

# Package ‘mixtox’

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**Type** Package

**Title** Dose Response Curve Fitting and Mixture Toxicity Assessment

**Version** 1.4.0

**Depends** R (>= 4.2.0)

**Imports** minpack.lm

**Description** Curve Fitting of monotonic(sigmoidal) & non-monotonic(J-shaped) dose-response data. Predicting mixture toxicity based on reference models such as 'concentration addition', 'independent action', and 'generalized concentration addition'.

**License** GPL-2

**Encoding** UTF-8

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antibiotox

*Toxicity of Seven Antibiotics on Photobacteria*


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## Description

Seven antibiotics are: Neomycin sulfate(NEO), streptomycin sulfate(STR), kanamycin sulfate(KAN), spectinomycin dihydrochloridehydrate(SPE), paromomycin sulfate(PAR), dihydrostreptomycin sesquisulfate hydrate(DIH), and gentamycin sulfate(GEN). Their toxicity on photobacteria Q67 were tested using microplate toxicity analysis.

The concentration-responses include the toxicity of seven antibiotics, two eecr mixtures, and ten mixtures designed by udcr. The curve fitting information of seven antibiotics and a total of 12 mixtures.

## Usage

```
data(antibiotox)
```

## Format

A list with concentration-response data of 7 antibiotics, 12 mixtures, and associated fitting information.

PAR\$x a numeric vector of concentrations

PAR\$y a numeric matrix of responses

PAR\$name name of test substance

PAR\$concNum the number of concentrations  
 PAR\$tierNum the number of repetitions  
 PAR\$type type of test substance  
 sgl\$model models used to fit the concentration-response data  
 sgl\$param fitted coefficients of concentration-response curves  
 udcr.mix\$model models used to fit the concentration-response data of udcr mixtures on photobacteria  
 udcr.mix\$param fitted coefficients of concentration-response curves  
 udcr.pct the percentage of individual chemicals in the udcr mixtures  
 eecr.mix\$model models used to fit the concentration-response data of eecr mixtures on photobacteria  
 eecr.mix\$param fitted coefficients of concentration-response curves  
 eecr.pct the proportion of individual chemicals in the eecr mixtures

### Details

Quantal responses[0, 1] are needed for curve fitting using the following six equaitons: i.e., Weibull, Logit, Hill, BCL, GL, BCW. The following equation could transform continous responses to quantal ones:

$$E = \frac{I_0 - I_i}{I_0}$$

where  $I_0$  is the average of controls for inhibition tests or the average of the maximum effect for stimulation tests and  $I_i$  the average effect of the  $i^{th}$  treatment.

### Examples

```

# example 1
## Retrieve the toxicity information of PAR on photobacteria.
antibiotox$PAR
# example 2
## Retrieve the toxicity information of two eecr mixtures on photobacteria.
antibiotox$eecr.mix

```

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BMD

*Calculating benchmark dose (BMD) and lower limit of benchmark dose (BMDL)*

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### Description

Calculation of BMD and BMDL for both quantal and continuous dose responses. Six 2- or 3-paramter models ('Hill', 'Weibull', 'Logit', 'Weibull\_three', 'Hill\_three', 'Logit\_three') were employed for quantal dose responses. Three 4-parameter models ('Weibull\_four', 'Logit\_four', 'Hill\_four') were employed for continuous data.

**Usage**

```
BMD(object, bmr = 0.10, backg = 0, def = 'additional', eq = 'as.is',
      sigLev = 0.05, ci = 'CI', sav = FALSE)
```

**Arguments**

object	object of class curveFit.
bmr	numeric vector of bench mark response levels for which to calculate benchmark doses (should be between 0 and 1)
backg	numeric value specifying the background level (defaults to 0)
def	character string specifying the definition of the benchmark dose to use in the calculations. "excess" and "additional" are for binomial response whereas "relative" and "hybrid" (additive hybrid) are for continuous response.
eq	default list of equations.
sigLev	the significance level for Dunnett's test. The default is 0.05.
ci	types of confidence intervals (CI or PI).CI: non-simultaneous confidence intervals; PI: non-simultaneous prediction intervals.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**Details**

Selecting the Benchmark Response Level (BMR) ([https://www.epa.gov/bmds/ benchmark-dose-bmd-methods#bmr](https://www.epa.gov/bmds/benchmark-dose-bmd-methods#bmr)).BMR is usually set as 0.10.

**Value**

bmds	values of BMDL, BMD, and BMDU.
------	--------------------------------

**Note**

three default equations (Hill, Weibull, and Logit) were used to calculate BMD for quantal dose response. Three default equations('Weibull\_four', 'Logit\_four', 'Hill\_four') were used to calculate BMD for continuous dose response. BMD calculation is only available for monotonic dose responses in this version.

**References**

Benchmark Dose Technical Guidance, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC 20460, EPA/100/R-12/001, June 2012  
 Kennyp (2002). Critical Issues in Benchmark Calculations from Continuous Data. Crit. Rev. Toxicol., 32, 133-153.

## Examples

```
## example 1
# calculate the BMD of heavy metal Ni(2+) on the MCF-7 cells
x <- cytotox$Ni$x
rspn <- cytotox$Ni$y
obj <- curveFit(x, rspn, eq = 'Logit', param = c(12, 3), effv = c(0.05, 0.5), rtype = 'quantal')
BMD(obj, bmr = 0.10, backg = 0, def = 'additional', eq = 'default', sigLev = 0.05, ci = 'CI')
```

---

 caPred

---

*Mixture Toxicity Prediction Based on Concentration Addition*


---

## Description

Predicting mixture toxicity based on individual concentration-response information fitted only based on the following six models: Hill, Weibull, Logit, BCW, BCL, and GL. Three optional mixture design methods are provided: (1) arbitrary concentration ratio (acr), users can set an arbitrary proportion for each component in a mixture; (2) equal effect concentration ratio (eocr); (3) uniform design concentration ratio (udcr).

## Usage

```
caPred(model, param, mixType = "eocr", effv, effPoints, sav = FALSE)
```

## Arguments

model	vector of models: Hill, Weibull, Logit, BCW, BCL, and GL
param	numeric matrix of fitting coefficients with row names (model selected) and column names (Alpha, Beta, and Gamma). For models with only two parameters (i.e., Hill, Weibull, and Logit), Gamma can be set to zero or any other numeric value.
mixType	experimental design of the mixture. acr: arbitrary concentration ratio; eocr: equal effect concentration ratio; udcr: uniform design concentration ratio.
effv	numeric vector with single or multiple effects (0 ~ 1).
effPoints	numeric vector [0 ~ 1] of effects to predict effect concentrations.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

## Details

Concentration addition (CA) is designed for mixtures of chemicals that have similar mechanisms of action. For a well-defined mixture (e.g., a mixture of  $n$  components), CA is expressed mathematically as:

$$\sum_{i=1}^n \frac{c_i}{ECx_i} = 1$$

where  $EC_{x_i}$  is the effect concentration of the  $i^{th}$  compound that causes  $x\%$  effect when applied individually at  $c_i$ . The  $c_i$  can be computed from the following equation:

$$c_i = p_i \cdot c_{mix} = p_i \cdot EC_{x,mix}$$

where  $p_i$  is the proportion of  $i^{th}$  component in the mixture,  $c_{mix}$  the mixture concentration and  $EC_{x,mix}$  the concentration of the mixture at a specific effect  $x\%$ . The prediction of combined effects of mixture-components based on CA can then be expressed as:

$$EC_{x,mix} = \left( \sum_{i=1}^n \frac{p_i}{EC_{x,i}} \right)^{-1}$$

### Value

ca	a series of effect concentrations predicted by CA at effPoints
e	a series of effects (effPoints) associated with the effect concentrations in ca
pct	the proportion of every component in a mixture
uniTab	the uniform design table used to construct the mixture when mixType is 'udcr'

### Note

Note that effv is dependent on the mixType.

If the mixType is acr, effv is supposed to be a vector with the ratio of each components and its length should be the same as the number of components. For instance, effv can be c(4, 1) if one wants to mix two compounds with a ratio of 4:1. One can also set effv as c(80, 20) or c(0.8, 0.2) or any other values with the same ratio as 4:1. The program will convert the ratio to a range of 0 to 100%.

If the mixType is eecr, effv is supposed to be the effect values. For instance, effv = c(0.5) means one mixture will be prepared and each of its components will be mixed in a ratio equal to EC50. More than one eecr mixtures can be achieved by assigning more effect values to effv, e.g., effv = c(0.05, 0.10, 0.5)

If the mixType is udcr, elements in effv are levels in a uniform table, the length of effv is the same as the number of runs. the number of runs should be consistent with the number of components in the uniform design.

### References

Liang, Yi-zeng, Kai-tai Fang, and Qing-song Xu. 2001. Uniform Design and Its Applications in Chemistry and Chemical Engineering. *Chemometrics and Intelligent Laboratory Systems* 58(1):43-57.

Backhaus, T., Faust, M., 2012. Predictive environmental risk assessment of chemical mixtures: A conceptual framework. *Environmental Science and Technology*. 46, 2564-2573.

### See Also

[iaPred](#)

## Examples

```
## example 1
# using CA to predict the toxicity of mixture designed by eecr at the
# effect concentration of EC05 and EC50
# eecr mixture design is based on seven antibiotics(factors).
model <- antibiotox$sgl$model
param <- antibiotox$sgl$param
caPred(model, param, mixType = "eecr", effv = c(0.05, 0.5))

## example 2
# using CA to predict the mixtures designed by udcr
# the udcr mixture design is based on four heavy metals and four ionic liquids (eight factors).
# five levels (EC05, EC10, EC20, EC30, and EC50 ) are allocated in the uniform table using the
# pseudo-level technique (Liang et al., 2001)
model <- cytotox$sgl$model
param <- cytotox$sgl$param
effv <- c(0.05, 0.05, 0.10, 0.10, 0.20, 0.20, 0.30, 0.30, 0.50, 0.50)
caPred(model, param, mixType = "udcr", effv)

## example 3
# using CA to predict the mixtures designed by acr
# the udcr mixture design is based on five antibiotics (five factors).
# the every component in the mixture shares exactly the same ratio (0.20)
model <- antibiotox$sgl$model[1 : 5]
param <- antibiotox$sgl$param[1 : 5, ]
effv <- c(0.2, 0.2, 0.2, 0.2, 0.2)
caPred(model, param, mixType = "acr", effv)
```

---

CEx

*Effect Calculation for All Nineteen Curves*


---

## Description

Calculating responses at particular concentrations.

## Usage

```
CEx(model, param, conc, sav = FALSE)
```

## Arguments

model	a character vector of equation names
param	a numeric matrix of fitting coefficients with rownames (equation selected) and colnames (ALpha, Beta, and Gamma). For equations with two parameters, Gamma can be set as zero or any other numeric value.
conc	a numeric vector with single or multiple concentrations.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**Details**

Responses will be calculated with provided equations (model), associated fitting parameters (param), and concentrations.

**Value**

effv                    a numeric vector of effect(s)

**References**

Zhu X-W, et.al. 2013. Modeling non-monotonic dose-response relationships: Model evaluation and hormetic quantities exploration. *Ecotoxicol. Environ. Saf.* 89:130-136.  
 Hill equation (biochemistry) [http://en.wikipedia.org/wiki/Hill\\_equation\\_\(biochemistry\)](http://en.wikipedia.org/wiki/Hill_equation_(biochemistry))  
 Scholze, M. et al. 2001. A General Best-Fit Method for Concentration-Response Curves and the Estimation of Low-Effect Concentrations. *Environmental Toxicology and Chemistry* 20(2):448-457.

**Examples**

```
## example 1
# calculate the responses of hormesis curves at the concentration of 0.1 and 0.02 mol/L
model <- hormesis$sgl$model
param <- hormesis$sgl$param
CEx(model, param, conc = c(0.1, 0.02))

## example 2
# calculate the effect caused by four heavy metals and four ionic liquids at the concentration of
# 0.00001 and 0.00002 mol/L on the MCF-7 cells
model <- cytotox$sgl$model
param <- cytotox$sgl$param
CEx(model, param, conc = c(0.00001, 0.00002))

## example 3
# calculate the response ranges
model <- hormesis$sgl$model
param <- hormesis$sgl$param
CEx(model, param, conc = c(0, 1e20))
```

---

 curveFit

---

*Curve Fitting*


---

**Description**

Thirteen monotonic(sigmoidal) models ("Hill", "Hill\_two", "Hill\_three", "Hill\_four", "Weibull", "Weibull\_three", "Weibull\_four", "Logit", "Logit\_three", "Logit\_four", "BCW(Box-Cox-Weibull)", "BCL(Box-Cox-Logit)", "GL(Generalized Logit)") and four non-monotonic(J-shaped) models ("Brain\_Consens", "BCV", "Biphasic", "Hill\_five") are provided to fit dose-response data. The goodness of fit of a model is evaluated by the following statistics: coefficient of determination ( $R^2$ ), adjusted coefficient



of determination ( $R_{adj}^2$ ), root mean squared error (RMSE), mean absolute error (MAE), Akaike information criterion (AIC), bias-corrected Akaike information criterion(AICc), and Bayesian information criterion (BIC).

### Usage

```
curveFit(x, rspn, eq, param, effv, rtype = 'quantal', sigLev = 0.05, sav = FALSE, ...)
```

### Arguments

x	a numeric vector of experimental concentration.
rspn	a numeric matrix of experimental responses with one or more replicates.
eq	equation used for curve fitting: "Hill", "Hill_two", "Hill_three", "Hill_four", "Weibull", "Weibull_three", "Weibull_four", "Logit", "Logit_three", "Logit_four", "BCW", "BCL", "GL", "Brain_Consens", "BCV", "Biphasic", "Hill_five".
param	a vector of starting parameters. Use tuneFit to get the starting values.
effv	a numeric vector of responses for the calculation of effect concentrations. Minus values(e.g., -5%) are permitted only in the condition of 'hormesis' dose-responses. Relative values(e.g., 5%, 10%) in the condition of 'continuous' dose-responses.
rtype	three dose-response types: 'quantal', 'continuous', 'hormesis'. Default is 'quantal'. 'quantal': dose-responses with lower limit fixed at 0 and higher limit at 1 (100%). 'continuous': dose-responses with no fixed lower or higher limits. 'hormesis': non-monotonic J or U-shaped dose-responses with lower limit fixed at 0 and higher limit at 1 (100%).
sigLev	the significant level for confidence intervals and Dunnett's test. Default is 0.05.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.
...	other arguments passed to nlsLM in minpack.lm.

### Details

Curve fitting is dependent on the package minpack.lm (<http://cran.r-project.org/web/packages/minpack.lm/index.html>). Monotonic(sigmoidal) equations are as follows:

Hill:

$$E = 1 / \left( 1 + (\alpha/c)^\beta \right)$$

Hill\_two:

$$E = \beta c / (\alpha + c)$$

Hill\_three:

$$E = \gamma / \left( 1 + (\alpha/c)^\beta \right)$$

Hill\_four:

$$E = \delta + (\gamma - \delta) / \left( 1 + (\alpha/c)^\beta \right)$$

where  $\alpha$  = EC50,  $\beta$  = H (Hill coefficient),  $\gamma$  = Top, and  $\delta$  = Bottom

Weibull:

$$E = 1 - \exp(-\exp(\alpha + \beta \log(c)))$$

Weibull\_three:

$$E = \gamma (1 - \exp(-\exp(\alpha + \beta \log(c))))$$

Weibull\_four:

$$E = \gamma + (\delta - \gamma) \exp(-\exp(\alpha + \beta \log(c)))$$

Logit:

$$E = (1 + \exp(-\alpha - \beta \log(c)))^{-1}$$

Logit\_three:

$$E = \gamma / (1 + \exp((-\alpha) - \beta \log(c)))$$

Logit\_four:

$$E = \delta + (\gamma - \delta) / (1 + \exp((-\alpha) - \beta \log(c)))$$

where  $\alpha$  is the location parameter and  $\beta$  slope parameter.  $\gamma$  = Top, and  $\delta$  = Bottom

BCW:

$$E = 1 - \exp\left(-\exp\left(\alpha + \beta \left(\frac{c^\gamma - 1}{\gamma}\right)\right)\right)$$

BCL:

$$E = (1 + \exp(-\alpha - \beta((c^\gamma - 1)/\gamma)))^{-1}$$

GL:

$$E = 1/(1 + \exp(-\alpha - \beta \log(c)))^\gamma$$

Non-monotonic(J-shaped) models:

Hill\_five:

$$E = 1 - \left(1 + (\gamma - 1) / \left(1 + (\alpha/c)^\beta\right)\right) \left(1 - 1 / (1 + (\delta/c)^\epsilon)\right)$$

Brain\_Consens:

$$E = 1 - (1 + \alpha c) / (1 + \exp(\beta \gamma) c^\beta)$$

where  $\alpha$  is the initial rate of increase at low concentration,  $\beta$  the way in which response decreases with concentration, and  $\gamma$  no simple interpretation.

BCV:

$$E = 1 - \alpha (1 + \beta c) / \left(1 + (1 + 2\beta \gamma) (c/\gamma)^\delta\right)$$

where  $\alpha$  is untreated control,  $\beta$  the initial rate of increase at low concentration,  $\gamma$  the concentration cause 50% inhibition, and  $\delta$  no simple interpretation.

Cedergreen:

$$E = 1 - (1 + \alpha \exp(-1/(c^\beta))) / (1 + \exp(\gamma (\ln(c) - \ln(\delta))))$$

where  $\alpha$  the initial rate of increase at low concentration,  $\beta$  the rate of hormetic effect manifests itself,  $\gamma$  the steepness of the curve after maximum hormetic effect, and  $\delta$  the lower bound on the

EC50 level.

Beckon:

$$E = (\alpha + (1 - \alpha) / (1 + (\beta/c)^\gamma)) / (1 + (c/\delta)^\epsilon)$$

where  $\alpha$  is the minimum effect that would be approached by the downslope in the absence of the upslope,  $\beta$  the concentration at the midpoint of the falling slope,  $\gamma$  the steepness of the rising(positive) slope,  $\delta$  the concentration at the midpoint of the rising slope, and  $\epsilon$  the steepness of the falling(negative) slope.

Biphasic:

$$E = \alpha - \alpha / (1 + 10^{((c-\beta)\gamma)}) + (1 - \alpha) / (1 + 10^{((\delta-c)\epsilon)})$$

where  $\alpha$  is the minimum effect that would be approached by the downslope in the absence of the upslope,  $\beta$  the concentration at the midpoint of the falling slope,  $\gamma$  the steepness of the rising(positive) slope,  $\delta$  the concentration at the midpoint of the rising slope, and  $\epsilon$  the steepness of the falling(negative) slope.

In all,  $E$  represents effect and  $c$  represents concentration.

## Value

fitInfo	curve fitting information.
eq	equation used in curve fitting.
p	fitted parameters.
res	residual.
sta	goodness of fit.
crcInfo	a numeric matrix with the experimental concentration (x), predicted and experimental responses, experimental responses, lower and upper bounds of (non-simultaneous) prediction intervals (PI.low and PI.up), and lower and upper bounds of (non-simultaneous) confidence intervals (CI.low and CI.up).
ecx	effect concentrations only if effv is provided.
effvAbs	Absolute effects corresponding to effv only in the condition of 'continuous' dose-responses.
rtype	dose-response type.
rspnRange	response range. The lower limit is the response at extremely low dose. The higher limit is the response at infinite high dose.
minx	concentration to induce the maximum stimulation for 'continuous' dose-response
miny	the maximum stimulation for 'continuous' data.

## Note

tuneFit is recommended to find the starting values.

## References

- Scholze, M. et al. 2001. A General Best-Fit Method for dose-response Curves and the Estimation of Low-Effect Concentrations. *Environmental Toxicology and Chemistry* 20(2):448-457.
- Zhu X-W, et.al. 2013. Modeling non-monotonic dose-response relationships: Model evaluation and hormetic quantities exploration. *Ecotoxicol. Environ. Saf.* 89:130-136.
- Howard GJ, Webster TF. 2009. Generalized concentration addition: A method for examining mixtures containing partial agonists. *J. Theor. Biol.* 259:469-477.
- Spiess, A.-N., Neumeyer, N., 2010. An evaluation of R2 as an inadequate measure for nonlinear models in pharmacological and biochemical research: A Monte Carlo approach. *BMC Pharmacol.* 10, 11.
- Huet, S., Bouvier, A., Poursat, M.-A., Jolivet, E., 2004. *Statistical tools for nonlinear regression: a practical guide with S-PLUS and R examples.* Springer Science & Business Media.
- Gryze, S. De, Langhans, I., Vandebroek, M., 2007. Using the correct intervals for prediction: A tutorial on tolerance intervals for ordinary least-squares regression. *Chemom. Intell. Lab. Syst.* 87, 147-154.

## Examples

```
## example 1
# Fit hormesis dose-response data.
# Calculate the concentrations that cause 5% of 50% inhibition.
x <- hormesis$OmimCl$x
rspn <- hormesis$OmimCl$y
curveFit(x, rspn, eq = 'Biphasic', param = c(-0.34, 0.001, 884, 0.01, 128),
effv = 0.5, rtype = 'hormesis')

x <- hormesis$HmimCl$x
rspn <- hormesis$HmimCl$y
curveFit(x, rspn, eq = 'Biphasic', param = c(-0.59, 0.001, 160, 0.05, 19),
effv = c(0.05, 0.5), rtype = 'hormesis')

x <- hormesis$ACN$x
rspn <- hormesis$ACN$y
curveFit(x, rspn, eq = 'Brain_Consens', param = c(2.5, 2.8, 0.6, 2.44),
effv = c(0.05, 0.5), rtype = 'hormesis')

x <- hormesis$Acetone$x
rspn <- hormesis$Acetone$y
curveFit(x, rspn, eq = 'BCV', param = c(1.0, 3.8, 0.6, 2.44), effv = c(0.05, 0.5),
rtype = 'hormesis')

## example 2
# Fit quantal dose-responses: the inhibition of heavy metal Ni(2+) on the growth of MCF-7 cells.
# Calculate the concentrations that cause 5% and 50% inhibition.
x <- cytotox$Ni$x
rspn <- cytotox$Ni$y
curveFit(x, rspn, eq = 'Logit', param = c(12, 3), effv = c(0.05, 0.5), rtype = 'quantal')

## example 3
# Fit quantal dose-responses: the inhibition effect of Paromomycin Sulfate (PAR) on photobacteria.
# Calculate the concentrations that cause 5% and 50% inhibition.
```

```
x <- antibiotox$PAR$x
rspn <- antibiotox$PAR$y
curveFit(x, rspn, eq = 'Logit', param = c(26, 4), effv = c(0.05, 0.5))
```

cytotox

*Cytotoxicity of Heavy Metal Ions and Ionic Liquids on MCF-7***Description**

Chemicals include four heavy metal ions:  $\text{NiNO}_3 \cdot 6\text{H}_2\text{O}$  (Ni),  $\text{ZnSO}_4 \cdot 7\text{H}_2\text{O}$  (Zn),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (Cu), and  $\text{MnCl}_2 \cdot 4\text{H}_2\text{O}$  (Mn); four ionic liquids are 1-Octyl-3-methylimidazolium chloride (Omim), 1-Dodecyl-3-methylimidazolium chloride (Dmim), 1-Ethyl-3-methylimidazolium tetrafluoroborate (Emim), and 1-Hexyl-3-Methylimidazolium tetrafluoroborate (Hmim).

The concentration-response data include the cytotoxicity of eight compounds, two mixtures designed by eecr, and ten mixtures designed by udcr.

The fitting information of eight chemicals and a total of 12 mixtures.

**Usage**

```
data(cytotox)
```

**Format**

A list with concentration-response data of 8 chemicals, 2 eecr mixtures, 10 udcr mixtures, and associated fitting information.

Ni\$x a numeric vector of test concentrations

Ni\$y a numeric matrix of responses

Ni\$name test substances

Ni\$concNum the number of test concentrations

Ni\$tierNum the number of repetitions

Ni\$type type of test substance: single chemicals or mixtures

sgl\$model models used to fit the concentration-response data of individual chemicals

sgl\$param fitted coefficients of concentration-response curves

udcr.mix\$model models used to fit the concentration-response data of udcr mixtures

udcr.mix\$param fitted coefficients of the concentration-response curves corresponding to udcr.mix\$model

\$udcr.pct the proportion of individual chemicals in udcr mixtures

**Details**

Quantal responses[0, 1] are needed for curve fitting using the following six equaitons: i.e., Weibull, Logit, Hill, BCL, GL, BCW. The following equation could transform continous responses to quantal ones:

$$E = \frac{I_0 - I_i}{I_0}$$

where  $I_0$  is the average of controls for inhibition tests or the average of the maximum effect for stimulation tests and  $I_i$  the average effect of the  $i^{\text{th}}$  treatment.

**Source**

The cytotoxicity experiments were conducted in our lab

**Examples**

```
# example 1
## Retrieve the toxicity data of Ni on MCF-7.
cytotox$Ni

# example 2
## Retrieve the toxicity information of ten udcr mixtures on MCF-7.
cytotox$udcr.mix
```

---

DTcv	<i>critical value for Dunnett's test</i>
------	--

---

**Description**

DTcv provides the critical constants calculated based step-down Dunnett test procedure. Three significance level (0.01, 0.05, and 0.1) each with two alternative hypothesis ("U"=upper one-sided test; "B"=two-sided test) are supported.

**Usage**

```
data(DTcv)
```

**Format**

at most 30 treatments (1 : 30), and 35 degree of freedom(c(5 : 30, 40, 50, 60, 80, 100, 120, 200, 1000, 3000)).

DTcv a matrix of critical value for Dunnett's test

**Details**

```
> head(DTcv)
df p twoside.01 twoside.05 twoside.10 onside.01 onside.05 onside.10
[1,] 5 1 4.032 2.571 2.015 3.365 2.015 1.476
[2,] 5 2 4.627 3.030 2.433 3.900 2.440 1.873
[3,] 5 3 4.948 3.294 2.669 4.225 2.681 2.095
[4,] 5 4 5.218 3.474 2.831 4.434 2.848 2.245
[5,] 5 5 5.416 3.616 2.956 4.585 2.974 2.360
[6,] 5 6 5.538 3.727 3.055 4.723 3.080 2.451
df: degree of freedom; p: the number of treatment.
```

**Source**

The critical constants (store in DTcv) were calculated using step-down Dunnett test procedure( the cvSDDT funtion in R package DunnettTests).

---

ecaPred	<i>Mixture Effect Predicted by CA at Particular Concentration of a Mixture</i>
---------	--

---

### Description

According to the fitted concentration-response information of mixtures. The concentration (e.g., EC<sub>x</sub>) that causes certain effect in the mixture will be calculated. ecaPred will predict how much effect will be caused at EC<sub>x</sub> according to concentration addition. The individual concentration-responses should be fitted only based on the following six models: Hill, Weibull, Logit, BCW, BCL, and GL.

### Usage

```
ecaPred(effv, sgl, mix, pctMix, sav = FALSE)
```

### Arguments

effv	numeric vector with single or multiple effect values (0 ~ 1).
sgl	A list with sgl\$model and sgl\$param. sgl\$model is character vector of equations used to fit the concentration-response data of individual chemicals: Hill, Weibull, Logit, BCW, BCL, GL. sgl\$param is numeric matrix of fitting coefficients with rownames (equations) and colnames (Alpha, Beta, and Gamma). For equations with only two parameters, Gamma can be set as zero or any other numeric value.
mix	A list with mix\$model and mix\$param. mix\$model is character vector of equations used to fit the concentration-response data of mixtures: Hill, Weibull, Logit, BCW, BCL, GL. mix\$param is numeric matrix of fitting coefficients of mixtures' concentration-response data with rownames (selected equations) and colnames (Alpha, Beta, and Gamma). For equations with only two parameters, Gamma can be set as zero or any other numeric value.
pctMix	A numeric matrix, the concentration ratio (percent) of every component in the mixture.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

### Details

ecaPred calculate the effect concentrations based on the fitted concentration-response information of the mixture according to the input effects effv (e.g., 0.05 and 0.5). The concentration of individual component  $c_i$  is computed based on mixture's EC<sub>x</sub> and the proportion of component in the mixture  $p_i$ . Then the CA effect will be calculated based on the concentration addition.

### Value

A numeric matrix of predicted effects

**See Also**[eiaPred](#)**Examples**

```
## example
# predict the CA predicted response at the concentrations that cause 5%, 10%, 20%, and 50%
# effect of antibiotic mixtures
# each mixture contains eight components. Totally, there are 10 mixtures designed by the udcr.

sgl <- antibiotox$sgl
mix <- antibiotox$udcr.mix
pct <- antibiotox$udcr.pct
ecaPred(effv = c(0.05, 0.1, 0.20, 0.5), sgl, mix, pct)
```

ECx

*Effect Concentration Calculation for Sigmoidal Models***Description**

Effect concentrations are calculated at particular effects based on the fitting coefficients of 13 sigmoidal models.

**Usage**

```
ECx(model, param, effv, rtype = 'quantal', Scaled = TRUE, sav = FALSE)
```

**Arguments**

model	a character vector of equations:("Hill", "Hill_two", "Hill_three", "Hill_four", "Weibull", "Weibull_three", "Weibull_four", "Logit", "Logit_three", "Logit_four", "BCW(Box-Cox-Weibull)", "BCL(Box-Cox-Logit)", "GL(Generalized Logit)")
param	a numeric matrix of fitting coefficients with rownames (equations) and colnames (Alpha, Beta, Gamma, Delta, and Epsilon).
effv	a numeric vector with single or multiple effect values
rtype	the response type of endpoint: 'continuous' or 'quantal' data.
Scaled	only for 'continuous' data. To indicate if the effv is scaled by response ranges to 0~1 or not (default is TRUE).
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.



## Details

effect concentrations will be calculated with provided equations (model), associated fitting parameters (param), and effect levels (effv). For example, *effv* should be 0.5 if we want to calculate a concentration causes 50% effect.

The inverse functions of the six quantal sigmoidal equations are listed as follows:

inverse Hill\_two:

$$c = \beta E / (\alpha - E)$$

inverse Weibull:

$$c = 10^{(\ln(-\ln(1-E))-\alpha)/\beta}$$

inverse Logit:

$$c = 10^{(\ln(E/(1-E))-\alpha)/\beta}$$

inverse BCW:

$$c = ((\gamma/\beta)(\ln(-\ln(1-E)) - \alpha) + 1)^{1/\gamma}$$

inverse BCL:

$$c = ((\gamma/\beta)(-\ln((1-E)/E) - \alpha) + 1)^{1/\gamma}$$

inverse GL:

$$c = 10^{((-\ln((1/E)^{1/\gamma}-1)-\alpha)/\beta)}$$

where *E* is effect and *c* is the concentration.

## Value

<code>ecx</code>	a numeric vector of effect concentration(s)
<code>effvAbs</code>	absolute effect levels. Only for 'continuous' data with scaled <code>effv</code> . The corresponding absolute effect is calculated.

## References

Hill equation (biochemistry) [http://en.wikipedia.org/wiki/Hill\\_equation\\_\(biochemistry\)](http://en.wikipedia.org/wiki/Hill_equation_(biochemistry))  
Reference to `curveFit`

## Examples

```
## example 1
# calculate EC5 and EC50 of seven antibiotics on the photobacteria
model <- antibiotox$sgl$model
param <- antibiotox$sgl$param
effv <- c(0.05, 0.5)
ECx(model, param, effv = c(0.05, 0.50))

## example 2
# calculate EC5 and EC50 of four heavy metals and four ionic liquids on the MCF-7 cells
model <- cytotox$sgl$model
param <- cytotox$sgl$param
ECx(model, param, effv = c(0.05, 0.50), rtype = 'quantal')
```

---

eiaPred	<i>Mixture Effect Predicted by IA at Particular Concentration of a Mixture</i>
---------	--

---

### Description

According to the fitted concentration-response information of mixtures. The concentration (e.g., EC<sub>x</sub>) that causes certain effect in the mixture will be calculated. eiaPred will predict how much effect will be caused at those concentrations according to independent action. The individual concentration-responses should be fitted only based on the following six models: Hill, Weibull, Logit, BCW, BCL, and GL.

### Usage

```
eiaPred(effv, sgl, mix, pctMix, sav = FALSE)
```

### Arguments

effv	numeric vector with single or multiple effect values (0 ~ 1).
sgl	A list with sgl\$model and sgl\$param. sgl\$model is character vector of equations used to fit the concentration-response data of individual chemicals: Hill, Weibull, Logit, BCW, BCL, GL. sgl\$param is numeric matrix of fitting coefficients with rownames (selected equations) and colnames (Alpha, Beta, and Gamma). For equations with only two parameters, Gamma can be set as zero or any other numeric value.
mix	A list with mix\$model and mix\$param. mix\$model is character vector of equations used to fit the concentration-response data of mixtures: Hill, Weibull, Logit, BCW, BCL, GL. mix\$param is numeric matrix of fitting coefficients of mixtures' concentration-response data with rownames ( equations) and colnames (Alpha, Beta, and Gamma). For equations with two parameters, Gamma can be set as zero or any other numeric value.
pctMix	A numeric matrix, the concentration ratio (percent) of every component in the mixture.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

### Details

eiaPred calculate the effect concentrations based on the fitted concentration-response information of the mixture according to the input effects effv (e.g., 0.05 and 0.5). The concentration of individual component  $c_i$  is computed based on mixture's EC<sub>x</sub> and the proportion of component in the mixture  $p_i$ . Then the IA effect will be calculated based on the independent action.

### Value

A numeric matrix of predicted effects

**See Also**[ecaPred](#)**Examples**

```
## example 1
# predict the IA predicted response (cytotoxicity) at the concentrations that cause 10% and 50%
# effect of an mixture.
# each mixture contains eight components. Totally, there are 10 mixtures designed by the udcr.

sgl <- cytotox$sgl
mix <- cytotox$udcr.mix
pct <- cytotox$udcr.pct
eiaPred(effv = c(0.1, 0.5), sgl, mix, pct)

## example 2
# predict the IA predicted response at the concentrations that cause 5% and 50% effect
# of antibiotic mixtures.
# each mixture contains eight components. Totally, there are 2 mixtures designed by the eecr.

sgl <- antibiotox$sgl
mix <- antibiotox$eecr.mix
pct <- antibiotox$eecr.pct
eiaPred(effv = c(0.05, 0.5), sgl, mix, pct)

## example 2
# predict the IA predicted response at the concentrations that cause 5%, 10%, 20%, and
# 50% effect of antibiotic mixtures.
# each mixture contains eight components. Totally, there are 10 mixtures designed by the udcr.

sgl <- antibiotox$sgl
mix <- antibiotox$udcr.mix
pct <- antibiotox$udcr.pct
eiaPred(effv = c(0.05, 0.10, 0.20, 0.5), sgl, mix, pct)
```

---

**figPlot***Plotting concentration response curve*

---

**Description**

Plotting concentration response curves with/without confidence intervals.

**Usage**

```
figPlot(object, logT = TRUE, xlabel = "concentration (mol/L)", ylabel = "Response",
        ylimit, lgd = NULL)
```

**Arguments**

object	object of class curveFit.
logT	logarithm transformation on concentration: TRUE or FALSE(default if TRUE).
xlabel, ylabel	plot labels.
ylimit	range of the y axis.
lgd	legend of the plot.

**Details**

Plot the concentration response curves, experimental data, CI, and PI in one figure.

**Examples**

```
## example 1
#
x <- antibiotox$PAR$x
expr <- antibiotox$PAR$y
obj <- curveFit(x, expr, eq = 'Logit', rtype = 'quantal', param = c(26, 4), effv = c(0.05, 0.5))
figPlot(obj)

## example 2
#
x <- hormesis$HmimCl$x
rspn <- hormesis$HmimCl$y
obj <- curveFit(x, rspn, eq = 'Biphasic', param = c(-0.59, 0.001, 160, 0.05, 19),
               effv = c(0.05, 0.5), rtype = 'hormesis')
figPlot(obj, logT = TRUE)
```

---

gcaHill

---

*Mixture Toxicity Prediction Using GCA (Hill\_two)*


---

**Description**

Predict the mixture toxicity based on individual concentration-response information fitted by Hill\_two equation. An explicit formula for gca prediction were used instead of the dichotomy algorithm in gcaPred. Three optional mixture design methods are provided. One is the arbitrary concentration ratio (acr) for mixture components.

Users can deign random ratios for components in the mixture. Other two options are equal effect concentration ratio (eocr) and uniform design concentration ratio (udcr).

**Usage**

```
gcaHill(model, param, mixType, effv, refEffv = c(0.10, 0.50), rtype, sav = FALSE)
```

**Arguments**

model	character vector of equation names, just Hill_two
param	numeric matrix of fitting coefficients with rownames (equations) and colnames (Alpha, Beta).
mixType	experimental design of the mixture. acr: arbitrary concentration ratio; eecr: equal effect concentration ratio; udcr: uniform design concentration ratio.
effv	numeric vector with single or multiple (scaled) effect values (0 ~ 1).
refEffv	to determine the concentration ranges for predicting effect. Use scaled values (0 ~ 1).
rtype	the response type of endpoint: 'continuous' or 'quantal' data.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**Details**

The generalized concentration addition (GCA) model was proposed by Howard and Webster to predict mixtures containing partial agonists (Howard and Webster, 2009). Empirical data are used to fit concentration-response function, and then predict the mixture response using the inverse function.

$$E_{mix}^{GCA} = \frac{\sum_{i=1}^n \frac{\alpha_i c_i}{K_i}}{1 + \sum_{i=1}^n \frac{c_i}{K_i}}$$

where  $c_i$  is the concentration of component  $i$  in the mixture. Parameter  $\alpha_i$  and  $K_i$  are fitted coefficient of  $i^{th}$  component, which are the same as  $\beta$  and  $\alpha$  in Hill\_two equation. Right, the  $\alpha_i$  and  $K_i$  are corresponding to  $\beta$  and  $\alpha$  in Hill\_two equation.

**Value**

x	a series of concentrations
e	a series of effects caused by the concentrations (x) as predicted by gca
pct	the concentration ratio (percent) of every component in the mixture
uniTab	the uniform design table used to construct the mixture when mixType is udcr

**Note**

Only for concentration-response curves fitted by the Hill\_two equation in curveFit.

**References**

- Howard, G.J., Schlezinger, J.J., Hahn, M.E., Webster, T.F., 2010. Generalized Concentration Addition Predicts Joint Effects of Aryl Hydrocarbon Receptor Agonists with Partial Agonists and Competitive Antagonists. *Environ. Health Perspect.* 118, 666-672.
- Howard, G.J., Webster, T.F., 2009. Generalized concentration addition: A method for examining mixtures containing partial agonists. *J. Theor. Biol.* 259, 469-477.
- Hadrup, N., Taxvig, C., Pedersen, M., Nellemann, C., Hass, U., Vinggaard, A.M., 2013. Concentration addition, independent action and generalized concentration addition models for mixture effect prediction of sex hormone synthesis in vitro. *PLoS One* 8, e70490.

**See Also**[gcaPred](#)**Examples**

```

model <- c("Hill_two", "Hill_two", "Hill_two", "Hill_two")
param <- matrix(c(3.94e-5, 0.97, 0, 5.16e-4, 1.50, 0, 3.43e-6, 1.04, 0, 9.18e-6, 0.77, 0),
  nrow = 4, ncol = 3, byrow = TRUE)
rownames(param) <- c('Ni', 'Zn', 'Cu', 'Mn')
colnames(param) <- c('Alpha', 'Beta', 'Gamma')
## example 1
# using GCA to predict the mixtures designed by equal effect concentration ratio (eecr) at
# the effect concentration of EC05 and EC50
# the eecr mixture design is based on four heavy metals (four factors).
gcaHill(model, param, mixType = "eecr", effv = c(0.05, 0.5), rtype = 'continuous')

## example 2
# using GCA to predict the mixtures designed by uniform design concentration ratio (udcr)
# the udcr mixture design is based on four heavy metals (four factors).
# Seven levels (EC05, EC10, EC15, EC20, EC25, EC30, and EC50 ) are allocated in
# the uniform table
effv <- c(0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.50)
gcaHill(model, param, mixType = "udcr", effv, rtype = 'quantal')

## example 3
# using GCA to predict the mixtures designed by arbitrary concentration ratio (acr)
# the udcr mixture design is based on four heavy metals (four factors).
# the every component in the mixture shares exactly the same ratio (0.25)
effv <- c(0.25, 0.25, 0.25, 0.25)
gcaHill(model, param, mixType = "acr", effv)

```

gcaPred

*Mixture Toxicity Prediction Using GCA (General)***Description**

Predict the mixture toxicity based on individual concentration-response information. Thirteen monotonic(sigmoidal) models ("Hill", "Hill\_two", "Hill\_three", "Hill\_four", "Weibull", "Weibull\_three", "Weibull\_four", "Logit", "Logit\_three", "Logit\_four", "BCW(Box-Cox-Weibull)", "BCL(Box-Cox-Logit)", "GL(Generalized Logit)") are incorporated to construct the GCA equation. The dichotomy technique is used to solve the constructed equation. Three optional mixture design methods are provided. One is the arbitrary concentration ratio (acr) for mixture components. Users can arbitrarily deign a random ratio for each component in the mixture. Other two options are equal effect concentration ratio (eecr) and uniform design concentration ratio (udcr).

**Usage**

```
gcaPred(model, param, mixType, effv, refEffv, rtype, lb, ub, sav = FALSE)
```

**Arguments**

model	vector of equation names
param	numeric matrix of fitting coefficients with rownames (equation selected) and colnames (ALpha, Beta, and Gamma). For equations with two parameters, Gamma can be set as zero or any other numeric value.
mixType	experimental design of the mixture. acr: arbitrary concentration ratio; eecr: equal effect concentration ratio; udcr: uniform design concentration ratio.
effv	numeric vector with single or multiple (scaled) effect values (0 ~ 1).
refEffv	to determine the concentration ranges for predicting effect. Use scaled values (0 ~ 1).
lb	lower bound for solving constructed IA using dichotomy method (default is 1E-9).
ub	upper bound bound for solving constructed IA using dichotomy method(default is 9).
rtype	the response type of endpoint: 'continuous' or 'quantal' data.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**Details**

The generalized concentration addition (GCA) model was proposed by Howard and Webster to predict mixtures containing partial agonists (Howard and Webster, 2009).

$$\sum_{i=1}^n \frac{c_i}{f_i^{-1}(E)} = 1$$

Empirical data were used to fit concentration-response function, and then predict the mixture response using the inverse function. Previous studies used Hill\_two function to fit individual concentration response curves in the GCA prediction (Hadrup et al., 2013; Howard et al., 2010). Here, we incorporated thirteen functions to construct the GCA equation and the dichotomy technique is used to solve the constructed equation.

**Value**

x	a series of concentrations
e	a series of effects caused by the concentrations (x) as predicted by gca
pct	the concentration ratio (percent) of every component in the mixture
uniTab	the uniform design table used to construct the mixture when mixType is udcr

**References**

- Howard, G.J., Schlezinger, J.J., Hahn, M.E., Webster, T.F., 2010. Generalized Concentration Addition Predicts Joint Effects of Aryl Hydrocarbon Receptor Agonists with Partial Agonists and Competitive Antagonists. *Environ. Health Perspect.* 118, 666-672.
- Howard, G.J., Webster, T.F., 2009. Generalized concentration addition: A method for examining mixtures containing partial agonists. *J. Theor. Biol.* 259, 469-477.

**See Also**[gcaHill](#)**Examples**

```
## example 1
# using GCA to predict the mixtures designed by equal effect concentration ratio (eecr) at the
# effect concentration of EC50
# the eecr mixture design is based on seven antibiotics(seven factors).
model <- antibiotox$sgl$model
param <- antibiotox$sgl$param
refEffv <- c(0.1, 0.50, 0.80)
gcaPred(model, param, mixType = "eecr", effv = 0.5, refEffv, rtype = 'quantal')

## example 2
# using GCA to predict the mixtures designed by uniform design concentration ratio (udcr)
# the udcr mixture design is based on 2 antibiotics(2 factors) and
# three levels (EC05, EC20, and EC50 )
model <- antibiotox$sgl$model[1 : 2]
param <- antibiotox$sgl$param[1 : 2, ]
effv <- c(0.05, 0.20, 0.50)
refEffv <- c(0.1, 0.80)
gcaPred(model, param, mixType = "udcr", effv, refEffv, rtype = 'quantal')

## example 3
# using GCA to predict the mixtures designed by arbitrary concentration ratio (acr)
# the udcr mixture design is based on 2 heavy metals (2 factors).
# the every component in the mixture shares exactly the same ratio (0.5)
model <- cytotox$sgl$model[1 : 2]
param <- cytotox$sgl$param[1 : 2, ]
effv <- c(0.5, 0.5)
refEffv <- c(0.1, 0.80)
gcaPred(model, param, mixType = "acr", effv, refEffv, rtype = 'quantal')
```

getCI

*Calculating Confidence Intervals***Description**

calculating non-simultanous confidence intervals and prediction intervals

**Usage**

```
getCI(object, effv, Scaled = TRUE, sigLev = 0.05, sav = FALSE)
```

**Arguments**

object	object of class curveFit.
effv	numeric matrix of experimental responses with at least three replicates.



Scaled	indicating if effv was scaled or not(TRUE/FALSE) in continuous dose-response (rtype = 'continuous')
sigLev	significance level(default is 0.05).
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

### Details

The Delta method (Dybowski et al, 2001) is used to construct confidence intervals for predicted responses.

### Value

xmat	effect concentration(s) and corresponding CIs and PIs
emat	effect(s) and and corresponding CIs and PIs
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

### References

- Zhu, X.-W. and Chen, J.-Y. (2016). mixtox: An R Package for Mixture Toxicity Assessment. R Journal, 8(2).
- Dybowski, R. and Gant, V. (2001). Clinical applications of artificial neural networks. Cambridge University Press, Cambridge.
- Gryze, S. De, Langhans, I., and Vandebroek, M. (2007). Using the correct intervals for prediction: A tutorial on tolerance intervals for ordinary least-squares regression. Chemom. Intell. Lab. Syst., 87, 147-154.

### Examples

```
## example 1
x <- cytotox$Ni$x
rspn <- cytotox$Ni$y
obj <- curveFit(x, rspn, eq = 'Logit', param = c(12, 3), effv = c(0.05, 0.5), rtype = 'quantal')
getCI(obj, effv = c(0.05, 0.50))
```

---

hormesis

*Non-monotonic Concentration-response Data*


---

### Description

Two ionic liquids: 1-Octyl-3-methylimidazolium chloride (Omim) and 1-Hexyl-3-Methylimidazolium tetrafluoroborate (Hmim). Two organic solvents: Acetonitrile(ACN) and acetone.

The concentration-response data include the effect of these four compounds on firefly luciferase. Those concentration-responses were fitted using non-monotonic models.

**Usage**

```
data(hormesis)
```

**Format**

A list with non-monotonic concentration-responses of four chemicals and associated fitting information.

`OmimCl$x` a numeric vector of concentrations

`OmimCl$y` a numeric matrix of responses

`OmimCl$name` name of test substance

`OmimCl$concNum` the number of concentrations

`OmimCl$tierNum` the number of repetitions

`OmimCl$type` type of test substance

`sgl$model` model used to fit the concentration-response data

`sgl$param` fitted coefficients of those curves corresponding to `sgl$model`

`sgl$minx` numeric vector with multiple concentrations that induce maximum stimulation

`sgl$miny` the largest stimulation

**Details**

The non-monotonic concentration-responses need to be scaled into [0, 1] using the following equation:

$$E = \frac{I_0 - I_i}{I_0}$$

where  $I_0$  is the average of controls for inhibition test or the average of the maximum effect for the stimulation test and  $I_i$  the average effect of the  $i^{th}$  treatment.

**Source**

Experiments were conducted in our lab. Detailed description can be found in references

**References**

Zhu X-W, et.al. 2013. Modeling non-monotonic dose-response relationships: Model evaluation and hormetic quantities exploration. *Ecotoxicol. Environ. Saf.* 89:130-136.

**Examples**

```
#example 1
## Retrieve the toxicity data of acetonitrile on firefly luciferase.
hormesis$ACN

#example 2
## Retrieve the minx of OmimCl, HmimCl, ACN, and Acetone
hormesis$sgl$minx
```

iaPred

*Mixture Toxicity Prediction Based on Independent Action***Description**

Predict the mixture toxicity based on individual concentration-response information fitted only based on the following six models: Hill, Weibull, Logit, BCW, BCL, and GL. Three optional mixture design methods are provided: (1) arbitrary concentration ratio (acr), users can set an arbitrary proportion for each component in a mixture; (2) equal effect concentration ratio (eocr); (3) uniform design concentration ratio (udcr).

**Usage**

```
iaPred(model, param, mixType, effv, effPoints, lb = 1e-9, ub = 6, sav = FALSE)
```

**Arguments**

model	character vector of models: Hill, Weibull, Logit, BCW, BCL, GL
param	numeric matrix of fitting coefficients with row names (selected equations) and column names (Alpha, Beta, and Gamma). For equations with two parameters, Gamma can be set to zero or any other numeric value.
mixType	experimental design of the mixture. acr: arbitrary concentration ratio; eocr: equal effect concentration ratio; udcr: uniform design concentration ratio.
effv	numeric vector with single or multiple effect values
effPoints	numeric vector [0 ~ 1] to predict effect concentrations.
lb	lower bound for solving constructed IA using dichotomy method.
ub	upper bound bound for solving constructed IA using dichotomy method.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**Details**

IA is designed for mixtures of chemicals that have distinct mechanisms of action. The IA model is commonly defined as:

$$E(c_{mix}) = 1 - (1 - E(c_1))(1 - E(c_2)) \cdots (1 - E(c_n)) = 1 - \prod_{i=1}^n (1 - E(c_i))$$

where  $E(c_{mix})$  is the overall effect caused by  $c_{mix}$ , and  $E(c_i)$  is the effect elicited by  $c_i$  when applied individually. For a fitted function  $f_i$  based on the concentration-response data of the  $i^{th}$  component,  $E(c_i)$  is equal to  $f_i(c_i)$ . When  $E(c_{mix}) = x$ , the equation can be expressed as:

$$x\%_0 = 1 - \prod_{i=1}^n (1 - f_i(p_i(EC_{x,mix})))$$

This equation can be used to predict the combined effects of mixture-components based on IA. The dichotomy technique is used to solve the constructed equation.

**Value**

ia	a series of effect concentrations predicted by IA
e	a series of effects (effPoints) associated with the effect concentrations in ia
pct	the proportion of every component in a mixture
uniTab	the uniform design table to construct the mixture when mixType is 'udcr'

**Note**

Note that effv is dependent on the mixType.

If the mixType is acr, effv is supposed to be a vector with the ratio of each components and its length should be the same as the number of components. For instance, effv can be c(4, 1) if one wants to mix two compounds with a ratio of 4:1. One can also set effv as c(80, 20) or c(0.8, 0.2) or any other values with the same ratio as 4:1. The program will convert the ratio to a range of 0 to 100%.

If the mixType is eecr, effv is supposed to be the effect values. For instance, effv = c(0.5) means one mixture will be prepared and each of its components will be mixed in a ratio equal to EC50. More than one eecr mixtures can be achieved by assigning more effect values to effv, e.g., effv = c(0.05, 0.10, 0.5)

If the mixType is udcr, elements in effv are levels in a uniform table, the length of effv is the same as the number of runs. the number of runs should be consistent with the number of components in the uniform design.

**References**

Liang, Yi-zeng, Kai-tai Fang, and Qing-song Xu. 2001. Uniform Design and Its Applications in Chemistry and Chemical Engineering. *Chemometrics and Intelligent Laboratory Systems* 58(1):43-57.

Backhaus, T., Faust, M., 2012. Predictive environmental risk assessment of chemical mixtures: A conceptual framework. *Environmental Science and Technology*. 46, 2564-2573.

**See Also**

[caPred](#)

**Examples**

```
# data(cytotox)

## example 1
# using IA to predict the mixtures designed by equal effect concentration ratio (eecr) at the
# effect concentration of EC05 and EC50
# the eecr mixture design is based on four heavy metals and four ion liquids(eight factors).
model <- cytotox$sgl$model
param <- cytotox$sgl$param
iaPred(model, param, mixType = "eecr", effv = c(0.05, 0.5))

## example 2
# using IA to predict the mixtures designed by uniform design concentration ratio (udcr)
# the udcr mixture design is based on seven antibiotics (seven factors).
```

```

# five levels (EC05, EC10, EC20, EC30, and EC50 ) are allocated in the uniform table using the
# pseudo-level technique (Liang et al., 2001)
model <- antibiotox$sgl$model
param <- antibiotox$sgl$param
effv <- c(0.05, 0.05, 0.10, 0.10, 0.20, 0.20, 0.30, 0.30, 0.50, 0.50)
iaPred(model, param, mixType = "udcr", effv)

## example 3
# using IA to predict the mixtures designed by arbitrary concentration ratio (acr)
# the udcr mixture design is based on four antibiotics (four factors).
# the every component in the mixture shares exactly the same ratio (0.25)
model <- antibiotox$sgl$model[1 : 4]
param <- antibiotox$sgl$param[1 : 4, ]
effv <- c(0.25, 0.25, 0.25, 0.25)
iaPred(model, param, mixType = "acr", effv)

```

---

jacobian

*Jacobian Matrix Calculation*


---

## Description

calculating the Jacobian matrix for confidence intervals

## Usage

```
jacobian(eq, x, paraHat)
```

## Arguments

eq	equation
x	numeric vector of experimental concentrations
paraHat	fitted parameters

## Details

Jacobian matrix is the matrix of all first-order partial derivatives of a vector-valued function.

## Value

jac                    Jacobian matrix.

## References

[https://en.wikipedia.org/wiki/Jacobian\\_matrix\\_and\\_determinant](https://en.wikipedia.org/wiki/Jacobian_matrix_and_determinant)

## Examples

```
## example 1
x <- cytotox$Ni$x
rspn <- cytotox$Ni$y
obj <- curveFit(x, rspn, eq = 'Logit', param = c(12, 3), effv = c(0.05, 0.5), rtype = 'quantal')
jacobian('Logit', x, obj$p)
```

---

mixtox

*Dose-Response Curve Fitting and Mixture Toxicity Assessment*

---

## Description

Curve Fitting for monotonic(sigmoidal) & non-monotonic(J-shaped) concentration-response data. Prediction of mixture toxicity based on reference models such as 'concentration addition', 'independent action', and 'generalized concentration addition'.

## Details

Package: mixtox  
Type: Package  
Version: 1.3.3  
Date: 2022-06-19  
License: GPL-2

- (1) Curve fitting of concentration-responses based on 13 monotonic(sigmoidal) and 4 non-monotonic(J-shaped) models, goodness of fit, and calculation of confidence interval .
- (2) Experimental design for mixture toxicity. acr: arbitrary concentration ratio; eecr: equal effect concentration ratio; udcr: uniform design concentration ratio.
- (3) Mixture toxicity prediction based on reference models such as concentration addition (CA), independent action (IA), and generalized concentration addition (GCA).

## Author(s)

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## References

- Zhu, X.-W., Chen, J.-Y. (2016). mixtox: An R Package for Mixture Toxicity Assessment. R Journal, 8(2), 422-434.
- Zhu, X.-W., Ge, H.-L., Cao, Y.-B. (2016). Mixture cytotoxicity assessment of ionic liquids and heavy metals in MCF-7 cells using mixtox. Chemosphere, 163, 544-551.
- Zhu X-W, Liu S-S, Qin L-T, Chen F, Liu H-L. 2013. Modeling non-monotonic dose-response relationships: Model evaluation and hormetic quantities exploration. Ecotoxicology and Environmental

- Safety 89:130-136.
- Dunnett, C. W. 1964. New Tables for Multiple Comparisons with a Control. *Biometrics* 30(3):482-491.
- Hickernell, Fred J. 1996. A Generalized Discrepancy and Quadrature Error Bound. *Mathematics of Computation* 67(211):299-322.
- Howard, Gregory J., Jennifer J. Schlezinger, Mark E. Hahn, and Thomas F. Webster. 2010. Generalized Concentration Addition Predicts Joint Effects of Aryl Hydrocarbon Receptor Agonists with Partial Agonists and Competitive Antagonists. *Environmental Health Perspectives* 118(5):666-672.
- Scholze, M. et al. 2001. A General Best-Fit Method for Concentration-Response Curves and the Estimation of Low-Effect Concentrations. *Environmental Toxicology and Chemistry* 20(2):448-457.
- Wang, Yuan and Kai-Tai Fang. 1996. Uniform Design of Experiments with Mixtures. *Science in China Series A-Mathematics Physics Astronomy* 39(3):264-275.
- Backhaus, T., Faust, M., 2012. Predictive environmental risk assessment of chemical mixtures: A conceptual framework. *Environmental Science and Technology*. 46, 2564-2573.

nmECx

*Effect Concentration Calculation for J-shaped Models***Description**

Effect concentrations are calculated at particular effects based on the fitting coefficients of J-shaped Models.

**Usage**

```
nmECx(model, param, effv, minx, gap = -1e-6, sav = FALSE)
```

**Arguments**

model	a character vector of equations:("Brain_Consens", "BCV", "Biphasic", "Hill_five").
param	a numeric matrix of fitting coefficients with rownames (models) and colnames (ALpha, Beta, Gamma, Delta, and Epsilon).
effv	a numeric value (vector) with single or multiple effect values (miny ~ 1).
minx	a numeric value (vector) with single or multiple concentrations that induce maximum stimulation.
gap	theoretical response at the extreme low concentration predicted by a fitted model.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**Details**

effect concentrations will be calculated with provided equations(model), associated fitting parameters (param), and effects (effv). Effect (effv) should be a value(s) between miny ~ 1. For example, *effv* should be 0.5 if we want to calculate a concentration causes 50% effect. *minx* should be calculated by curveFit or tuneFit.

**Value**

ecx                    a numeric vector of effect concentration.

**References**

Zhu X-W, Liu S-S, Qin L-T, Chen F, Liu H-L. 2013. Modeling non-monotonic dose-response relationships: Model evaluation and hormetic quantities exploration. *Ecotoxicology and Environmental Safety* 89:130-136.

**See Also**

[CEx curveFit](#)

**Examples**

```
## example 1
# calculate ECL-10, ECR-10, EC5, and EC50 of the four hormetic curves
model <- hormesis$sgl$model
param <- hormesis$sgl$param
minx <- hormesis$sgl$minx
nmECx(model, param, effv = c(-0.10, 0.05, 0.50), minx)
```

---

 NOEC

*NOEC and LOEC Calculation*


---

**Description**

calculating the NOEC and LOEC using Dunnett's test

**Usage**

```
NOEC(x, rspn, blankC = FALSE, sigLev = 0.05, alternertive = 'B', sav = FALSE)
```

**Arguments**

x	a numeric vector of experimental concentrations
rspn	a numeric matrix of experimental responses with at least three replicates.
blankC	TRUE if rspn contains responses of blank control. The default is FALSE.
sigLev	the significance level for Dunnett's test. The default is 0.05.
alternertive	the alternative hypothesis: "U"=upper one-sided test; "B"=two-sided test(default).
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.



## Details

Dunnett's test (Dunnett, 1964) is performed to compare the treatment groups with the blank controls. The critical constants (store in DTcv) were calculated using step-down Dunnett test procedure. Three significance level (0.01, 0.05, and 0.1) are supported. ## Q: One dataset has four blank controls (C1, C2, C3, C4) and one treatment has three replicates (T1, T2, T3), ## another treatment has five replicates (R1, R2, R3, R4, R5), how to arrange the response matrix (rspn)? ## A: Label the missing values as NA, the response matrix (rspn) can be arranged as follows:

```
C1 C2 C3 C4 NA
T1 T2 T3 NA NA
R1 R2 R3 R4 R5
```

The adjustment of critical value for the unequal variances or unequal number of control and replicates is skipped in this program.

## Value

mat	information on Dunnett's test.DT: Dunnett's test values; DTcv: critical values for Dunnett's test at the significance level of sigLev.
noec	non-observed effect concentration (NOEC).
loec	least-observed effect concentration (LOEC).
sigLev	the significance level used in the Dunnett's test.
DF	the number of treatments and degree of freedom.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

## Note

x a vector of concentrations or levels in an ascending order. response matrix with at least 3 replicates. if the response matrix (rspn) contains blank controls (blankC = TRUE), the blank controls should be allocated in the first row of rspn matrix. missing values should be labeled as NA.

## References

Dunnett, C.W., 1964. New tables for multiple comparisons with a control. *Biometrics* 30, 482-491.

## Examples

```
## example 1
# calculate the NOEC and LOEC of heavy metal Ni(2+) on the MCF-7 cells at the default significance
# level of 0.05
x <- cytotox$Ni$x
rspn <- cytotox$Ni$y
NOEC(x, rspn)

## example 2
# calculate the NOEC and LOEC of Neomycin sulfate on the photobacteria at the significance
```

```
# level of 0.01
x <- antibiotox$NE0$x
rspn <- antibiotox$NE0$y
NOEC(x, rspn, sigLev = 0.01)
```

---

qq4res

*Residual Normal QQ Plot*

---

### Description

Producing a side-by-side QQ plot of the residuals against standard normal quantiles.

### Usage

```
qq4res(object, xlabel = 'Theoretical Quantiles', ylabel = 'Residuals',
        lgd = NULL)
```

### Arguments

object	object of class curveFit.
xlabel, ylabel	plot labels.
lgd	legend of the plot

### Details

The empirical quantiles are plotted against the quantiles of a standard normal distribution. If the residuals are from a normal distribution with mean 0, the points tend to fall along the reference line that has an intercept of 0 and a slope equal to the estimated standard deviation.

### Examples

```
## example 1
#
x <- antibiotox$PAR$x
expr <- antibiotox$PAR$y
obj <- curveFit(x, expr, eq = 'Logit', rtype = 'quantal', param = c(26, 4), effv = c(0.05, 0.5))
qq4res(obj)
```

---

readModel	<i>Read curve fitting information</i>
-----------	---------------------------------------

---

**Description**

Read curve fitting information in specific format from a txt or csv file

**Usage**

```
readModel(File)
```

**Arguments**

File            a txt or csv file with curve fitting information. a txt file should be tab or space separated; a csv file should be comma separated.

**Format**

a file contains curve fitting information  
The file extension needs to be .txt if it's a space or tab separated file.  
The file extension needs to be .csv if it's a comma-separated values file.

**Details**

The file needs three paramters (alpha beta gamma), just set gamma to 0 for models with only 2 parameters(e.g., Logit/Weibull)  
> The format of the file readModel can read:  
ID Model alpha beta gamma  
Cu Logit 9.91 22.15 0  
PAR Weibull 18.31 3.32 0

---

readTox	<i>Read dose-response data</i>
---------	--------------------------------

---

**Description**

Read dose-response data of specific format from a txt or csv file

**Usage**

```
readTox(File, light=TRUE)
```

**Arguments**

File	a txt or csv file with dose-response data. a txt file should be tab or space separated; a csv file should be comma separated.
light	TRUE: the file only contains doses and responses (light version); FALSE: the file also contains information about experiment design and data type (complex version)

**Format**

Dose-response data contains the following information: the name of compound, the number of doses, the repetitions, and the data type.

The file extension needs to be .txt if it's a space or tab separated file.

The file extension needs to be .csv if it's a comma-separated values file.

**Details**

> The light format of the file readTox can read:

```

conc tier1 tier2 tier3
2.50E-07 0.06 0.03 0.07
3.50E-07 0.04 0.07 0.04
5.34E-07 0.07 0.15 0.06
7.68E-07 0.16 0.14 0.10
1.13E-06 0.21 0.26 0.23
1.67E-06 0.34 0.30 0.31
2.50E-06 0.46 0.44 0.48
3.50E-06 0.52 0.59 0.61
5.34E-06 0.73 0.69 0.71
7.68E-06 0.79 0.67 0.78
1.13E-05 0.80 0.72 0.81
1.67E-05 0.82 0.80 0.82

```

> The complex format of the file readTox can read:

```

cu 12 3 type
ID conc tier1 tier2 tier3
1 2.50E-07 0.06 0.03 0.07
2 3.50E-07 0.04 0.07 0.04
3 5.34E-07 0.07 0.15 0.06
4 7.68E-07 0.16 0.14 0.10
5 1.13E-06 0.21 0.26 0.23
6 1.67E-06 0.34 0.30 0.31
7 2.50E-06 0.46 0.44 0.48
8 3.50E-06 0.52 0.59 0.61
9 5.34E-06 0.73 0.69 0.71
10 7.68E-06 0.79 0.67 0.78
11 1.13E-05 0.80 0.72 0.81
12 1.67E-05 0.82 0.80 0.82

```

---

`showEq`*List Requested Equations*

---

**Description**

Show the formula of different equations upto request.

**Usage**

```
showEq(eq)
```

**Arguments**

`eq`                    equation name to query

**Details**

Thirteen monotonic(sigmoidal) equations ("Hill", "Hill\_two", "Hill\_three", "Hill\_four", "Weibull", "Weibull\_three", "Weibull\_four", "Logit", "Logit\_three", "Logit\_four", "BCW(Box-Cox-Weibull)", "BCL(Box-Cox-Logit)", "GL(Generalized Logit)") and four non-monotonic(J-shaped) equations ("Brain\_Consens", "BCV", "Biphasic", "Hill\_five") are provided to fit concentration-response data.

**Value**

The formula of requested equations (with abbr.) will show up.

**References**

- Scholze, M. et al. 2001. A General Best-Fit Method for Concentration-Response Curves and the Estimation of Low-Effect Concentrations. *Environmental Toxicology and Chemistry* 20(2):448-457.
- Zhu X-W, et.al . 2013. Modeling non-monotonic dose-response relationships: Model evaluation and hormetic quantities exploration. *Ecotoxicol. Environ. Saf.* 89:130-136.
- Howard GJ, Webster TF. 2009. Generalized concentration addition: A method for examining mixtures containing partial agonists. *J. Theor. Biol.* 259:469-477.
- Spiess, A.-N., Neumeyer, N., 2010. An evaluation of R2 as an inadequate measure for nonlinear models in pharmacological and biochemical research: A Monte Carlo approach. *BMC Pharmacol.* 10, 11.
- Di Veroli GY, Fornari C, Goldlust I, Mills G, Koh SB, Bramhall JL, et al. 2015. An automated fitting procedure and software for dose-response curves with multiphasic features. *Scientific Report* 5: 14701.
- Gryze, S. De, Langhans, I., Vandebroek, M., 2007. Using the correct intervals for prediction: A tutorial on tolerance intervals for ordinary least-squares regression. *Chemom. Intell. Lab. Syst.* 87, 147-154.

**See Also**

[curveFit](#)

**Examples**

```
# example 1
## show Weibull model
showEq('Weibull')

# example 2
## show the name of all sigmoidal models
showEq('sigmoid')
```

---

staval

*Starting Values for 13 Sigmoidal and 4 Hormetic Models*


---

**Description**

providing starting values for function tuneFit.

**Usage**

```
data(staval)
```

**Format**

A list with starting values for 13 sigmoidal models and six hormetic models

staval\$Hill starting values for Hill model

staval\$GL starting values for generalized logit model

staval starting values for 13 sigmoidal and five hormetic models

**Details**

Thirteen monotonic(sigmoidal) models ("Hill", "Hill\_two", "Hill\_three", "Hill\_four", "Weibull", "Weibull\_three", "Weibull\_four", "Logit", "Logit\_three", "Logit\_four", "BCW(Box-Cox-Weibull)", "BCL(Box-Cox-Logit)", "GL(Generalized Logit)") and four non-monotonic(J-shaped) models ("Brain\_Consens", "BCV", "Biphasic", "Hill\_five")

**Examples**

```
# example 1
## Retrieve the starting values for Hill.
staval$Hill

# example 2
## Retrieve the starting values for Weibull.
staval$Weibull
```

tuneFit

*Find Optimal Starting values for Curve Fitting***Description**

Curve fitting is dependent on the package `minpack.lm`. This generic function first searches optimal starting values based on trial and error. The the concentration response data will be fitted using the optimal starting values. The statistics for goodness of fit is evaluated by the following statistics: coefficient of determination ( $R^2$ ), adjusted coefficient of determination ( $R_{adj}^2$ ), root mean squared error (RMSE), mean absolute error (MAE), Akaike information criterion (AIC), bias-corrected Akaike information criterion(AICc), and Bayesian information criterion (BIC). Thirteen sigmoidal models ("Hill", "Hill\_two", "Hill\_three", "Hill\_four", "Weibull", "Weibull\_three", "Weibull\_four", "Logit", "Logit\_three", "Logit\_four", "BCW(Box-Cox-Weibull)", "BCL(Box-Cox-Logit)", "GL(Generalized Logit)") and four J-shaped models ("Brain\_Consens", "BCV", "Biphasic", "Hill\_five") are provided to fit the concentration-response data.

**Usage**

```
tuneFit(conc, rspn, eq = 'Weibull', effv, rtype = 'quantal', rsq = 0.6, highBar = 5000,
bar = 1000, sav = FALSE)
```

**Arguments**

<code>conc</code>	a numeric vector (matrix) of experimental concentrations
<code>rspn</code>	a numeric vector (matrix) of responses corresponding to <code>conc</code> , it should have the same length (or rows and columns for matrix) as <code>conc</code> .
<code>eq</code>	models for curve fitting: "Hill", "Hill_two", "Hill_three", "Hill_four", "Weibull", "Weibull_three", "Weibull_four", "Logit", "Logit_three", "Logit_four", "BCW", "BCL", "GL", "Brain_Consens", "BCV", "Biphasic", "Hill_five".
<code>rtype</code>	the response type of endpoint: 'continuous' or 'quantal' data.
<code>effv</code>	numeric response to calculate effect concentration, scaled responses [0, 1].
<code>rsq</code>	r2 below which would be ignored.
<code>highBar</code>	if the number of starting values exceeds <code>highBar</code> , a random sample of starting values will be taken.
<code>bar</code>	the number of random samples.
<code>sav</code>	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**Details**

`tuneFit` provides high frequency trial and error approach to find appropriate starting values for users. It will deploy those starting values one by one until finding the right one. Function `tuneFit` can also be used to fit the concentration response data for a batch of chemicals and calculate corresponding effect concentration.

**Value**

sta                    goodness of fit statistics: ( $R^2$ ,  $R_{adj}^2$ , MAE, RMSE, AIC, AICc, and BIC)

**Note**

tuneFit will load the file staval.rda which contains hundreds of starting values for each of the sigmoidal and hormetic models. However, those starting values are also limited. Users are encouraged to send their fitted coefficients to us to extent the coverage of staval.

**Examples**

```
## example 1
# Fit the non-monotonic concentration-response data
# we'll get a fit with r2 of 0.740
x <- hormesis$OmimCl$x
expr <- hormesis$OmimCl$y
y <- rowMeans(expr)
tuneFit(x, y, eq = 'Biphasic')

## example 2
# Fit the non-monotonic concentration-response data
# use r2 (rsq) of 0.9, we'll get a fit with r2 of 0.989
# calculate the effect concentration that causes 5% inhibition
x <- hormesis$OmimCl$x
expr <- hormesis$OmimCl$y
y <- rowMeans(expr)
tuneFit(x, y, eq = 'Biphasic', effv = 0.05, rsq = 0.9)

## example 3
# Fit the concentration-response data of heavy metal Ni(2+) on MCF-7 cells.
# Calculate the concentration that causes 5% inhibition on the growth of MCF-7

x <- cytotox$Ni$x
expr <- cytotox$Ni$y
y <- rowMeans(expr)
tuneFit(x, y, eq = 'Logit', effv = 0.05)

## example 4
# Fit the concentration-response data of Paromomycin Sulfate (PAR) on photobacteria.
# Calculate the concentrations that cause 50% inhibition on the growth of photobacteria

x <- antibiotox$PAR$x
expr <- antibiotox$PAR$y
y <- rowMeans(expr)
tuneFit(x, y, eq = 'Logit', effv = 0.5)
```



## Description

The good lattice point method with a power generator was used to construct the uniform experimental tables. The centered L2-discrepancy (CD2) and the symmetric discrepancy algorithms (sd2) were employed to measure the uniformity and find the one with lowest discrepancy.

## Usage

```
unidTab(lev, fac, algo = "cd2", sav = FALSE)
```

## Arguments

lev	the number of runs (levels or pseudo-levels)
fac	the number of factors
algo	algorithms used to calculate the discrepancy. "cd2": the centered L2-discrepancy algorithm. "sd2": the symmetric discrepancy algorithm.
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

## Details

Uniform design (UD) was proposed by Fang et al (Acta Math Appl Sin 3:363-372 (1980)). An appropriate uniform design table is constructed according to the factor (the number mixture components) and level (the number of experiments need to run). Many methods can be used to construct the uniform table. In the past decades many methods have been proposed for constructing (nearly) uniform designs, such as the good lattice point (glp) method, the glp method with a power generator (pglp method) (Fang 1980; Fang and Wang 1994), the cutting method (Ma and Fang 2004), the optimization method (Winker and Fang 1998).

However, when  $s$  is large, the glp method has a large computational cost. And the pglp method has the lowest computation complexity among various methods in quasi-Monte Carlo methods and a good performance when  $n$  or  $n + 1$  is a prime number and  $s$  is small (Fang 1980; Fang and Wang 1994), while the pglp method may have a poor performance when  $s$  is large. Here, we choose the glp method with a power generator to construct the uniform table. The centered L2-discrepancy (cd2) is set as default over the symmetric discrepancy algorithm for its accuracy. The cd2 algorithm is defined as follows:

$$CD_2(P) = \left[ \left( \frac{13}{12} \right)^s - \frac{2^{1-s}}{n} \sum_{k=1}^n \prod_{i=1}^s \theta_{ki} + \frac{1}{n^2} \sum_{k,l=1}^n \prod_{i=1}^s \phi_{k,li} \right]^{\frac{1}{2}}$$

With the definition of  $\theta_{ki}$  and  $\phi_{k,li}$  as follows:

$$\theta_{ki} = 2 + \left| x_{ki} - \frac{1}{2} \right| - \left| x_{ki} - \frac{1}{2} \right|^2$$

$$\phi_{k,li} = 1 + \frac{1}{2} \left( \left| x_{ki} - \frac{1}{2} \right| + \left| x_{li} - \frac{1}{2} \right| - |x_{ki} - x_{li}| \right)$$

where  $n$ ,  $s$  are the number of runs (levels or multiple of levels) and the number of input variables (factors), respectively.

**Value**

T	the selected uniform table(s) . It may contain one or more uniform tables with the same discrepancy
D	the discrepancy of the constructed uniform table
sav	TRUE: save output to a default file; FALSE: output will not be saved; a custom file directory: save output to the custom file directory.

**References**

- Wang, Y., Fang, K.-T., 1996. Uniform design of experiments with mixtures. *Sci. China Ser. A-Mathematics Phys. Astron.* 39, 264-275.
- Hickernell, F.J., 1996. A generalized discrepancy and quadrature error bound. *Math. Comput.* 67, 299-322.

**Examples**

```
## example 1
# construct uniform table with 11 runs and 7 factors using the default centered L2-discrepancy
# algorithm
unidTab(11, 7)

## example 2
# construct uniform table with 37 runs and 13 factors using the symmetric discrepancy algorithm
unidTab(lev = 37, fac = 13, algo = "sd2")

## example 3
# construct uniform table with 37 runs and 13 factors using default centered L2-discrepancy
# algorithm
unidTab(lev = 37, fac = 13, algo = "cd2")
```

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