Package 'ToxicR'

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Type Package

Title Analyzing Toxicology Dose-Response Data

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Description Toxicology routines for analyzing dose-response data include dose-response analysis
and trend tests. Dose-
Response methods are based upon the US EPA's benchmark dose software 3. Methods have
been extended to include additional functionality based on World Health Organization
guidelines. It further supports the European Food Safety Authority's
draft guidance on model averaging. The dose-
response methods and datasets used in this package are
described in Wheeler et al. (2019) <doi:10.1111/risa.13218>, Wheeler et al. (2020) <doi:10.1111/risa.13537>,
and Wheeler et al. (2022) <doi:10.1002/env.2728>. NTP routines are described in
Bailer and Portier (1988) <doi:10.2307/2531856>, Bieler and Williams (1993) <doi:10.2307/2532200>,
Williams (1971) <doi:10.2307/2528930>, and Shirley (1977) <doi:10.2307/2529789>.

Depends R (>= 4.1.0)

License LGPL (>= 3)

URL https://github.com/NIEHS/ToxicR

LazyData true

Imports Rcpp (>= 1.0.0), ggplot2 (>= 3.3.2), shiny (>= 1.5.0), coda
(>= 0.19-4), scales (>= 1.1.1), tidyverse (>= 1.3.0), forcats,
ggridges (>= 0.5.3), doBy (>= 4.6.11), multcomp (>= 1.4), dplyr
(>= 1.0.7)

LinkingTo Rcpp, RcppEigen, RcppGSL

RoxygenNote 7.1.2

VignetteBuilder knitr

Suggests rmarkdown, actuar (>= 3.2-0),ggpubr (>= 0.4.0), testthat (>=
3.1.0),gridExtra (>= 2.3), VIM (>= 6.1.1), knitr (>= 1.36),
modules, plotly (>= 4.9.2.1)

NeedsCompilation yes

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R **topics documented:**

---

cleveland_plot	*cleveland_plot - Create a Cleveland plot from a model averaged model.*

Description

Create a Cleveland plot from a model averaged model.

Usage

```
cleveland_plot(A)
```

Arguments

A	the model averaged model to plot

Value

Returns a `ggplot2` graphics object.

Examples

```
mData <- matrix(c(0, 2,50,
                  1, 2,50,
                  3, 10, 50,
                  16, 18,50,
                  32, 18,50,
                  33, 17,50),nrow=6,ncol=3,byrow=TRUE)
D <- mData[,1]
Y <- mData[,2]
N <- mData[,3]

model = ma_dichotomous_fit(D,Y,N)
cleveland_plot(model)
```

---

create_continuous_prior	
	create_continuous_prior Given priorlist, a model, and a distribution. Create a prior for a given analysis.

Description

create_continuous_prior Given priorlist, a model, and a distribution. Create a prior for a given analysis.

Usage

```
create_continuous_prior(prior_list, model, distribution, deg = 2)
```

Arguments

prior_list	First Prior
model	Model to be used one of "hill","exp-3","exp-5","power","polynomial"
distribution	- Normal "normal", Normal non-constant variance "normal-ncv", or log-normal "lognormal"
deg	- For polynomial models only, the degree of the polynomial.

Value

new BMDprior list. This object is essentially a prior list constructed by `create_prior_lists` with a model type and variance type.

Examples

```
plist<- create_prior_list(normprior(0,0.1,-100,100), # a
                          normprior(0,1,  -1e2,1e2),     # b
                          lnormprior(1,0.2,0,18),  #k
                          normprior(0,1,-18,18))

 power_normal <- create_continuous_prior(plist,"power","normal")
```

---

create_dichotomous_prior

> *create_dichotomous_prior Given priorlist, a model, and a distribution. Create a prior for a given analysis.*

Description

create_dichotomous_prior Given priorlist, a model, and a distribution. Create a prior for a given analysis.

Usage

```
create_dichotomous_prior(prior, model)
```

Arguments

prior	First Prior
model	Model to be used should be one of"hill","gamma","logistic","log-logistic","log-probit","multistage", "probit", "qlinear", or "weibull"

Value

new BMDprior list that can be used in a dichotomous fit.

Examples

```
plist<- create_prior_list(normprior(0,0.1,-100,100), # a
                          lnormprior(1,0.2,0,18))

 power_normal <- create_dichotomous_prior(plist,"logistic")
```

---

create_prior_list	*create_prior_lists .. Given priors created using the ToxicR prior functions, create a list of priors for a model.*

Description

create_prior_lists .. Given priors created using the ToxicR prior functions, create a list of priors for a model.

Usage

```
create_prior_list(x1, x2, ...)
```

Arguments

x1	First Prior
x2	Second Prior
...	Aditional arguments

Value

new BMDprior list. This object is essentailly a matrix where each row is an element defined by a prior object (e.g., normprior or lnormprior).

Examples

```
plist<- create_prior_list(normprior(0,0.1,-100,100), # a
                          normprior(0,1,  -1e2,1e2),     # b
                          lnormprior(1,0.2,0,18),  #k
                          normprior(0,1,-18,18))
```

---

dichotomousDR	*733 unique dose-response datasets*

Description

A dataset containing 733 dichotomous dose-response studies that were involved in regulatory risk assessment.

Usage

```
dichotomousDR
```

Format

A data frame with 2727 rows and 11 variables:

ID -The study ID in the database.

chemical -Name of the Chemical in the study.

data.source -Source of the risk assessment data.

CASRN -Chemical's CASRN

dose -Dose spacing of the study using the original study.

r.dose -Doses of the experiment relative to 1 being the maximum dose tested.

n -Number of animals on test.

obs -Number of adverse events.

organ -Organ impacted.

effect -Type of adverse effect.

study.source -Publication related to the experiment.

More information at: doi:10.1111/risa.13218

---

lnormprior	*lnormprior - create a lognormal prior.*

Description

Specify a log-normal prior for a ToxicR Bayesian model fit.

Usage

```
lnormprior(mean = 0, sd = 1, lb = -100, ub = 100)
```

Arguments

mean	log-mean of the prior distribution.
sd	log-sd of the prior distribution.
lb	lower bound on the distribution. Necessary for the optimization algorithms, To make sure it is a fully normal prior, make lb small relative to the mean/sd.
ub	Upper bound on the distribution. Necessary for the optimization algorithms, To make sure it is a fully normal prior, make ub large relative to the mean/sd.

Value

a normal prior model object This object essentially a vector with the first element as 2 (for log-normal), the second element the mean, the third element the log-variance, the fourth and fifth elements the lower and upper bounds, respectively.

Examples

```
# Log-Normal Prior with mean 0,sd-1
lnormprior(mean = 0, sd = 1, lb = -1e4, ub=1e4)

# Truncated Log-Normal prior, Truncated below at 1
lnormprior(mean = 0, sd = 1, lb = 1, ub=1e4)
```

MAdensity_plot	*MAdensity_plot - Create a density plot from a model averaged model.*

Description

Create a density plot from a model averaged model fit with MCMC.

Usage

```
MAdensity_plot(A)
```

Arguments

A	the model averaged model to plot

Value

Returns a `ggplot2` graphics object.

Examples

```
doses  <- cbind(c(0,25,50,100,200))
y <- cbind(c(6,5.2,2.4,1.1,0.75),
                c(20,20,19,20,20),
                c(1.2,1.1,0.81,0.74,0.66))
model <- ma_continuous_fit(doses,y,
                        fit_type = "mcmc",BMD_TYPE = 'sd',BMR = 1)
MAdensity_plot(model)
```

---

ma_continuous_fit   *ma_continuous_fit - Fit a model averaged continuous BMD model.*

Description

Fit a model averaged continuous BMD model.

Usage

```
ma_continuous_fit(
  D,
  Y,
  model_list = NA,
  fit_type = "laplace",
  BMD_TYPE = "sd",
  BMR = 0.1,
  point_p = 0.01,
  alpha = 0.05,
  samples = 21000,
  burnin = 1000
)
```

Arguments

D	doses matrix
Y	response matrix
model_list	a list of configurations for the single models (priors, model type). To create a model list, one creates a list of continuous model priors using `create_continuous_prior`.
fit_type	the method used to fit ("laplace", "mle", or "mcmc")
BMD_TYPE	BMD_TYPE specifies the type of benchmark dose analysis to be performed. For continuous models, there are four types of BMD definitions that are commonly used.
	- Standard deviation is the default option, but it can be explicitly specified with 'BMR_TYPE = "sd"' This definition defines the BMD as the dose associated with the mean/median changing a specified number of standard deviations from the mean at the control dose., i.e., it is the dose, BMD, that solves

$$\mid f(dose) - f(0) \mid = BMR \times \sigma$$

- Relative deviation can be specified with 'BMR_TYPE = "rel"'. This defines the BMD as the dose that changes the control mean/median a certain percentage from the background dose, i.e. it is the dose, BMD that solves $\mid f(dose) - f(0) \mid = (1 \pm BMR)f(0)$

- Hybrid deviation can be specified with 'BMR_TYPE = "hybrid"'. This defines the BMD that changes the probability of an adverse event by a stated amount relitive to no exposure (i.e 0). That is, it is the dose, BMD, that solves $\frac{Pr(X>x|dose)-Pr(X>x|0)}{Pr(X<x|0)} = BMR$. For this definition, $Pr(X < x|0) = 1 - Pr(X > X|0) = \pi_0$, where $0 \le \pi_0 < 1$ is defined by the user as "point_p," and it defaults to 0.01. Note: this discussion assumed increasing data. The fitter determines the direction of the data and inverts the probability statements for decreasing data.

- Absolute deviation can be specified with 'BMR_TYPE="abs"'. This defines the BMD as an absolute change from the control dose of zero by a specified amount. That is the BMD is the dose that solves the equation $\mid f(dose) - f(0) \mid = BMR$

BMR   This option specifies the benchmark response BMR. The BMR is defined in relation to the BMD calculation requested (see BMD). By default, the "BMR = 0.1."

point_p   This option is only used for hybrid BMD calculations. It defines a probability that is the cutpoint for observations. It is the probability that observations have this probability, or less, of being observed at the background dose.

alpha   Alpha is the specified nominal coverage rate for computation of the lower bound on the BMDL and BMDU, i.e., one computes a $100 \times (1 - \alpha)\%$ confidence interval. For the interval (BMDL,BMDU) this is a $100 \times (1-2\alpha)\%$. By default, it is set to 0.05.

samples   the number of samples to take (MCMC only)

burnin   the number of burnin samples to take (MCMC only)

Value

This function model object containing a list of individual fits and model averaging fits

- Individual_Model_X: Here X is a number $1 \le X \le n$, where n is the number of models in the model average. For each X, this is an individual model fit identical to what is returned in 'single_continuous_fit.'

- ma_bmd: The CDF of the model averaged BMD distribution.

- posterior_probs: The posterior model probabilities used in the MA.

- bmd: The BMD and the $100 \times (1 - 2\alpha)\%$ confidence intervals.

Examples

```
hill_m <- function(doses){
        returnV <-   481  -250.3*doses^1.3/(40^1.3 + doses^1.3)
        return(returnV)
```

```
}
doses <- rep(c(0,6.25,12.5,25,50,100),each=10)
mean <- hill_m(doses)
y <- rnorm(length(mean),mean,20.14)
model <- ma_continuous_fit(doses, y, fit_type = "laplace", BMD_TYPE = 'sd', BMR = 1)
summary(model)
```

---

ma_dichotomous_fit   *ma_dichotomous_fit - Fit a model averaged dichotomous BMD model.*

Description

Fit a model averaged dichotomous BMD model.

Usage

```
ma_dichotomous_fit(
  D,
  Y,
  N,
  model_list = integer(0),
  fit_type = "laplace",
  BMD_TYPE = "extra",
  BMR = 0.1,
  point_p = 0.01,
  alpha = 0.05,
  samples = 21000,
  burnin = 1000
)
```

Arguments

D	doses matrix
Y	response matrix
N	number of replicates matrix
model_list	a list of configurations for the single models (priors, model type)
fit_type	the method used to fit (laplace, mle, or mcmc)
BMD_TYPE	BMD_TYPE specifies the type of benchmark dose analysis to be performed. For continuous models, there are four types of BMD definitions that are commonly used. - Standard deviation is the default option, but it can be explicitly specified with 'BMR_TYPE = "sd"' This definition defines the BMD as the dose associated with the mean/median changing a specified number of standard deviations from the mean at the control dose., i.e., it is the dose, BMD, that solves $\mid f(dose) - f(0) \mid = BMR \times \sigma$

- Relative deviation can be specified with 'BMR_TYPE = "rel"'. This defines the BMD as the dose that changes the control mean/median a certain percentage from the background dose, i.e. it is the dose, BMD that solves $\mid f(dose) - f(0) \mid = (1 \pm BMR)f(0)$

- Hybrid deviation can be specified with 'BMR_TYPE = "hybrid"'. This defines the BMD that changes the probability of an adverse event by a stated amount relitive to no exposure (i.e 0). That is, it is the dose, BMD, that solves $\frac{Pr(X>x|dose) - Pr(X>x|0)}{Pr(X<x|0)} = BMR$. For this definition, $Pr(X < x|0) = 1 - Pr(X > X|0) = \pi_0$, where $0 \leq \pi_0 < 1$ is defined by the user as "point_p," and it defaults to 0.01. Note: this discussion assumed increasing data. The fitter determines the direction of the data and inverts the probability statements for decreasing data.

- Absolute deviation can be specified with 'BMR_TYPE="abs"'. This defines the BMD as an absolute change from the control dose of zero by a specified amount. That is the BMD is the dose that solves the equation $\mid f(dose) - f(0) \mid = BMR$

BMR   This option specifies the benchmark response BMR. The BMR is defined in relation to the BMD calculation requested (see BMD). By default, the "BMR = 0.1."

point_p   This option is only used for hybrid BMD calculations. It defines a probability that is the cutpoint for observations. It is the probability that observations have this probability, or less, of being observed at the background dose.

alpha   Alpha is the specified nominal coverage rate for computation of the lower bound on the BMDL and BMDU, i.e., one computes a $100 \times (1-\alpha)\%$. For the interval (BMDL,BMDU) this is a $100 \times (1-2\alpha)\%$. By default, it is set to 0.05.

samples   the number of samples to take (MCMC only)

burnin   the number of burnin samples to take (MCMC only)

Value

a model object containing a list of single models

- Individual_Model_X: Here X is a number $1 \leq X \leq n$, where n is the number of models in the model average. For each X, this is an individual model fit identical to what is returned in 'single_continuous_fit.'

- ma_bmd: The CDF of the model averaged BMD distribution.

- posterior_probs: The posterior model probabilities used in the MA.

- bmd: The BMD and the $100 \times (1-2\alpha)\%$ confidence intervals.

Examples

```
mData <- matrix(c(0, 2,50,
                  1, 2,50,
                  3, 10, 50,
                  16, 18,50,
                  32, 18,50,
                  33, 17,50),nrow=6,ncol=3,byrow=TRUE)
```

```
D <- mData[,1]
Y <- mData[,2]
N <- mData[,3]
model = ma_dichotomous_fit(D,Y,N)
summary(model)
```

---

normprior   *normprior - create a normal prior object*

Description

Specify a normal prior for a ToxicR Bayesian model fit.

Usage

```
normprior(mean = 0, sd = 1, lb = -100, ub = 100)
```

Arguments

mean	mean of the prior
sd	sd of the prior distribution.
lb	lower bound on the distribution. Necessary for the optimization algorithms, To make sure it is a fully normal prior, make lb small relative to the mean/sd.
ub	Upper bound on the distribution. Necessary for the optimization algorithms, To make sure it is a fully normal prior, make ub large relative to the mean/sd.

Value

a normal prior model object. This object essentially a vector with the first element as 1 (for normal), the second element the mean, the third element the variance, the fourth and fifth elements the lower and upper bounds, respectively.

Examples

```
# Normal Prior with mean 0,sd-1
normprior(mean = 0, sd = 1, lb = -1e4, ub=1e4)

# Truncated Normal prior, Truncated below at 0
normprior(mean = 0, sd = 1, lb = 0, ub=1e4)
```

---

ntp_599_female	*Long term Thyroid Adenoma data from NTP Report 599*

Description

This dataset contains Thyroid Adenoma data for female rats for the technical report TR-599: Sodium Tungstate Dihydrate.

Usage

```
ntp_599_female
```

Format

A data frame with 200 rows and 4 variables:

treatment -The dose group for the observation.

days_on_study -Number of days on the study 730 is the max.

adenoma - Thyroid Adenoma (Yes/No) (1/0).

dose -The dose in mg/L

For more information see: doi:10.22427/NTPDATATR599

---

ntp_599_hemotology	*Clinical Chemistry data from NTP Report 599*

Description

This dataset contains clinical chemistry data for all rats in the short term 90-day study.

Usage

```
ntp_599_hemotology
```

Format

A data frame with 200 rows and 4 variables:

concentration -The dose group for the observation.

sex - Male/Female.

response - Response variable

response_type - The type of response measured

For more information see: doi:10.22427/NTPDATATR599

---

ntp_dunn   *ntp_dunn Dunn's test*

Description

ntp_dunn Dunn's test

Usage

```
ntp_dunn(formula, data, dose_name = "dose")
```

Arguments

formula   An equation of the form $Y \sim X$. Here the variable Y is the response of interest, and X represents discrete experimental conditions. For example, if weight is the dependent variable, and you are interested in looking at the trend across sex one would have 'weight ~ sex'.

data   A data frame with column names in the formula.

dose_name   The name of the variable containing the doses in the data frame $data$. It is expected multiple doses for each of the experimental conditions X.

Value

The results of a Dunn's test for each level in $dose_name$.

Examples

```
a = ntp_dunn(response ~ sex + response_type,data=ntp_599_hemotology,
                                        dose_name="concentration")
summary(a)
```

---

ntp_dunnett   *ntp_dunett Dunnett's test*

Description

ntp_dunett Dunnett's test

Usage

```
ntp_dunnett(formula, data, dose_name = "dose")
```

Arguments

formula	An equation of the form $Y \sim X$. Here the variable Y is the response of interest, and X represents discrete experimental conditions. For example, if weight is the dependent variable, and you are interested in looking at the trend across sex one would have 'weight ~ sex'.
data	A data frame with column names in the formula.
dose_name	The name of the variable containing the doses in the data frame $data$. It is expected multiple doses for each of the experimental conditions X.

Value

The results of Dunnet's test for each level in $dose_name$

Examples

```
a = ntp_dunnett(response ~ sex + response_type,data=ntp_599_hemotology,dose_name="concentration")
summary(a)
```

---

ntp_jonckeere	*ntp_jonckeere Jonckherre's test for significant differences from background dose*

Description

ntp_jonckeere Jonckherre's test for significant differences from background dose

Usage

```
ntp_jonckeere(formula, data, dose_name = "dose", pair = "Williams")
```

Arguments

formula	An equation of the form $Y \sim X$. Here the variable Y is the response of interest, and X represents discrete experimental conditions. For example, if weight is the dependent variable, and you are interested in looking at the trend across sex one would have 'weight ~ sex'.
data	A data frame with column names in the formula.
dose_name	The name of the variable containing the doses in the data frame $data$. It is expected multiple doses for each of the experimental conditions X.
pair	The type of test used for pairwise comparison. It can either be "Williams" or "Shirley"

Value

The results of a global test for difference from background.

Examples

```
ntp_jonckeere(response ~ sex + response_type,data=ntp_599_hemotology,dose_name="concentration")
```

---

ntp_polyk   *Poly-k test This function implements the NTP's polyK trend test.*

Description

Poly-k test This function implements the NTP's polyK trend test.

Usage

```
ntp_polyk(dose, tumor, daysOnStudy)
```

Arguments

dose	An equation of the form $Y \sim X$. Here the variable Y is the response of interest, and X represents discrete experimental conditions. For example, if weight is the dependent variable, and you are interested in looking at the trend across sex one would have 'weight ~ sex'.
tumor	A data frame with column names in the formula.
daysOnStudy	The name of the variable containing the doses in the data frame $data$. It is expected multiple doses for each of the experimental conditions X.

Value

The results of a Williams trend test for each level in dose_name. More information on this procedure at: doi:10.2307/2531856 and doi:10.2307/2532200 This procedure returns a vector of three p-values for the poly-1.5, poly-3, and poly-6 test respectively.

Examples

```
ntp_polyk(ntp_599_female$dose,ntp_599_female$adenoma,ntp_599_female$days_on_study)
```

---

ntp_shirley | *ntp_shirley Shirley's test as programmed at the NTP*

Description

ntp_shirley Shirley's test as programmed at the NTP

Usage

```
ntp_shirley(formula, data, dose_name = "dose")
```

Arguments

formula
: An equation of the form $Y \sim X$. Here the variable Y is the response of interest, and X represents discrete experimental conditions. For example, if weight is the dependent variable, and you are interested in looking at the trend across sex one would have 'weight ~ sex'.

data
: A data frame with column names in the formula.

dose_name
: The name of the variable containing the doses in the data frame $data$. It is expected multiple doses for each of the experimental conditions X.

Value

The results of a non-parametric Shirley's isotone test for trend on each level in $dose_name$. For more information see: doi:10.2307/2529789 The returned list contains:

- X: this represents all the class objects on the right hand side of $Y \sim X$ above.

- dose: the dose groups relative to control.

- testStats: Value of the Shirley test statistic.

- mult_comp_signif: Test's significance as 0, 1, or 2 which is not-significant, significant at the 0.05

- mult_comp_test: The type of test, i.e. "SHIRLEY"

Examples

```
a = ntp_shirley(weight ~ sex, data=ntp_weight_data)
summary(a)
```

---

ntp_weight_data   *Short term terminal body-weight data from NTP Report 599*

Description

This dataset contains terminal body-weight data for male and female rats for the technical report TR-599: Sodium Tungstate Dihydrate.

Usage

```
ntp_weight_data
```

Format

A data frame with 120 rows and 4 variables:

Dose_Group -The dose group for the observation.

dose -The dose in mg/L

sex -Animal's Sex

weight -Terminal body-weight

For more information see: doi:10.22427/NTPDATATR599

---

ntp_williams   *Wiliam's trend test*

Description

Williams Trend test for

Usage

```
ntp_williams(formula, data, dose_name = "dose")
```

Arguments

formula	An equation of the form $Y \sim X$. Here the variable Y is the response of interest, and X represents discrete experimental conditions. For example, if weight is the dependent variable, and you are interested in looking at the trend across sex one would have 'weight ~ sex'.
data	A data frame with column names in the formula.
dose_name	The name of the variable containing the doses in the data frame $data$. It is expected multiple doses for each of the experimental conditions X.

Value

The results of a Williams trend test for each level in $dose_name$. For more information on the Williams trend test: doi:10.2307/2528930 #'

- X: this represents all the class objects on the right hand side of $Y \sim X$ above.
- dose: the dose groups relative to control.
- willStat: Value of the Shirley test statistic.
- mult_comp_signif: Test's significance as 0, 1, or 2 which is not-significant, significant at the 0.05
- mult_comp_test: The type of test, i.e. "William"

Examples

```
a = ntp_williams(weight ~ sex, data=ntp_weight_data)
summary(a)
```

---

single_continuous_fit   *single_continuous_fit - Fit a single continuous BMD model.*

Description

Fit a single continuous BMD model.

Usage

```
single_continuous_fit(
  D,
  Y,
  model_type = "hill",
  fit_type = "laplace",
  prior = NA,
  BMD_TYPE = "sd",
  BMR = 0.1,
  point_p = 0.01,
  distribution = "normal-ncv",
  alpha = 0.05,
  samples = 25000,
  degree = 2,
  burnin = 1000,
  ewald = FALSE,
  transform = FALSE
)
```

Arguments

D	doses matrix
Y	response matrix
model_type	Mean model. It should be one of $"hill", "exp\text{-}3", "exp\text{-}5", "power", "polynomial"$
fit_type	the method used to fit (laplace, mle, or mcmc)
prior	Prior / model for the continuous fit. If this is specified, it overrides the parameters 'model_type' and 'distribution.'
BMD_TYPE	BMD_TYPE specifies the type of benchmark dose analysis to be performed. For continuous models, there are four types of BMD definitions that are commonly used.

- Standard deviation is the default option, but it can be explicitly specified with 'BMR_TYPE = "sd"' This definition defines the BMD as the dose associated with the mean/median changing a specified number of standard deviations from the mean at the control dose., i.e., it is the dose, BMD, that solves $\mid f(dose) - f(0) \mid = BMR \times \sigma$

- Relative deviation can be specified with 'BMR_TYPE = "rel"'. This defines the BMD as the dose that changes the control mean/median a certain percentage from the background dose, i.e. it is the dose, BMD that solves $\mid f(dose) - f(0) \mid = (1 \pm BMR)f(0)$

- Hybrid deviation can be specified with 'BMR_TYPE = "hybrid"'. This defines the BMD that changes the probability of an adverse event by a stated amount relitive to no exposure (i.e 0). That is, it is the dose, BMD, that solves $\frac{Pr(X>x|dose) - Pr(X>x|0)}{Pr(X<x|0)} = BMR$. For this definition, $Pr(X < x|0) = 1 - Pr(X > X|0) = \pi_0$, where $0 \le \pi_0 < 1$ is defined by the user as "point_p," and it defaults to 0.01. Note: this discussion assumed increasing data. The fitter determines the direction of the data and inverts the probability statements for decreasing data.

- Absolute deviation can be specified with 'BMR_TYPE="abs"'. This defines the BMD as an absolute change from the control dose of zero by a specified amount. That is the BMD is the dose that solves the equation $\mid f(dose) - f(0) \mid = BMR$.

BMR	This option specifies the benchmark response BMR. The BMR is defined in relation to the BMD calculation requested (see BMD). By default, the "BMR = 0.1."
point_p	This option is only used for hybrid BMD calculations. It defines a probability that is the cutpoint for observations. It is the probability that observations have this probability, or less, of being observed at the background dose.
distribution	The underlying distribution used as the data distribution.
alpha	Alpha is the specified nominal coverage rate for computation of the lower bound on the BMDL and BMDU, i.e., one computes a $100 \times (1 - \alpha)\%$ confidence interval. For the interval (BMDL,BMDU) this is a $100 \times (1 - 2\alpha)\%$ confidence interval. By default, it is set to 0.05.
samples	the number of samples to take (MCMC only)

degree	the number of degrees of a polynomial model. Only used for polynomial models.
burnin	the number of burnin samples to take (MCMC only)
ewald	perform Wald CI computation instead of the default profile likelihood computation. This is the the 'FAST BMD' method of Ewald et al (2021)
transform	Transforms doses using $\log(dose + \sqrt{dose^2 + 1})$. Note: this is a log transform that has a derivative defined when dose =0.

Value

Returns a model object class with the following structure:

- `full_model`: The model along with the likelihood distribution.
- `bmd`: A vector containing the benchmark dose (BMD) and $100 \times (1-2\alpha)$ confidence intervals.
- `parameters`: The parameter estimates produced by the procedure, which are relative to the model ' given in `full_model`. The last parameter is always the estimate for $\log(sigma^2)$.
- `covariance`: The variance-covariance matrix for the parameters.
- `bmd_dis`: Quantiles for the BMD distribution.
- `maximum`: The maximum value of the likelihod/posterior.
- `Deviance`: An array used to compute the analysis of deviance table.
- `prior`: This value gives the prior for the Bayesian analysis.
- `model`: Parameter specifies t mean model used.
- `options`: Options used in the fitting procedure.
- `data`: The data used in the fit.
- `transformed`: Are the data $\log(x + \sqrt{x^2 + 1})$ transformed?
    When MCMC is specified, an additional variable `mcmc_result` has the following two variables:
    - `PARM_samples`: matrix of parameter samples.
    - `BMD_samples`: vector of BMD sampled values.

Examples

```
M2            <- matrix(0,nrow=5,ncol=4)
colnames(M2) <- c("Dose","Resp","N","StDev")
M2[,1] <- c(0,25,50,100,200)
M2[,2] <- c(6,5.2,2.4,1.1,0.75)
M2[,3] <- c(20,20,19,20,20)
M2[,4] <- c(1.2,1.1,0.81,0.74,0.66)
model = single_continuous_fit(M2[,1,drop=FALSE], M2[,2:4], BMD_TYPE="sd", BMR=1, ewald = TRUE,
                       distribution = "normal",fit_type="laplace",model_type = "hill")

summary(model)
```

---

single_dichotomous_fit

Fit a single dichotomous dose-response model to data.

Description

Fit a single dichotomous dose-response model to data.

Usage

```
single_dichotomous_fit(
  D,
  Y,
  N,
  model_type,
  fit_type = "laplace",
  prior = NULL,
  BMR = 0.1,
  alpha = 0.05,
  degree = 2,
  samples = 21000,
  burnin = 1000
)
```

Arguments

D	A numeric vector or matrix of doses.
Y	A numeric vector or matrix of responses.
N	A numeric vector or matrix of the number of replicates at a dose.
model_type	The mean model for the dichotomous model fit. It can be one of the following: "hill","gamma","logistic", "log-logistic", "log-probit" ,"multistage" ,"probit","qlinear","weibull"
fit_type	the method used to fit (laplace, mle, or mcmc)
prior	Used if you want to specify a prior for the data.
BMR	This option specifies the benchmark response BMR. The BMR is defined in relation to the BMD calculation requested (see BMD). By default, the "BMR = 0.1."
alpha	Alpha is the specified nominal coverage rate for computation of the lower bound on the BMDL and BMDU, i.e., one computes a $100 \times (1-\alpha)\%$. For the interval (BMDL,BMDU) this is a $100 \times (1-2\alpha)\%$ confidence interval. By default, it is set to 0.05.
degree	the number of degrees of a polynomial model. Only used for polynomial models.
samples	the number of samples to take (MCMC only)
burnin	the number of burnin samples to take (MCMC only)

Value

Returns a model object class with the following structure:

- `full_model`: The model along with the likelihood distribution.
- `parameters`: The parameter estimates produced by the procedure, which are relative to the model ' given in `full_model`. The last parameter is always the estimate for $\log(\sigma^2)$.
- `covariance`: The variance-covariance matrix for the parameters.
- `bmd_dist`: Quantiles for the BMD distribution.
- `bmd`: A vector containing the benchmark dose (BMD) and $100 \times (1 - 2\alpha)$ confidence intervals.
- `maximum`: The maximum value of the likelihod/posterior.
- `gof_p_value`: GOF p-value for the Pearson χ^2 GOF test.
- `gof_chi_sqr_statistic`: The GOF statistic.
- `prior`: This value gives the prior for the Bayesian analysis.
- `model`: Parameter specifies t mean model used.
- `data`: The data used in the fit.
    When MCMC is specified, an additional variable `mcmc_result` has the following two variables:
    - `PARM_samples`: matrix of parameter samples.
    - `BMD_samples`: vector of BMD sampled values.

Examples

```
mData <- matrix(c(0, 2,50,
                  1, 2,50,
                  3, 10, 50,
                  16, 18,50,
                  32, 18,50,
                  33, 17,50),nrow=6,ncol=3,byrow=TRUE)
D <- mData[,1]
Y <- mData[,2]
N <- mData[,3]
model = single_dichotomous_fit(D, Y, N, model_type = "hill", fit_type = "laplace")
summary(model)
```

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