind(c(0.05,1), c(0.15,3), c(0.4,8),
                                        c(0.7,8)), doses = c(0,1))
plot(sigEmaxModList)
sigEmaxGrad(dose = (0:4)/4, eMax = 1, ed50 = 0.5, h = 8)

## some exponential example shapes
expoModList <- Mods(exponential = c(0.1,0.25,0.5,2), doses=c(0,1))
plot(expoModList)

exponentialGrad(dose = (0:4)/4, e1 = 1, delta = 2)

## some beta model example shapes
betaModList <- Mods(betaMod = rbind(c(1,1), c(1.5,0.75), c(0.8,2.5),
                                         c(0.4,0.9)), doses=c(0,1), addArgs=list(scal = 1.2))
plot(betaModList)
betaModGrad(dose = (0:4)/4, eMax = 1, delta1 = 1, delta2 = 1, scal = 5)

## some logistic model example shapes
logistModList <- Mods(logistic = rbind(c(0.5,0.05), c(0.5,0.15),
                                         c(0.2,0.05), c(0.2,0.15)), doses=c(0,1))
plot(logistModList)

logisticGrad(dose = (0:4)/4, eMax = 1, ed50 = 0.5, delta = 0.05)

## some linInt shapes
genModList <- Mods(linInt = rbind(c(0.5,1,1), c(0,1,1), c(0,0,1)), doses=c(0,0.5,1,1.5))
plot(genModList)

linIntGrad(dose = (0:4)/4, resp=c(0,0.5,1,1), nodes=(0:4)/4)
**FitMod**

*Fit non-linear dose-response model*

**Description**

Fits a dose-response model. Built-in dose-response models are "linlog", "linear", "quadratic", "emax", "exponential", "sigEmax", "betaMod" and "logistic" (see `drmodels`).

When `type = "normal"` ordinary least squares is used and additional additive covariates can be specified in `addCovars`. The underlying assumption is hence normally distributed data and homoscedastic variance.

For `type = "general"` a generalized least squares criterion is used

\[(f(dose, \theta) - resp)'S^{-1}(f(dose, \theta) - resp)\]

and an inverse weighting matrix is specified in `S`. `type = "general"` is primarily of interest, when fitting a model to AN(C)OVA type estimates obtained in a first stage fit, then `resp` contains the estimates and `S` is the estimated covariance matrix for the estimates in `resp`. Statistical inference (e.g. confidence intervals) rely on asymptotic normality of the first stage estimates, which makes this method of interest only for sufficiently large sample size for the first stage fit. A modified model-selection criterion can be applied to these model fits (see also Pinheiro et al. 2013 for details).

For details on the implemented numerical optimizer see the Details section below.

**Usage**

```r
fitMod(dose, resp, data = NULL, model, S = NULL, type = c("normal", "general"), addCovars = ~1, placAdj = FALSE, bnds, df = NULL,
      start = NULL, na.action = na.fail, control = NULL,
      addArgs = NULL)
```

## S3 method for class 'DRMod'
```
coef(object, sep = FALSE, ...)
```

## S3 method for class 'DRMod'
```
predict(object, predType = c("full-model", "ls-means", "effect-curve"),
         newdata = NULL, doseSeq = NULL, se.fit = FALSE, ...)
```

## S3 method for class 'DRMod'
```
vcov(object, ...)
```

## S3 method for class 'DRMod'
```
plot(x, CI = FALSE, level = 0.95,
     plotData = c("means", "meansCI", "raw", "none"),
     plotGrid = TRUE, colMn = 1, colFit = 1, ...)
```
### fitMod

```r
## S3 method for class 'DRMod'
logLik(object, ...)

## S3 method for class 'DRMod'
AIC(object, ..., k = 2)

## S3 method for class 'DRMod'
gAIC(object, ..., k = 2)
```

#### Arguments

dose, resp
Either vectors of equal length specifying dose and response values, or names of variables in the data frame specified in 'data'.

data
Data frame containing the variables referenced in dose and resp if 'data' is not specified it is assumed that 'dose' and 'resp' are variables referenced from data (and no vectors)

model
The dose-response model to be used for fitting the data. Built-in models are "linlog", "linear", "quadratic", "emax", "exponential", "sigEmax", "betaMod" and "logistic" (see drmodels).

S
The inverse weighting matrix used in case, when 'type = "general"', see Description. For later inference statements (vcov or predict methods) it is assumed this is the estimated covariance of the estimates in the first stage fit.

type
Determines whether inference is based on an ANCOVA model under a homoscedastic normality assumption (when 'type = "normal"'), or estimates at the doses and their covariance matrix and degrees of freedom are specified directly in 'resp', 'S' and 'df'. See also the Description above and Pinheiro et al. (2013).

addCovars
Formula specifying additional additive linear covariates (only for 'type = "normal"')

placAdj
Logical, if true, it is assumed that placebo-adjusted estimates are specified in 'resp' (only possible for 'type = "general"')

bnds
Bounds for non-linear parameters. If missing the the default bounds from defBnds is used.

When the dose-response model has only one non-linear parameter (for example Emax or exponential model), 'bnds' needs to be a vector containing upper and lower bound. For models with two non-linear parameters 'bnds' needs to be a matrix containing the bounds in the rows, see the Description section of defBnds for details on the formatting of the bounds for the individual models.

df
Degrees of freedom to use in case of 'type = "general"'. If this argument is missing 'df = Inf' is used. For 'type = "normal"' this argument is ignored as the exact degrees of freedom can be deduced from the model.

start
Vector of starting values for the nonlinear parameters (ignored for linear models). When equal to NULL, a grid optimization is performed and the best value is used as starting value for the local optimizer.

na.action
A function which indicates what should happen when the data contain NAs.
fitMod

control
A list with entries: "nlminbcontrol", "optimizetol" and "gridSize".
The entry nlminbcontrol needs to be a list and it is passed directly to control argument in the nlminb function, that is used internally for models with 2 non-linear parameters.
The entry optimizetol is passed directly to the tol argument of the optimize function, which is used for models with 1 nonlinear parameters.
The entry gridSize needs to be a list with entries dim1 and dim2 giving the size of the grid for the gridssearch in 1d or 2d models.

addArgs
List containing two entries named "scal" and "off" for the "betaMod" and "lin-log" model. When addArgs is NULL the following defaults is used 'list(scal = 1.2*max(doses), off = PNPQ*maxHdosesII)

object, x
DRMod object

sep
Logical determining whether all coefficients should be returned in one numeric or separated in a list.

predType, newdata, doseSeq, se.fit
predType determines whether predictions are returned for the full model (including potential covariates), the ls-means (SAS type) or the effect curve (difference to placebo).
newdata gives the covariates to use in producing the predictions (for predType = "full-model"), if missing the covariates used for fitting are used.
doseSeq dose-sequence on where to produce predictions (for predType = "effect-curve" and predType = "ls-means"). If missing the doses used for fitting are used.
se.fit: logical determining, whether the standard error should be calculated.

CI, level, plotData, plotGrid, colMn, colfit
Arguments for plot method. ‘CI’ determines whether confidence intervals should be plotted. ‘level’ determines the level of the confidence intervals. ‘plotData’ determines how the data are plotted: Either as means or as means with CI, raw data or none. In case of ‘type = "normal"’ and covariates the ls-means are displayed, when ‘type = "general"’ the option "raw" is not available. ‘colMn’ and ‘colfit’ determine the colors of fitted model and the raw means.

k
Penalty to use for model-selection criterion (AIC uses 2, BIC uses log(n)).

Details
Details on numerical optimizer for model-fitting:
For linear models fitting is done using numerical linear algebra based on the QR decomposition. For nonlinear models numerical optimization is performed only in the nonlinear parameters in the model and optimizing over the linear parameters in each iteration (similar as the Golub-Pereyra implemented in nls). For models with 1 nonlinear parameter the optimize function is used for 2 nonlinear parameters the nlminb function is used. The starting value is generated using a grid-search (with the grid size specified via ‘controlDgridsize’), or can directly be handed over via ‘start’.
For details on the asymptotic approximation used for ‘type = "normal"’, see Seber and Wild (2003, chapter 5). For details on the asymptotic approximation used for ‘type = "general"’, and the gAIC, see Pinheiro et al. (2013).
Value
An object of class DRMod. Essentially a list containing information about the fitted model coefficients, the residual sum of squares (or generalized residual sum of squares),

Author(s)
Bjoern Bornkamp

References

See Also
defBnds, drmodels

Examples
```r
## Fit the emax model to the IBScovars data set
data(IBScovars)
fitemax <- fitMod(dose, resp, data=IBScovars, model="emax",
                 bnds = c(0.01, 4))

## methods for DRMod objects
summary(fitemax)
## extracting coefficients
coeff(fitemax)
## (asymptotic) covariance matrix of estimates
vcov(fitemax)
## predicting
newdat <- data.frame(dose = c(0, 0.5, 1), gender=factor(1))
predict(fitemax, newdata=newdat, predType = "full-model", se.fit = TRUE)
## plotting
plot(fitemax, plotData = "meansCI", CI=TRUE)

## now include (additive) covariate gender
fitemax2 <- fitMod(dose, resp, data=IBScovars, model="emax",
                   addCovars = ~gender, bnds = c(0.01, 4))

vcov(fitemax2)
plot(fitemax2)
## fitted log-likelihood
logLik(fitemax2)
## extracting AIC (or BIC)
AIC(fitemax2)

## Illustrating the "general" approach for a binary regression
## produce first stage fit (using dose as factor)
data(migraine)
PFRate <- migraine$painfree/migraine$ntrt
```
glycobrom

Glycopyrronium Bromide dose-response data

doseVec <- migraine$dose
doseVecFac <- as.factor(migraine$dose)
## fit logistic regression with dose as factor
fitBin <- glm(PFrate~doseVecFac-1, family = binomial,
             weights = migraine$ntrt)
drEst <- coef(fitBin)
vCov <- vcov(fitBin)
## now fit an Emax model (on logit scale)
gfit <- fitMod(doseVec, drEst, S=vCov, model = "emax", bnds = c(0,100),
               type = "general")
## model fit on logit scale
plot(gfit, plotData = "meansCI", CI = TRUE)
## model on probability scale
logitPred <- predict(gfit, predType ="ls-means", doseSeq = 0:200,
                      se.fit=TRUE)
plot(0:200, 1/(1+exp(-logitPred$fit)), type = "l",
     ylim = c(0, 0.5), ylab = "Probability of being painfree",
     xlab = "Dose")
LB <- logitPred$fit-qnorm(0.975)*logitPred$se.fit
UB <- logitPred$fit+qnorm(0.975)*logitPred$se.fit
lines(0:200, 1/(1+exp(-LB)))
lines(0:200, 1/(1+exp(-UB)))

## now illustrate "general" approach for placebo-adjusted data (on
## IBScovars) note that the estimates are identical to fitemax2 above
anovaMod <- lm(resp~factor(dose)+gender, data=IBScovars)
drFit <- coef(anovaMod)[2:5] # placebo adjusted estimates at doses
vCov <- vcov(anovaMod)[2:5,2:5]
dose <- sort(unique(IBScovars$dose))[-1]
## now fit an emax model to these estimates
gfit2 <- fitMod(dose, drFit, S=vCov, model = "emax", type = "general",
                placAdj = TRUE, bnds = c(0, 0.1, 2))
## some outputs
summary(gfit2)
coef(gfit2)
vcov(gfit2)
predict(gfit2, se.fit = TRUE, doseSeq = c(1,2,3,4), predType = "effect-curve")
plot(gfit2, CI=TRUE, plotData = "meansCI")
gAIC(gfit2)

glycobrom

Glycopyrronium Bromide dose-response data

Description

Data from a clinical study evaluating Efficacy and Safety of Four Doses of Glycopyrronium Bromide in Patients With Stable Chronic Obstructive Pulmonary Disease (COPD). This data set was obtained from clinicaltrials.gov (NCT00501852). The study design was a 4 period incomplete cross-over design. The primary endpoint is the trough forced expiratory volume in 1 second (FEV1) following 7 days of Treatment.

The data given here are summary estimates (least-square means) for each dose.
Usage
data(glycobrom)

Format
A data frame with 5 summary estimates (one per dose). Variables:
dose a numeric vector containing the dose values
dev a numeric vector containing the least square mean per dose
dev a numeric vector containing the standard errors of the least square means per dose
n Number of participants analyzed per treatment group

Source
http://clinicaltrials.gov/ct2/show/results/NCT00501852

Examples
```r
## simulate a full data set with given means and sdv (here we ignore
## the original study was a cross-over design, and simulate a parallel
## group design)
simData <- function(mns, sd, n, doses, fixed = TRUE){
  ## simulate data with means (mns) and standard deviations (sd), for
  ## fixed = TRUE, the data set will have observed means and standard
  ## deviations as given in mns and sd
  resp <- numeric(sum(n))
  uppind <- cumsum(n)
  lowind <- c(0,uppind)+1
  for(i in 1:length(n)){
    rv <- rnorm(n[i])
    if(fixed)
      rv <- scale(rv)
    resp[lowind[i]:uppind[i]] <- mns[i] + sd[i]*rv
  }
  data.frame(doses=rep(doses, n), resp=resp)
}
data(glycobrom)
fullDat <- simData(glycobrom$fev1, glycobrom$sdev, glycobrom$n,
glycobrom$dose)
```

Description
Calculate guesstimates based on prior knowledge

Calculates guesstimates for standardized model parameter(s) using the general approach described in Pinheiro et al. (2006).
Usage

guesst(d, p, model = c("emax", "exponential", "logistic", "quadratic", "betaMod", "sigEmax"), less = TRUE, local = FALSE, dMax, Maxd, scal)

Arguments

d Vector containing dose value(s).

p Vector of expected percentages of the maximum effect achieved at d.

model Character string. Should be one of "emax", "exponential", "quadratic", "betaMod", "sigEmax", "logistic".

less Logical, only needed in case of quadratic model. Determines if d is smaller ('less=TRUE') or larger ('less=FALSE') than dopt (see Pinheiro et al. (2006) for details).

local Logical indicating whether local or asymptotic version of guesstimate should be derived (defaults to 'FALSE'). Only needed for emax, logistic and sigEmax model. When 'local=TRUE' the maximum dose must be provided via 'Maxd'.

dMax Dose at which maximum effect occurs, only needed for the beta model

Maxd Maximum dose to be administered in the trial

scal Scale parameter, only needed for the beta model

Details

Calculates guesstimates for the parameters $\theta_2$ of the standardized model function based on the prior expected percentage of the maximum effect at certain dose levels. Note that this function should be used together with the plotNmods function to ensure that the guesstimates are reflecting the prior beliefs.

For the logistic and sigmoid emax models at least two pairs (d,p) need to be specified.

For the beta model the dose at which the maximum effect occurs (dMax) has to be specified in addition to the (d,p) pair.

For the exponential model the maximum dose administered (Maxd) needs to be specified in addition to the (d,p) pair.

For the quadratic model one (d,p) pair is needed. It is advisable to specify the location of the maximum within the dose range with this pair.

For the emax, sigmoid Emax and logistic model one can choose between a local and an asymptotic version. In the local version one explicitly forces the standardized model function to pass through the specified points (d,p). For the asymptotic version it is assumed that the standardized model function is equal to 1 at the largest dose (this is the approach described in Pinheiro et al. (2006)). If the local version is used, convergence problems with the underlying nonlinear optimization can occur.

Value

Returns a numeric vector containing the guesstimates.
References


See Also

`emax`, `logistic`, `betaMod`, `sigEmax`, `quadratic`, `exponential`, `plot.Mods`

Examples

```r
## Emax model
## Expected percentage of maximum effect: 0.8 is associated with
## dose 0.3 (d,p)=(0.3, 0.8), dose range [0,1]
emx1 <- guesst(d=0.3, p=0.8, model="emax")
## local approach
emx2 <- guesst(d=0.3, p=0.8, model="emax", local = TRUE, Maxd = 1)
## plot models
models <- Mods(emax=c(emx1, emx2), doses=c(0,1))
plot(models)

## Logistic model
## Select two (d,p) pairs (0.2, 0.5) and (0.6, 0.95)
lgc1 <- guesst(d = c(0.2, 0.5), p = c(0.6, 0.95), "logistic")
## local approach
lgc2 <- guesst(d = c(0.2, 0.5), p = c(0.6, 0.95), "logistic",
               local = TRUE, Maxd = 1)
## plot models
models <- Mods(logistic = rbind(lgc1, lgc2), doses=c(0,1))
plot(models)

## Beta Model
## Select one pair (d,p): (0.5,0.5)
## dose, where maximum occurs: 0.8
bta <- guesst(d=0.5, p=0.5, model="betaMod", dMax=0.8, scal=1.2, Maxd=1)
## plot
models <- Mods(betaMod = bta, doses=c(0,1), addArgs = list(scal = 1.2))
plot(models)

## Sigmoid Emax model
## Select two (d,p) pairs (0.2, 0.5) and (0.6, 0.95)
gE1 <- guesst(d = c(0.2, 0.5), p = c(0.6, 0.95), "sigEmax")
## local approach
gE2 <- guesst(d = c(0.2, 0.5), p = c(0.6, 0.95), "sigEmax",
               local = TRUE, Maxd = 1)
models <- Mods(sigEmax = rbind(gE1, gE2), doses=c(0,1))
plot(models)

## Quadratic model
## For the quadratic model it is assumed that the maximum effect occurs at
```
## Description

A subset of the data used by (Biesheuvel and Hothorn, 2002). The data are part of a dose ranging trial on a compound for the treatment of the irritable bowel syndrome with four active treatment arms, corresponding to doses 1,2,3,4 and placebo. Note that the original dose levels have been blinded in this data set for confidentiality. The primary endpoint was a baseline adjusted abdominal pain score with larger values corresponding to a better treatment effect. In total 369 patients completed the study, with nearly balanced allocation across the doses.

## Usage

data(IBScovars)

## Format

A data frame with 369 observations on the following 2 variables.

- gender  a factor specifying the gender
- dose a numeric vector
- resp   a numeric vector

## Source

Description

Tests for a dose-response effect using a model-based multiple contrast test (see MCTtest), selects one (or several) model(s) from the significant shapes, fits them using fitMod. For details on the method see Bretz et al. (2005).

Usage

MCPMod(dose, resp, data, models, S = NULL, type = c("normal", "general"),
        addCovars = ~1, placAdj = FALSE, selModel = c("AIC", "maxT", "aveAIC"),
        alpha = 0.025, df = NULL, critV = NULL, doseType = c("TD", "ED"),
        Delta, p, pVal = TRUE, alternative = c("one.sided", "two.sided"),
        na.action = na.fail, mvtncontrol = mvtnorm.control(),
        bnds, control = NULL)

## S3 method for class 'MCPMod'
predict(object,
        predType = c("full-model", "ls-means", "effect-curve"),
        newdata = NULL, doseSeq = NULL, se.fit = FALSE, ...)

## S3 method for class 'MCPMod'
plot(x, CI = FALSE, level = 0.95,
     plotData = c("means", "meansCI", "raw", "none"),
     plotGrid = TRUE, colMn = 1, colFit = 1, ...)
Logical, if true, it is assumed that placebo-adjusted estimates are specified in ‘resp’ (only possible for ‘type = “general”’).

Optional character vector specifying the model selection criterion for dose estimation. Possible values are

- AIC: Selects model with smallest AIC (this is the default)
- maxT: Selects the model corresponding to the largest t-statistic.
- aveAIC: Uses a weighted average of the models corresponding to the significant contrasts. The model weights are chosen by the formula: \( w_i = \exp(-0.5AIC_i)/\sum_i(\exp(-0.5AIC_i)) \) See Buckland et al. (1997) for details.

For ‘type = “general”’ the “gAIC” is used.

Significance level for the multiple contrast test

Specify the degrees of freedom to use in case ‘type = ”general”’, for the call to MCTtest and fitMod. Infinite degrees of (‘df=Inf”) correspond to the multivariate normal distribution. For type = ”normal” the degrees of freedom deduced from the AN(C)OVA fit are used and this argument is ignored.

Supply a pre-calculated critical value. If this argument is NULL, no critical value will be calculated and the test decision is based on the p-values. If ‘critV = TRUE’ the critical value will be calculated.

‘doseType’ determines the dose to estimate, ED or TD (see also Mods), and ‘Delta’ and ‘p’ need to be specified depending on whether TD or ED is to be estimated. See TD and ED for details.

Logical determining, whether p-values should be calculated.

Character determining the alternative for the multiple contrast trend test.

A function which indicates what should happen when the data contain NAs.

A list specifying additional control parameters for the ‘qmv’ and ‘pmv’ calls in the code, see also mvtnorm.control for details.

Bounds for non-linear parameters. This needs to be a list with list entries corresponding to the selected bounds. The names of the list entries need to correspond to the model names. The defBnds function provides the default selection.

Control list for the optimization.

A list with entries: "nlminbcontrol", "optimizetol" and "gridSize".

The entry nlminbcontrol needs to be a list and is passed directly to control argument in the nlminb function, that is used internally for models with 2 nonlinear parameters (e.g. sigmoid Emax or beta model).

The entry optimizetol is passed directly to the tol argument of the optimize function, which is used for models with 1 nonlinear parameters (e.g. Emax or exponential model).

The entry gridSize needs to be a list with entries dim1 and dim2 giving the size of the grid for the gridsearch in 1d or 2d models.

MCPMod object
predType, newdata, doseSeq, se.fit, ...

predType determines whether predictions are returned for the full model (including potential covariates), the ls-means (SAS type) or the effect curve (difference to placebo).

newdata gives the covariates to use in producing the predictions (for `predType = "full-model"`), if missing the covariates used for fitting are used.

doseSeq dose-sequence on where to produce predictions (for `predType = "effect-curve"` and `predType = "ls-means"`). If missing the doses used for fitting are used.

se.fit: logical determining, whether the standard error should be calculated.

...: Additional arguments, for plot.MCPMod these are passed to plot.DRMod.

CI, level, plotData, plotGrid, colMn, colFit

Arguments for plot method: `CI` determines whether confidence intervals should be plotted. `level` determines the level of the confidence intervals. `plotData` determines how the data are plotted: Either as means or as means with CI, raw data or none. In case of `type = "normal"` and covariates the ls-means are displayed, when `type = "general"` the option "raw" is not available. `colMn` and `colFit` determine the colors of fitted model and the raw means.

Value

An object of class `MCPMod`, which contains the fitted `MCTtest` object as well as the `DRMod` objects and additional information (model selection criteria, dose estimates, selected models).

Author(s)

Bjoern Bornkamp

References


See Also

`MCTtest`, `fitMod`, `drmodels`
Examples

data(biom)
## first define candidate model set (only need "standardized" models)
models <- Mods(linear = NULL, emax=c(0.05,0.2), linInt=c(1, 1, 1, 1),
doses=c(0,0.05,0.2,0.6,1))

## perform MCPMod procedure
MM <- MCPMod(dose, resp, biom, models, Delta=0.5)
## a number of things can be done with an MCPMod object
MM # print method provides basic information
summary(MM) # more information
## predict all significant dose-response models
predict(MM, se.fit=TRUE, doseSeq=c(0,0.2,0.4, 0.9, 1),
  predType="ls-means")
## display all model functions
plot(MM, plotData="meansCI", CI=TRUE)

## now perform model-averaging
MM2 <- MCPMod(dose, resp, biom, models, Delta=0.5, selModel = "aveAIC")
sq <- seq(0,1,length=11)
pred <- predict(MM, doseSeq=sq, predType="ls-means")
modWeights <- MM2$selMod
## model averaged predictions
pred <- do.call("cbind", pred)*modWeights
## model averaged dose-estimate
TDEst <- MM2$doseEst*modWeights

## now an example using a general fit and fitting based on placebo
## adjusted first-stage estimates
data(IBScovars)
## ANCOVA fit model including covariates
anovaMod <- lm(resp~factor(dose)+gender, data=IBScovars)
drFit <- coef(anovaMod)[2:5] # placebo adjusted estimates at doses
drCov <- vcov(anovaMod)[2:5,2:5]
dose <- sort(unique(IBScovars$dose))[-1] # no estimate for placebo
## candidate models
models <- Mods(emax = c(0.5, 1), betamod=c(1,1), doses=c(0,4))
## hand over placebo-adjusted estimates drFit to MCPMod
MM3 <- MCPMod(dose, drFit, S=drCov, models = models, type = "general",
  placAdj = TRUE, Delta=0.2)
plot(MM3, plotData="meansCI")

## The first example, but with critical value handed over
## this is useful, e.g. in simulation studies
MM4 <- MCPMod(dose, resp, biom, models, Delta=0.5, critV = 2.31)

MCTest

Performs multiple contrast test
Description

This function performs a multiple contrast test. The contrasts are either directly specified in ‘contMat’ or optimal contrasts derived from the ‘models’ argument. The directionality of the data (i.e. whether an increase or decrease in the response variable is beneficial is inferred from the ‘models’ object, see Mods).

For ‘type = "normal"’ an ANCOVA model based on a homoscedastic normality assumption (with additive covariates specified in ‘addCovars’) is fitted.

For ‘type = "general"’ it is assumed multivariate normally distributed estimates are specified in ‘resp’ with covariance given by ‘S’, and the contrast test statistic is calculated based on this assumption. Degrees of freedom specified in ‘df’.

Usage

MCTtest(dose, resp, data = NULL, models, S = NULL, type = c("normal", "general"),
addCovars = ~1, placAdj = FALSE, alpha = 0.025, df = NULL,
critV = NULL, pVal = TRUE,
alternative = c("one.sided", "two.sided"), na.action = na.fail,
mvtcontrol = mvtnorm.control(), contMat = NULL)

Arguments

dose, resp Either vectors of equal length specifying dose and response values, or names of variables in the data frame specified in ‘data’.
data Data frame containing the variables referenced in dose and resp if ‘data’ is not specified it is assumed that ‘dose’ and ‘resp’ are variables referenced from data (and no vectors)
models An object of class ‘Mods’, see Mods for details
S The covariance matrix of ‘resp’ when ‘type = "general"’, see Description.
type Determines whether inference is based on an ANCOVA model under a homoscedastic normality assumption (when ‘type = "normal"’), or estimates at the doses and their covariance matrix and degrees of freedom are specified directly in ‘resp’, ‘S’ and ‘df’. See also fitMod and Pinheiro et al. (2013).
addCovars Formula specifying additive linear covariates (for ‘type = "normal"’)
placAdj Logical, if true, it is assumed that placebo-adjusted estimates are specified in ‘resp’ (only possible for ‘type = "general"’).
alpha Significance level for the multiple contrast test
df Specify the degrees of freedom to use in case ‘type = "general"’. If this argument is missing ‘df = Inf’ is used (which corresponds to the multivariate normal distribution). For type = "normal" the degrees of freedom deduced from the AN(C)OVA fit are used and this argument is ignored.
critV Supply a pre-calculated critical value. If this argument is NULL, no critical value will be calculated and the test decision is based on the p-values. If ‘critV = TRUE’ the critical value will be calculated.
pVal Logical determining, whether p-values should be calculated.
alternative Character determining the alternative for the multiple contrast trend test.

na.action A function which indicates what should happen when the data contain NAs.

mvtcontrol A list specifying additional control parameters for the 'qmvt' and 'pmvt' calls in the code, see also mvtnorm.control for details.

contMat Contrast matrix to apply to the ANCOVA dose-response estimates. The contrasts need to be in the columns of the matrix (i.e. the column sums need to be 0).

Details
Integrals over the multivariate t and multivariate normal distribution are calculated using the 'mvtnorm' package.

Value
An object of class MCTtest, a list containing the output.

Author(s)
Bjoern Bornkamp

References


See Also
powMCT, optContr

Examples
```r
## example without covariates
data(biom)
## define shapes for which to calculate optimal contrasts
modlist <- Mods(emax = 0.05, linear = NULL, logistic = c(0.5, 0.1),
                 linInt = c(0, 1, 1, 1), doses = c(0, 0.05, 0.2, 0.6, 1))
m1 <- MCTtest(dose, resp, biom, models=modlist)
## now calculate critical value (but not p-values)
m2 <- MCTtest(dose, resp, biom, models=modlist, critV = TRUE, pVal = FALSE)
## now hand over critical value
m3 <- MCTtest(dose, resp, biom, models=modlist, critV = 2.24)

## example with covariates
data(IBScovars)
modlist <- Mods(emax = 0.05, linear = NULL, logistic = c(0.5, 0.1),
                 linInt = c(0, 1, 1, 1), doses = c(0, 1, 2, 3, 4))
MCTtest(dose, resp, IBScovars, models = modlist, addCovars = ~gender)
```
## Example using general approach (fitted on placebo-adjusted scale)

```r
ancMod <- lm(resp~factor(dose)+gender, data=IBScovars)
## extract estimates and information to feed into MCTtest
drEst <- coef(ancMod)[2:5]
vC <- vcov(ancMod)[2:5, 2:5]
doses <- 1:4
MCTtest(doses, drEst, S = vc, models = modlist, placAdj = TRUE,
    type = "general", df = Inf)
```

## Example with general alternatives handed over

```r
data(biom)
## calculate contrast matrix for the step-contrasts
## represent them as linInt models
models <- Mods(linInt=rbind(c(1,1,1,1),
    c(0,1,1,1),
    c(0,0,1,1),
    c(0,0,0,1)),
    doses=c(0,0.05,0.2,0.6,1))
plot(models)
## now calculate optimal contrasts for these means
## use weights from actual sample sizes
weights <- as.numeric(table(biom$dose))
contMat <- optContr(models, w = weights)
## plot contrasts
plot(contMat)
## perform multiple contrast test
MCTtest(dose, resp, data=biom, contMat = contMat)
```

## Example for using the Dunnett contrasts

```r
## Dunnett contrasts
doses <- sort(unique(biom$dose))
contMat <- rbind(~1, diag(4))
rownames(contMat) <- doses
colnames(contMat) <- paste("D", doses[-1], sep="")
MCTtest(dose, resp, data=biom, contMat = contMat)
```

### migraine

**Migraine Dose Response data**

## Description

Data set obtained from clinicaltrials.gov (NCT00712725). This was randomized placebo controlled dose-response trial for treatment of acute migraine. The primary endpoint was "pain freedom at 2 hours postdose" (a binary measurement).

## Usage

```r
data(migraine)
```
ModS

Format
A data frame with 517 columns corresponding to the patients that completed the trial

dose  a numeric vector containing the dose values
painfree  number of treatment responders
ntrt  number of subject per treatment group

Source
http://clinicaltrials.gov/ct2/show/results/NCT00712725

Define dose-response models

Description
The Mods functions allows to define a set of dose-response models. The function is used as input object for a number of other different functions.

The dose-response models used in this package (see drmodels for details) are of form

\[ f(d) = \theta_0 + \theta_1 f_0(d, \theta_2) \]

where the parameter \( \theta_2 \) is the only non-linear parameter and can be one- or two-dimensional, depending on the used model.

One needs to hand over the effect at placebo and the maximum effect in the dose range, from which \( \theta_0, \theta_1 \) are then back-calculated, the output object is of class "Mods". This object can form the input for other functions to extract the mean response ('getResp') or target doses (TD and ED) corresponding to the models. It is also needed as input to the functions powMCT, optDesign

Some models, for example the beta model ('scal') and the linlog model ('off') have parameters that are not estimated by the code, they need to be specified via the 'addArgs' argument.

NOTE: If a decreasing effect is beneficial for the considered response variable it needs to specified here, either by using 'direction = "decreasing"' or by specifying a negative "maxEff" argument.

Usage

```r
Mods(..., doses, placEff = 0, maxEff, direction = c("increasing", "decreasing"), addArgs=NULL, fullMod = FALSE)
getResp(fmodels, doses)
```

## S3 method for class 'Mods'
```r
plot(x, nPoints = 200, superpose = FALSE, xlab = "Dose", ylab = "Model means", modNams = NULL, plotTD = FALSE, Delta, ...)
```
Arguments

In function Mods:
Dose-response model names with parameter values specifying the guesstimates for the \( \theta_2 \) parameters. See `drmodels` for a complete list of dose-response models implemented. See below for an example specification.

In function `plot.Mods`:
Additional arguments to the `xyplot` call.

doses
Dose levels to be used, this needs to include placebo.

addArgs
List containing two entries named "scal" and "off" for the "betaMod" and "lin-log". When addArgs is NULL the following defaults are used ‘list(scal = 1.2*max(doses), off = 0.01*max(doses), nodes = doses)’.

fullMod
Logical determining, whether the model parameters specified in the Mods function (via the ... argument) should be interpreted as standardized or the full model parameters.

placEff, maxEff
Specify used placebo effect and the maximum effect over placebo. Either a numeric vector of the same size as the number of candidate models or of length one.

When these parameters are not specified ‘placEff = 0’ is assumed, for ‘maxEff = 1’ is assumed, if ‘direction = "increasing"’ and ‘maxEff = -1’ is assumed, for ‘direction = "decreasing"’.

direction
Character determining whether the beneficial direction is ‘increasing’ or ‘decreasing’ with increasing dose levels. This argument is ignored if ‘maxEff’ is specified.

fmodels
An object of class Mods

Delta
Delta: The target effect size use for the target dose (TD) (Delta should be > 0).

x
Object of class Mods with type Mods

nPoints
Number of points for plotting

superpose
Logical determining, whether model plots should be superposed

xlab, ylab
Label for y-axis and x-axis.

modNams
When ‘modNams == NULL’, the names for the panels are determined by the underlying model functions, otherwise the contents of ‘modNams’ are used.

plotTD
‘plotTD’ is a logical determining, whether the TD should be plotted. ‘Delta’ is the target effect to estimate for the TD.

Value

Returns an object of class ‘"Mods"’. The object contains the specified model parameter values and the derived linear parameters (based on ‘"placEff"’ and ‘"maxEff"’) in a list.

Author(s)

Bjoern Bornkamp
References


See Also

*Mods, drmodels, optDesign, powMCT*

Examples

```r
## Example on how to specify candidate models

## Suppose one would like to use the following models with the specified
## guesstimates for theta2, in a situation where the doses to be used are
## 0, 0.05, 0.2, 0.6, 1

## Model guesstimate(s) for theta2 parameter(s) (name)
## linear -
## linear in log -
## Emax 0.05 (ED50)
## Emax 0.3 (ED50)
## exponential 0.7 (delta)
## quadratic -0.85 (delta)
## logistic 0.4 0.09 (ED50, delta)
## logistic 0.3 0.1 (ED50, delta)
## betaMod 0.3 1.3 (delta1, delta2)
## sigmoid Emax 0.5 2 (ED50, h)
## linInt 0.5 0.75 1 1 (perc of max-effect at doses)
## linInt 0.5 1 0.7 0.5 (perc of max-effect at doses)

## for the linInt model one specifies the effect over placebo for
## each active dose.
## The fixed "scal" parameter of the betaMod is set to 1.2
## The fixed "off" parameter of the linlog is set to 0.1
## These (standardized) candidate models can be specified as follows

models <- Mods(linear = NULL, linlog = NULL, emax = c(0.05, 0.3),
                exponential = 0.7, quadratic = -0.85,
                logistic = rbind(c(0.4, 0.09), c(0.3, 0.1)),
                betaMod = c(0.3, 1.3), sigEmax = c(0.5, 2),
                linInt = rbind(c(0.5, 0.75, 1, 1), c(0.5, 1.0, 0.7, 0.5)),
                doses = c(0, 0.05, 0.2, 0.6, 1),
                addArgs = list(scal=1.2, off=0.1))

## "models" now contains the candidate model set, as placEff, maxEff and
## direction were not specified a placebo effect of 0 and an effect of 1
## is assumed

## display of specified candidate set
plot(models)

## example for creating a candidate set with decreasing response
```
mvtnorm.control

Control options for pmvt and qmvt functions

Description

Returns a list (an object of class "GenzBretz") with control parameters for the `pmvt` and `qmvt` functions from the `mvtnorm` package. Note that the DoseFinding package always uses "GenzBretz" algorithm. See the mvtnorm documentation for more information.
Usage

```r
mvtnorm.control(maxpts = 30000, abseps = 0.001, releps = 0,
interval = NULL)
```

**Arguments**

- `maxpts`: Maximum number of function values as integer.
- `abseps`: Absolute error tolerance as double.
- `releps`: Relative error tolerance as double.
- `interval`: Interval to be searched, when the quantile is calculated.

---

**Description**

This simulated data set is motivated by a real Phase 2 clinical study of a new drug for a neurodegenerative disease. The state of the disease is measured through a functional scale, with smaller values corresponding to more severe neurodeterioration. The goal of the drug is to reduce the rate of disease progression, which is measured by the linear slope of the functional scale over time.

The trial design includes placebo and four doses: 1, 3, 10, and 30 mg, with balanced allocation of 50 patients per arm. Patients are followed up for one year, with measurements of the functional scale being taken at baseline and then every three months.

The functional scale response is assumed to be normally distributed and, based on historical data, it is believed that the longitudinal progression of the functional scale over the one year of follow up can be modeled a simple linear trend. See the example below on how to analyse this type of data.

This data set was used in Pinheiro et al. (2013) to illustrate the generalized MCPMod methodology.

**Usage**

```r
data(neurodeg)
```

**Format**

A data frame with 100 observations on the following 2 variables.

- `resp`: a numeric vector containing the response values
- `dose`: a numeric vector containing the dose values
- `id`: Patient ID
- `time`: time of measurement

**Source**

Examples

```r
## Not run:
## reproduce analysis from Pinheiro et al. (2013)
data(neurodeg)
## first fit the linear mixed effect model
library(lme)
fml <- lme(resp ~ as.factor(dose):time, neurodeg, -time|id)
muh <- fixef(fml)[-1] # extract estimates
covh <- vcov(fml)[-1, -1]

## derive optimal contrasts for candidate shapes
doses <- c(0, 1, 3, 10, 30)
mod <- Mods(emax = 1.11, quadratic= -0.022, exponential = 8.867, linear = NULL, doses = doses) #
contMat <- optConstr(mod, S=covH) # calculate optimal contrasts
## multiple contrast test
MCTtest(doses, muH, S=covH, type = "general", critV = TRUE, contMat=contMat)
## fit the emax model
fitMod(doses, muH, S=covH, model="emax", type = "general",
       bnds=c(0.1, 10))

## alternatively one can also fit the model using nlme
nlme(resp ~ b0 + (e0 + eM * dose/(ed50 + dose))*time, neurodeg,
     fixed = b0 + e0 + eM + ed50 - 1, random = b0 + e0 - 1 | id,
     start = c(200, -4.6, 1.6, 3.2))
## both approaches lead to rather similar results
## End(Not run)
```

**optConstr**

*Calculate optimal contrasts*

**Description**

This function calculates a contrast vectors that are optimal for detecting certain alternatives. The contrast is optimal in the sense of maximizing the non-centrality parameter of the underlying contrast test statistic:

\[
\frac{c^\prime \mu}{\sqrt{c^\prime Sc}}
\]

Here \( \mu \) is the mean vector under the alternative and \( S \) the covariance matrix associated with the estimate of \( \mu \). The optimal contrast is given by

\[
c^{opt} \propto S^{-1} \left( \mu - \frac{\mu^\prime S^{-1} 1}{1^\prime S^{-1} 1} \right),
\]

see Pinheiro et al. (2013).
Note that the directionality (i.e. whether in "increase" in the response variable is beneficial or a "decrease", is inferred from the specified 'models' object, see Mods for details).

Constrained contrasts (type = "constrained") add the additional constraint in the optimization that the sign of the contrast coefficient for control and active treatments need to be different. The quadratic programming algorithm from the quadprog package is used to calculate the contrasts.

Usage

```r
optContr(models, doses, w, S, placAdj = FALSE,
          type = c("unconstrained", "constrained"))
```

## S3 method for class 'optContr'

plot(x, superpose = TRUE, xlab = "Dose",
     ylab = NULL, plotType = c("contrasts", "means"), ...)

Arguments

models An object of class 'Mods' defining the dose-response shapes for which to calculate optimal contrasts.

doses Optional argument. If this argument is missing the doses attribute in the 'Mods' object specified in 'models' is used.

w, S Arguments determining the matrix S used in the formula for the optimal contrasts. Exactly one of 'w' and 'S' has to be specified. Note that 'w' and 'S' only have to be specified up to proportionality

  - w Vector specifying weights for the different doses, in the formula for calculation of the optimal contrasts. Specifying a weights vector is equivalent to specifying S=diag(1/w) (e.g. in a homoscedastic case with unequal sample sizes, 'w' should be proportional to the group sample sizes).
  - S Directly specify a matrix proportional to the covariance matrix to use.

placAdj Logical determining, whether the contrasts should be applied to placebo-adjusted estimates. If yes the returned coefficients are no longer contrasts (i.e. do not sum to 0). However, the result of multiplying of this 'contrast' matrix with the placebo adjusted estimates, will give the same results as multiplying the original contrast matrix to the unadjusted estimates.

type For 'type = "constrained"' the contrast coefficients of the zero dose group are constrained to be different from the coefficients of the active treatment groups. So that a weighted sum of the active treatments is compared against the zero dose group. For an increasing trend the coefficient of the zero dose group is negative and all other coefficients have to be positive (for a decreasing trend the other way round).

x, superpose, xlab, ylab, plotType Arguments for the plot method for optContr objects. plotType determines, whether the contrasts or the underlying (standardized) mean matrix should be plotted.

... Additional arguments for plot method
Value

Object of class ‘optContr’. A list containing entries contMat and muMat (i.e. contrast, mean and correlation matrix).

Author(s)

Bjoern Bornkamp

References


See Also

MCTtest

Examples

doses <- c(0, 10, 25, 50, 100, 150)
models <- Mods(linear = NULL, emax = 25,
    logistic = c(50, 10.88111), exponential = 85,
    betaMod = rbind(c(0.33, 2.31), c(1.39, 1.39)),
    doses = doses, addArgs = list(scal = 200))
contMat <- optContr(models, w = rep(50, 6))
plot(contMat)

# now we would like the "contrasts" for placebo adjusted estimates
dosPlac <- doses[-1]
# matrix proportional to cov-matrix of plac. adj. estimates for balanced data
S <- diag(S)+matrix(1, 5, 5)
# note that we explicitly hand over the doses here
contMat0 <- optContr(models, doses=dosPlac, S = S, placAdj = TRUE)
# -> contMat0 is no longer a contrast matrix (columns do not sum to 0)
colSums(contMat0$contMat)
# calculate contrast matrix for unadjusted estimates from this matrix
# (should be same as above)
aux <- rbind(-colSums(contMat0$contMat), contMat0$contMat)
t(t(aux)/sqrt(colSums(aux^2))) # compare to contMat$contMat

# now calculate constrained contrasts
optContr(models, w = rep(50, 6), type = "constrained")
optContr(models, doses=dosPlac, S = S, placAdj = TRUE,
    type = "constrained")
**optDesign**

*Function to calculate optimal designs*

**Description**

Given a set of models (with full parameter values and model probabilities) the `optDesign` function calculates the optimal design for estimating the dose-response model parameters (D-optimal) or the design for estimating the target dose (TD-optimal design) (see Dette, Bretz, Pepelyshev and Pinheiro (2008)), or a mixture of these two criteria. The design can be plotted (together with the candidate models) using 'plotNdesign'. 'calcCrit' calculates the design criterion for a discrete set of design(s). 'rndDesign' provides efficient rounding for the calculated continuous design to a finite sample size.

**Usage**

```r
optDesign(models, probs, doses,
          designCrit = c("Dopt", "TD", "Dopt&TD", "userCrit"),
          Delta, standDopt = TRUE, weights,
          nold = rep(0, length(doses)), n,
          control=list(),
          optimizer = c("solnp", "Nelder-Mead", "nlminb", "exact"),
          lowbnd = rep(0, length(doses)), uppbnd = rep(1, length(doses)),
          userCrit, ...)
```

```r
# S3 method for class 'DRdesign'
plot(x, models, lwdDes = 10, colDes = rgb(0,0,0.3), ...)
```

```r
calcCrit(design, models, probs, doses,
          designCrit = c("Dopt", "TD", "Dopt&TD"),
          Delta, standDopt = TRUE, weights,
          nold = rep(0, length(doses)), n)
```

```r
rndDesign(design, n, eps = 0.0001)
```

**Arguments**

- **models**
  - An object of class `c(Mods, fullMod)`, see the `Mods` function for details. When an TD optimal design should be calculated, the TD needs to exist for all models. If a D-optimal design should be calculated, you need at least as many doses as there are parameters in the specified models.

- **probs**
  - Vector of model probabilities for the models specified in `models`, assumed in the same order as specified in models

- **doses**
  - Optional argument. If this argument is missing the doses attribute in the `c(Mods, fullMod)` object specified in `models` is used.

- **designCrit**
  - Determines which type of design to calculate. "TD&Dopt" uses both optimality criteria with equal weight.
Delta

Target effect needed for calculating "TD" and "TD&Dopt" type designs.

standDopt

Logical determining, whether the D-optimality criterion (specifically the log-

determinant) should be standardized by the number of parameters in the model

or not (only of interest if type = "Dopt" or type = "TD&Dopt"). This is of

interest, when there is more than one model class in the candidate model set

(traditionally standardization this is done in the optimal design literature).

weights

Vector of weights associated with the response at the doses. Needs to be of

the same length as the ‘doses’. This can be used to calculate designs for het-
eroscedastic or for generalized linear model situations.

nold, n

When calculating an optimal design at an interim analysis, ‘nold’ specifies the

vector of sample sizes already allocated to the different doses, and ‘n’ gives

sample size for the next cohort.

For ‘optimizer = "exact"’ one always needs to specify the total sample size via ‘n’.

control

List containing control parameters passed down to numerical optimization algo-
rithms (optim, nlminb or solnp function).

For ‘type = "exact"’ this should be a list with possible entries ‘maxvls1’ and

‘maxvls2’, determining the maximum number of designs allowed for passing to
the criterion function (default ‘maxvls2=1e5’) and for creating the initial unre-
stricted matrix of designs (default ‘maxvls1=1e6’). In addition there can be an
entry ‘groupSize’ in case the patients are allocated a minimum group size is
required.

optimizer

Algorithm used for calculating the optimal design. Options "Nelder-Mead" and

"nlminb" use the optim and nlminb function and use a trigonometric transfor-
mation to turn the constrained optimization problem into an unconstrained one
(see Atkinson, Donev and Tobias, 2007, pages 130,131).

Option "solnp" uses the solnp function from the Rsolnp package, which imple-
ments an optimizer for non-linear optimization under general constraints.

Option "exact" tries all given combinations of ‘n’ patients to the given dose

groups (subject to the bounds specified via ‘lowbnd’ and ‘uppbnd’) and reports
the best design. When patients are only allowed to be allocated in groups of a
certain ‘groupSize’, this can be adjusted via the control argument. ‘n/groupSize’
and ‘length(doses)’ should be rather small for this approach to be feasible.

When the number of doses is small (<8) usually ‘"Nelder-Mead"’ and ‘"nlminb"’
are best suited (‘"nlminb"’ is usually a bit faster but less stable than ‘"Nelder-Mead"’).

For a larger number of doses ‘"solnp"’ is the most reliable option (but also
slowest) (‘"Nelder-Mead"’ and ‘"nlminb"’ often fail). When the sample size
is small ‘"exact"’ provides the optimal solution rather quickly.

lowbnd, uppbnd

Vectors of the same length as dose vector specifying upper and lower limits for
the allocation weights. This option is only available when using the "solnp" and
"exact" optimizers.

userCrit

User defined design criterion, should be a function that given a vector of al-
location weights and the doses returns the criterion function. When specified
'models' does not need to be handed over.
The first argument of ‘userCrit’ should be the vector of design weights, while the second argument should be the ‘doses’ argument (see example below). Additional arguments to ‘userCrit’ can be passed via ...

For function ‘optDesign’ these are additional arguments passed to ‘userCrit’.

For function ‘plot.design’ these are additional parameters passed to ‘plot.Mods’.

design  Argument for ‘rndDesign’ and ‘calcCrit’ functions: Numeric vector (or matrix) of allocation weights for the different doses. The rows of the matrices need to sum to 1. Alternatively also an object of class "DRdesign" can be used for ‘rndDesign’. Note that there should be at least as many design points available as there are parameters in the dose-response models selected in models (otherwise the code returns an NA).

eps  Argument for ‘rndDesign’ function: Value under which elements of w will be regarded as 0.

x  Object of class ‘DRdesign’ (for ‘plot.design’)

1wdDes, colDes  Line width and color of the lines plotted for the design (in ‘plot.design’)

Details

Let $M_m$ denote the Fisher information matrix under model m (up to proportionality). $M_m$ is given by $\sum a_i w_i g_i^T g_i$, where $a_i$ is the allocation weight to dose i, $w_i$ the weight for dose i specified via ‘weights’ and $g_i$ the gradient vector of model m evaluated at dose i.

For ‘designCrit = "Dopt"’ the code minimizes the design criterion

$$-\sum_m p_m/k_m \log(\det(M_m))$$

where $p_m$ is the probability for model m and $k_m$ is the number of parameters for model m. When ‘standDopt = FALSE’ the $k_m$ are all assumed to be equal to one.

For ‘designCrit = "TD"’ the code minimizes the design criterion

$$\sum_m p_m \log(v_m)$$

where $p_m$ is the probability for model m and $v_m$ is proportional to the asymptotic variance of the TD estimate and given by $b_m^T M_m b_m$ (see Dette et al. (2008), p. 1227 for details).

For ‘designCrit = "Dopt&TD"’ the code minimizes the design criterion

$$\sum_m p_m (-0.5 \log(\det(M_m))/k_m + 0.5 \log(v_m))$$

Again, for ‘standDopt = FALSE’ the $k_m$ are all assumed to be equal to one.

For details on the ‘rndDesign’ function, see Pukelsheim (1993), Chapter 12.
Note

In some cases (particularly when the number of doses is large, e.g. 7 or larger) it might be necessary to allow a larger number of iterations in the algorithm (via the argument ‘control’), particularly for the Nelder-Mead algorithm. Alternatively one can use the solnp optimizer that is usually the most reliable, but not fastest option.

Author(s)

Bjoern Bornkamp

References


See Also

`Mods`, `drmodels`

Examples

```r
## calculate designs for Emax model
doses <- c(0, 10, 100)
emodel <- Mods(emax = 15, doses=doses, placEff = 0, maxEff = 1)
optDesign(emodel, probs = 1)
## TD-optimal design
optDesign(emodel, probs = 1, designCrit = "TD", Delta=0.5)
## 50-50 mixture of Dopt and TD
optDesign(emodel, probs = 1, designCrit = "Dopt&TD", Delta=0.5)
## use dose levels different from the ones specified in emodel object
des <- optDesign(emodel, probs = 1, doses = c(0, 5, 20, 100))
## plot models overlaid by design
plot(des, emodel)
## round des to a sample size of exactly 90 patients
rndDesign(des, n=90) ## using the round function would lead to 91 patients

## illustrating different optimizers (see Note above for more comparison)
optDesign(emodel, probs=1, optimizer="Nelder-Mead")
optDesign(emodel, probs=1, optimizer="nlminb")
## optimizer solnp (the default) can deal with lower and upper bounds:
optDesign(emodel, probs=1, designCrit = "TD", Delta=0.5,
          optimizer="solnp", lowbnd = rep(0.2,3))
## exact design using enumeration of all possibilites
optDesign(emodel, probs=1, optimizer="exact", n = 30)
## also allows to fix minimum groupSize
optDesign(emodel, probs=1, designCrit = "TD", Delta=0.5,
          optimizer="exact", n = 30, control = list(groupSize=5))
```
## optimal design at interim analysis

## assume there are already 10 patients on each dose and there are 30
## left to randomize, this calculates the optimal increment design

```r
optDesign(emodel, 1, designCrit = "TD", Delta=0.5, nold = c(10, 10, 10), n=30)
```

## use a larger candidate model set

doses <- c(0, 10, 25, 50, 100, 150)
fmods <- Mods(linear = NULL, emax = 25, exponential = 85, linlog = NULL, logistic = c(50, 10.8811), doses = doses, addArgs=list(off=1), placEff=0, maxEff=0.4)
probs <- rep(1/5, 5) # assume uniform prior
desDopt <- optDesign(fmods, probs, optimizer = "nlminb")
desTD <- optDesign(fmods, probs, designCrit = "TD", Delta = 0.2, optimizer = "nlminb")
desMix <- optDesign(fmods, probs, designCrit = "Dopt\&TD", Delta = 0.2)

## illustrate calcCrit function

## calculate optimal design for beta model

doses <- c(0, 0.49, 25.2, 100.07, 150)
models <- Mods(betaMod = c(0.33, 2.31), doses=doses, addArgs=list(scal=200), placEff=0, maxEff=0.4)
probs <- 1
deswgt <- optDesign(models, probs, designCrit = "Dopt", control=list(maxit=1000))

## now compare this design to equal allocations on
## 0, 10, 25, 50, 100, 150
doses2 <- c(0, 10, 25, 50, 100, 150)
design2 <- c(1/6, 1/6, 1/6, 1/6, 1/6, 1/6)
crit2 <- calcCrit(design2, models, probs, doses2, designCrit = "Dopt")

## ratio of determinants (returned criterion value is on log scale)
exp(deswgt$crit - crit2)

## example for calculating an optimal design for logistic regression

doses <- c(0, 0.35, 0.5, 0.65, 1)
fMod <- Mods(linear = NULL, doses=doses, placEff=-5, maxEff=10)

## now calculate weights to use in the covariance matrix

```r
mu <- as.numeric(getResp(fMod, doses=doses))
weights <- mu*(1-mu)
des <- optDesign(fMod, 1, doses, weights = weights)
```

## one can also specify a user defined criterion function

## here D-optimality for cubic polynomial

```r
CubeCrit <- function(w, doses){
  X <- cbind(1, doses, doses^2, doses^3)
  CVinv <- crossprod(X*w)
  ```
- \log(\text{det(CVinv)}) \}

\text{optDesign(doses = c(0, 0.05, 0.2, 0.6, 1),}
\enspace
\text{designCrit = "userCrit", userCrit = CubeCrit,}
\text{optimizer = "nlminb"
}

\begin{verbatim}
planMod

Evaluate performance metrics for fitting dose-response models

Description
This function evaluates the performance metrics for fitting dose-response models (using asymptotic approximations or simulations). Note that some metrics are available via the print method and others only via the summary method applied to planMod objects. The implemented metrics are

- Root of the mean-squared error to estimate the placebo-adjusted dose-response averaged over the used dose-levels, i.e. a rather discrete set (\text{dRMSE}). Available via the print method of planMod objects.
- Root of the mean-squared error to estimate the placebo-adjusted dose-response (\text{cRMSE}) averaged over fine (almost continuous) grid at 101 equally spaced values between placebo and the maximum dose. \text{NOTE: Available via the summary method applied to planMod objects.}
- Ratio of the placebo-adjusted mean-squared error (at the observed doses) of model-based vs ANOVA approach (\text{effMvsManova}). This can be interpreted on the sample size scale. \text{NOTE: Available via the summary method applied to planMod objects.}
- Power that the (unadjusted) one-sided 1-\alpha confidence interval comparing the dose with maximum effect vs placebo is larger than \tau. By default \alpha = 0.025 and \tau = 0 (Pow(maxDose)). Available via the print method of planMod objects.
- Probability that the EDP estimate is within the true [EDP\text{LB}, EDP\text{UB}] (by default \text{p=0.5}, 'pLB=0.25' and 'pUB=0.75'). This metric gives an idea on the ability to characterize the increasing part of the dose-response curve (P(EDP)). Available via the print method of planMod objects.
- Length of the quantile range for a target dose (TD or EDP). This is calculated by taking the difference of the dUB and dLB quantile of the empirical distribution of the dose estimates. (lengthTDCI and lengthEDPCI). It is NOT calculated by calculating confidence interval lengths in each simulated data-set and taking the mean. \text{NOTE: Available via the summary method of planMod objects.}

A plot method exists to summarize dose-response and dose estimations graphically.

Usage
planMod(model, altModels, n, sigma, S, doses, asyApprox = TRUE,
\enspace simulation = FALSE, alpha = 0.025, tau = 0, p = 0.5,
\enspace pLb = 0.25, pUb = 0.75, nSim = 100, cores = 1,
\enspace showSimProgress = TRUE, bnds, addArgs = NULL)
## Arguments

**model**  
Character vector determining the dose-response model(s) to be used for fitting the data. When more than one dose-response model is provided the best fitting model is chosen using the AIC. Built-in models are "linlog", "linear", "quadratic", "emax", "exponential", "sigEmax", "betaMod" and "logistic" (see drmodels).

**altModels**  
An object of class 'mods', defining the true mean vectors under which operating characteristics should be calculated.

**n, sigma, S**  
Either a vector 'n' and 'sigma' or 'S' need to be specified. When 'n' and 'sigma' are specified it is assumed computations are made for a normal homoscedastic ANOVA model with group sample sizes given by 'n' and residual standard deviation 'sigma', i.e. the covariance matrix used for the estimates is thus sigma^2*diag(1/n) and the degrees of freedom are calculated as sum(n)-nrow(contMat). When a single number is specified for 'n' it is assumed this is the sample size per group and balanced allocations are used.

When 'S' is specified this will be used as covariance matrix for the estimates.

**doses**  
Doses to use

**asyApprox, simulation**  
Logicals determining, whether asymptotic approximations or simulations should be calculated. If multiple models are specified in 'model' asymptotic approximations are not available.

**alpha, tau**  
Significance level for the one-sided confidence interval for model-based contrast of best dose vs placebo. Tau is the threshold to compare the confidence interval limit to. CI(MaxDCont) gives the percentage that the bound of the confidence interval was larger than tau.

**p, pLB, pUB**  
p determines the type of EDp to estimate. pLB and pUB define the bounds for the EDp estimate. The performance metric Pr(Ed-ED) gives the percentage that the estimated EDp was within the true EDpLB and EDpUB.

**nSim**  
Number of simulations

**cores**  
Number of cores to use for simulations. By default 1 cores is used, note that cores > 1 will have no effect Windows, as the mclapply function is used internally.

**showSimProgress**  
In case of simulations show the progress using a progress-bar.
bounds

Bounds for non-linear parameters. This needs to be a list with list entries corresponding to the selected bounds. The names of the list entries need to correspond to the model names. The `defBnds` function provides the default selection.

addArgs

See the corresponding argument in function `fitMod`. This argument is directly passed to `fitMod`.

x

An object of class `planMod`

type

Type of plot to produce

Delta, direction

Additional arguments determining what dose estimate to plot, when `type = "ED"` or `type = "TD"`

placAdj

When `type = "dose-response"`, this determines whether dose-response estimates are shown on placebo-adjusted or original scale

xlab, ylab

Labels for the plot (ylab only applies for `type = "dose-response"`)

len

Number of equally spaced points to determine the mean-squared error on a grid (cRMSE).

dLB, dUB

Which quantiles to use for calculation of `lengthTDCI` and `lengthEDpCI`. By default `dLB = 0.05` and `dUB = 0.95`, so that this corresponds to a 90% interval.

object, digits

object: A `planMod` object. digits: Digits in summary output

... Additional arguments (currently ignored)

Author(s)

Bjoern Bornkamp

References

TBD

See Also

`fitMod`

Examples

```r
## Not run:
doses <- c(0, 10, 25, 50, 100, 150)
fmodels <- Mods(linear = NULL, emax = 25,
                logistic = c(50, 10.88111), exponential = 85,
                betaMod = rbind(c(0.33, 2.31), c(1.39, 1.39)),
                doses = doses, addArgs = list(scal = 200),
                placEff = 0, maxEff = 0.4)
sigma <- 1
n <- rep(62, 6)*2

model <- "quadratic"
pObj <- planMod(model, fmodels, n, sigma, doses = doses,
                 simulation = TRUE,
```
powMCT

Calculate power for multiple contrast test

Description

Calculate power for a multiple contrast test for a set of specified alternatives.

Usage

powMCT(contMat, alpha = 0.025, altModels, n, sigma, S, placAdj=FALSE, alternative = c("one.sided", "two.sided"), df, critV, control = mvtnorm.control())

Arguments

contMat
Contrast matrix to use. The individual contrasts should be saved in the columns of the matrix

alpha
Significance level to use

altModels
An object of class 'Mods', defining the mean vectors under which the power should be calculated

n, sigma, S
Either a vector 'n' and 'sigma' or 'S' need to be specified. When 'n' and 'sigma' are specified it is assumed computations are made for a normal homoscedastic ANOVA model with group sample sizes given by 'n' and residual standard deviation 'sigma', i.e. the covariance matrix used for the estimates is thus sigma^2*diag(1/n) and the degrees of freedom are calculated as sum(n)-nrow(contMat). When a single number is specified for 'n' it is assumed this is the sample size per group and balanced allocations are used.

When 'S' is specified this will be used as covariance matrix for the estimates.

placAdj
Logical, if true, it is assumed that the standard deviation or variance matrix of the placebo-adjusted estimates are specified in 'sigma' or 'S', respectively. The contrast matrix has to be produced on placebo-adjusted scale, see optContr, so that the coefficients are no longer contrasts (i.e. do not sum to 0).

alternative
Character determining the alternative for the multiple contrast trend test.
df Degrees of freedom to assume in case ‘S’ (a general covariance matrix) is specified. When ‘n’ and ‘sigma’ are specified the ones from the corresponding ANOVA model are calculated.
critV Critical value, if equal to ‘TRUE’ the critical value will be calculated. Otherwise one can directly specify the critical value here.
control A list specifying additional control parameters for the ‘qmvt’ and ‘pmvt’ calls in the code, see also ‘mvtnorm.control’ for details.

Value
Numeric containing the calculated power values

Author(s)
Bjoern Bornkamp

References

See Also
powN, sampSizeMCT, MCTest, optContr, Mods

Examples

```r
## look at power under some dose-response alternatives
## first the candidate models used for the contrasts
doses <- c(0,10,25,50,100,150)
## define models to use as alternative
fmodels <- Mods(linear = NULL, emax = 25,
                 logistic = c(50, 10.88111), exponential= 85,
                 betaMod=rbind(c(0.33,2.31),c(1.39,1.39)),
                 doses = doses, addArgs=list(scal = 200),
                 placeEff = 0, maxEff = 0.4)
## plot alternatives
plot(fmodels)
## power for to detect a trend
contMat <- optContr(fmodels, w = 1)
powMCT(contMat, altModels = fmodels, n = 50, alpha = 0.05, sigma = 1)

## Not run:
## power under the Dunnett test
## contrast matrix for Dunnett test with informative names
contMatD <- rbind(-1, diag(5))
rownames(contMatD) <- doses
colnames(contMatD) <- paste("D", doses[-1], sep="-")
powMCT(contMatD, altModels = fmodels, n = 50, alpha = 0.05, sigma = 1)
```
## sampSize

### Description

The `sampSize` function implements a bisection search algorithm for sample size calculation. The user can hand over a general target function (via `targfunc`) that is then iterated so that a certain `target` is achieved. The `sampSizeMCT` is a convenience wrapper of `sampSize` for multiple contrast tests using the power as target function.

The `targN` functions calculates a general target function for different given sample sizes. The `pown` function is a convenience wrapper of `targN` for multiple contrast tests using the power as target function.

### Usage

```r
sampSize(upperN, lowerN = floor(upperN/2), targFunc, target, 
  tol = 0.001, alRatio, Ntype = c("arm", "total"),
  verbose = FALSE)

tsampsizemct(upperN, lowerN = floor(upperN/2), ..., power, sumFct = mean, 
  tol = 0.001, alRatio, Ntype = c("arm", "total"),
  df = 600, match.df = TRUE)

targN(upperN, lowerN, step, targFunc, alRatio, 
  Ntype = c("arm", "total"), sumFct = c("min", "mean", "max"))
```

```r
## now investigate power of the contrasts in contMat under "general" alternatives
altFmods <- Mods(linInt = rbind(c(0, 1, 1, 1, 1), 
  c(0.5, 1, 1, 1, 0.5)),
  doses=doses, placEff=0, maxEff=0.5)
plot(altFmods)
powMCT(contMat, altModels = altFmods, n = 50, alpha = 0.05, sigma = 1)

## now the first example but assume information only on the
## placebo-adjusted scale
## for balanced allocations and 50 patients with sigma = 1 one obtains
## the following covariance matrix
S <- 1^2/50*diag(6)
## now calculate variance of placebo adjusted estimates
CC <- cbind(-1,diag(5))
V <- (CC)%*%S%*%t(CC)
linMat <- optConstr(fmodels, doses = c(10,25,50,100,150),
  S = V, placAdj = TRUE)
powMCT(linMat, altModels = fmodels, placAdj=TRUE, 
  alpha = 0.05, S = V, df=600, match.df = TRUE) # match df with the df above

## End(Not run)
```
sampSize

\[
powN(upperN, lowerN, step, \ldots, alRatio,
Ntype = c("arm", "total"), sumFct = c("min", "mean", "max"))
\]

## S3 method for class 'targn'
plot(x, superpose = TRUE, line.at = NULL,
xlab = NULL, ylab = NULL, \ldots)

### Arguments

- **upperN**, **lowerN**: Upper and lower bound for the target sample size. `lowerN` defaults to `floor(upperN/2)`.
- **step**: Only needed for functions `targN` and `powN`. Stepsize for the sample size at which the target function is calculated. The steps are calculated via `seq(lowerN, upperN, by=step)`.
- **targFunc**, **target**: The target function needs to take as an input the vector of sample sizes in the different dose groups. For `sampSize` it needs to return a univariate number. For function `targN` it should return a numerical vector.
  
  Example: `targFunc` could be a function that calculates the power of a test, and `target` the desired target power value.
  
  For function `sampSize` the bisection search iterates the sample size so that a specific target value is achieved (the implicit assumption is that `targFunc` is monotonically increasing in the sample size).

- **tol**: A positive numeric value specifying the tolerance level for the bisection search algorithm. Bisection is stopped if the `targFunc` value is within `tol` of `target`.
- **alRatio**: Vector describing the relative patient allocations to the dose groups up to proportionality, e.g. `rep(1, length(doses))` corresponds to balanced allocations.
- **Ntype**: One of "arm" or "total". Determines, whether the sample size in the smallest arm or the total sample size is iterated in bisection search algorithm.
- **verbose**: Logical value indicating if a trace of the iteration progress of the bisection search algorithm should be displayed.
- **\ldots**: Arguments directly passed to the `powMCT` function in the `sampSizeMCT` and `powN` function.

The `placAdj` argument needs to be `FALSE` (which is the default value for this argument). If sample size calculations are desired for a placebo-adjusted formulation use `sampSize` or `targN` directly.

In case `S` is specified, the specified matrix needs to be proportional to the (hypothetical) covariance matrix of one single observation. The covariance matrix used for sample size calculation is `1/N*S`, where `N` is the total sample size. Hence `Ntype = "total"` needs to be used if `S` is specified. When `S` is specified, automatically `df = Inf` is assumed in the underlying `powMCT` calls.

For a homoscedastic normally distributed response variable only `sigma` needs to be specified, as the sample size `n` is iterated in the different `powMCT` calls.
sampSize

```r
power, sumFct  power is a numeric defining the desired summary power to achieve (in 'sampSizeMCT'). sumFct needs to be a function that combines the power values under the different alternatives into one value (in 'sampSizeMCT').

x, superpose, line.at, xlab, ylab arguments for the plot method of 'targN' and 'powN', additional arguments are passed down to the low-level lattice plotting routines.

Author(s)

Jose Pinheiro, Bjoern Bornkamp

References


See Also

powMCT

Examples

```r
## sampSize examples

## first define the target function
## first calculate the power to detect all of the models in the candidate set
fmodels <- Mods(linear = NULL, emax = c(25),
    logistic = c(50, 10.88111), exponential=c(85),
    betaMod=matrix(c(0.33, 2.31, 1.39, 1.39), byrow=TRUE, nrow=2),
    doses = c(0, 10, 25, 50, 100, 150), placEff=0, maxEff=0.4,
    addArgs = list(scal=200))

## contrast matrix to use
contMat <- optContr(fmodels, w=1)

## this function calculates the power under each model and then returns
## the average power under all models
tfunc <- function(n){
    powVals <- powMCT(contMat, altModels=fmodels, n=n, sigma = 1,
        alpha=0.05)
    mean(powVals)
}

## assume we want to achieve 80% average power over the selected shapes
## and want to use a balanced allocations
## Not run:
sSize <- sampSize(upperN = 80, targFunc = tFunc, target=0.8,
    alRatio = rep(1,6), verbose = TRUE)
sSize

## Now the same using the convenience sampSizeMCT function
```
Target Doses

\[
\text{TD} \Delta = \min \{ x | f(x) > f(0) + \Delta \}
\]

If a decreasing trend is beneficial the definition of the TD is

\[
\text{TD} \Delta = \min \{ x | f(x) < f(0) - \Delta \}
\]
When $\Delta$ is the clinical relevance threshold, then the TD is similar to the usual definition of the minimum effective dose (MED).

The ED (effective dose) is defined as the dose that achieves a certain percentage $p$ of the full effect size (within the observed dose-range!) over placebo (if there are multiple such doses, the smallest is chosen).

$$ED_p = \min\{x | f(x) > f(0) + p(f(d_{max}) - f(0))\}$$

Note that this definition of the EDp is different from traditional definition based on the Emax model, where the EDp is defined relative to the asymptotic maximum effect (rather than the maximum effect in the observed dose-range).

Usage

```r
TD(object, Delta, TDtype = c("continuous", "discrete"),
    direction = c("increasing", "decreasing"), doses)

ED(object, p, EDtype = c("continuous", "discrete"), doses)
```

Arguments

- **object**: An object of class c(Mods, fullMod), DRMod or bFitMod
- **Delta, p**: Delta: The target effect size use for the target dose (TD) (Delta should be > 0). p: The percentage of the dose to use for the effective dose.
- **TDtype, EDtype**: character that determines, whether the dose should be treated as a continuous variable when calculating the TD/ED or whether the TD/ED should be calculated based on a grid of doses specified in ‘doses’
- **direction**: Direction to be used in defining the TD. This depends on whether an increasing or decreasing of the response variable is beneficial.
- **doses**: Dose levels to be used, this needs to include placebo, ‘TDtype’ or ‘EDtype’ are equal to ‘"discrete"’.

Value

Returns the dose estimate

Author(s)

Bjoern Bornkamp

See Also

- Mods, fitMod, bFitMod, drmodels
Examples

```r
## example for creating a "full-model" candidate set placebo response
## and maxEff already fixed in Mods call
doses <- c(0, 10, 25, 50, 100, 150)
fmodels <- Mods(linear = NULL, emax = 25,
               logistic = c(50, 10.88111), exponential = 85,
               betaMod = rbind(c(0.33, 2.31), c(1.39, 1.39)),
               linInt = rbind(c(0, 1, 1, 1),
                              c(0, 0, 1, 1, 0.8)),
               doses=doses, placEff = 0, maxEff = 0.4,
               addArgs=list(scal=200))

## calculate doses giving an improvement of 0.3 over placebo
TD(fmodels, Delta=0.3)
## discrete version
TD(fmodels, Delta=0.3, TDtype = "discrete", doses=doses)
## doses giving 50% of the maximum effect
ED(fmodels, p=0.5)
ED(fmodels, p=0.5, EDtype = "discrete", doses=doses)

plot(fmodels, plotTD = TRUE, Delta = 0.3)
```
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