

# Package ‘OncoBayes2’

May 7, 2020

**Type** Package

**Title** Bayesian Logistic Regression for Oncology Dose-Escalation Trials

**Description** Bayesian logistic regression model with optional EXchangeability-NonEXchangeability parameter modelling for flexible borrowing from historical or concurrent data-sources. The safety model can guide dose-escalation decisions for adaptive oncology Phase I dose-escalation trials which involve an arbitrary number of drugs. Please refer to Neuenschwander et al. (2008) <doi:10.1002/sim.3230> and Neuenschwander et al. (2016) <doi:10.1080/19466315.2016.1174149> for details on the methodology.

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Rcpp (>= 0.12.0),  
methods

**Imports** assertthat (>= 0.2.1),  
checkmate,  
Formula,  
rstan (>= 2.19.3),  
rstantools (>= 2.0.0),  
bayesplot (>= 1.4.0),  
ggplot2 (>= 2.2.1),  
dplyr (>= 0.8.0),  
tibble,  
tidyr (>= 1.0.0),  
abind

**LinkingTo** StanHeaders (>= 2.19.2), rstan (>= 2.19.3), BH (>= 1.72.0), Rcpp (>= 0.12.0), RcppEigen (>= 0.3.3.3.0)

**License** GPL (>=3)

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**Suggests** rmarkdown,  
knitr,

testthat ( $\geq 2.0.0$ ),  
mvtnorm

**VignetteBuilder** knitr

**Biarch** true

**SystemRequirements** GNU make, pandoc ( $\geq 1.12.3$ ), pandoc-citeproc

**Encoding** UTF-8

**RoxygenNote** 7.1.0

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---

bind\_rows\_0*Bind rows of multiple data frames with zero fill*

---

**Description**

A version of bind\_rows out of dplyr that fills non-common columns with zeroes instead of NA. Gives an error if any of the input data contains NA already.

**Usage**

```
bind_rows_0(...)
```

**Arguments**

... Data frames to combine, passed into bind\_rows (see dplyr documentation)

**Examples**

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

library(tibble)

dose_info_A <- tibble(
  group_id = "hist_A",
  drug_A = 1
)

dose_info_B <- tibble(
  group_id = "hist_B",
  drug_B = 100 * (1:2)
)

bind_rows_0(dose_info_A, dose_info_B)

## Recover user set sampling defaults
options(.user_mc_options)
```

---

blrm\_exnex*Bayesian Logistic Regression Model for N-compounds with EXNEX*

---

**Description**

Bayesian Logistic Regression Model (BLRM) for N compounds using EXchangability and NonEX-changability (EXNEX) modeling.

**Usage**

```

blrm_exnex(
  formula,
  data,
  prior_EX_mu_mean_comp,
  prior_EX_mu_sd_comp,
  prior_EX_tau_mean_comp,
  prior_EX_tau_sd_comp,
  prior_EX_corr_eta_comp,
  prior_EX_mu_mean_inter,
  prior_EX_mu_sd_inter,
  prior_EX_tau_mean_inter,
  prior_EX_tau_sd_inter,
  prior_EX_corr_eta_inter,
  prior_is_EXNEX_inter,
  prior_is_EXNEX_comp,
  prior_EX_prob_comp,
  prior_EX_prob_inter,
  prior_NEX_mu_mean_comp,
  prior_NEX_mu_sd_comp,
  prior_NEX_mu_mean_inter,
  prior_NEX_mu_sd_inter,
  prior_tau_dist,
  iter = getOption("OncoBayes2.MC.iter", 2000),
  warmup = getOption("OncoBayes2.MC.warmup", 1000),
  thin = getOption("OncoBayes2.MC.thin", 1),
  init = getOption("OncoBayes2.MC.init", 0.5),
  chains = getOption("OncoBayes2.MC.chains", 4),
  cores = getOption("mc.cores", 1L),
  control = getOption("OncoBayes2.MC.control", list()),
  prior_PD = FALSE,
  verbose = FALSE
)

## S3 method for class 'blrmfit'
print(x, ..., prob = 0.95, digits = 2)

```

**Arguments**

formula	the model formula describing the linear predictors of the model. The lhs of the formula is a two-column matrix which are the number of occurred events and the number of times no event occurred. The rhs of the formula defines the linear predictors for the marginal models for each drug component, then the interaction model and at last the grouping and optional stratum factors of the models. These elements of the formula are separated by a vertical bar. The marginal models must follow a intercept and slope form while the interaction model must not include an interaction term. See the examples below for an example instantiation.
---------	--

data	optional data frame containing the variables of the model. If not found in data, the variables are taken from environment(formula).
prior_EX_mu_mean_comp, prior_EX_mu_sd_comp	Mean and sd for the prior on the mean parameters $\mu_i = (\mu_{\alpha i}, \mu_{\beta i})$ of each component. Two column matrix (intercept, log-slope) with one row per component.
prior_EX_tau_mean_comp, prior_EX_tau_sd_comp	Prior mean and sd for heterogeneity parameter $\tau_{si} = (\tau_{\alpha si}, \tau_{\beta si})$ of each stratum. If no differential discounting is required (i.e. if there is only one stratum $s = 1$ ), then it is a two-column matrix (intercept, log-slope) with one row per component. Otherwise it is a three-dimensional array whose first dimension indexes the strata, second dimension indexes the components, and third dimension of length two for (intercept, log-slope).
prior_EX_corr_eta_comp	Prior LKJ correlation parameter for each component given as numeric vector. If missing, then a 1 is assumed corresponding to a marginal uniform prior of the correlation.
prior_EX_mu_mean_inter, prior_EX_mu_sd_inter	Prior mean and sd for population mean parameters $\mu_{\eta k}$ of each interaction parameter. Vector of length equal to the number of interactions.
prior_EX_tau_mean_inter, prior_EX_tau_sd_inter	Prior mean and sd for heterogeneity parameter $\tau_{\eta sk}$ of each stratum. Matrix with one column per interaction and one row per stratum.
prior_EX_corr_eta_inter	Prior LKJ correlation parameter for interaction given as numeric. If missing, then a 1 is assumed corresponding to a marginal uniform prior of the correlations.
prior_is_EXNEX_inter	Defines if non-exchangability is admitted for a given interaction parameter. Logical vector of length equal to the number of interactions. If missing FALSE is assumed for all interactions.
prior_is_EXNEX_comp	Defines if non-exchangability is admitted for a given component. Logical vector of length equal to the number of components. If missing TRUE is assumed for all components.
prior_EX_prob_comp	Prior probability $p_{ij}$ for exchangability of each component per group. Matrix with one column per component and one row per group. Values must lie in [0-1] range.
prior_EX_prob_inter	Prior probability $p_{\eta kj}$ for exchangability of each interaction per group. Matrix with one column per interaction and one row per group. Values must lie in [0-1] range.
prior_NEX_mu_mean_comp, prior_NEX_mu_sd_comp	Prior mean $m_{ij}$ and sd $s_{ij} = \text{diag}(S_{ij})$ of each component for non-exchangable case. Two column matrix (intercept, log-slope) with one row per component. If missing set to the same prior as given for the EX part. It is required that the specification be the same across groups j.

prior_NEX_mu_mean_inter, prior_NEX_mu_sd_inter	Prior mean $m_{\eta_{kj}}$ and sd $s_{\eta_{kj}}$ for each interaction parameter for non-exchangable case. Vector of length equal to the number of interactions. If missing set to the same prior as given for the EX part.
prior_tau_dist	Defines the distribution used for heterogeneity parameters. Choices are 0=fixed to it's mean, 1=log-normal, 2=truncated normal.
iter	number of iterations (including warmup).
warmup	number of warmup iterations.
thin	period of saving samples.
init	positive number to specify uniform range on unconstrained space for random initialization. See <a href="#">stan</a> .
chains	number of Markov chains.
cores	number of cores for parallel sampling of chains.
control	additional sampler parameters for NuTS algorithm
prior_PD	Logical flag (defaults to FALSE) indicating if to sample the prior predictive distribution instead of conditioning on the data.
verbose	Logical flag (defaults to FALSE) controlling if additional output like stan progress is reported.
x	blrmfit object to print
...	not used in this function
prob	central probability mass to report, i.e. the quantiles 0.5-prob/2 and 0.5+prob/2 are displayed. Multiple central widths can be specified.
digits	number of digits to show

## Details

blrm\_exnex is a flexible function for Bayesian meta-analytic modeling of binomial count data. In particular, it is designed to model counts of the number of observed dose limiting toxicities (DLTs) by dose, for guiding dose-escalation studies in Oncology. To accommodate dose escalation over more than one agent, the dose may consist of combinations of study drugs, with any number of treatment components.

In the simplest case, the aim is to model the probability  $\pi$  that a patient experiences a DLT, by complementing the binomial likelihood with a monotone logistic regression

$$\text{logit } \pi(d) = \log \alpha + \beta t(d),$$

where  $\beta > 0$ . Most typically,  $d$  represents the dose, and  $t(d)$  is an appropriate transformation, such as  $t(d) = \log(d/d^*)$ . A joint prior on  $\theta = (\log \alpha, \log \beta)$  completes the model and ensures monotonicity  $\beta > 0$ .

Many extensions are possible. The function supports general combination regimens, and also provides framework for Bayesian meta-analysis of dose-toxicity data from multiple historical and concurrent sources.

For an example of a single-agent trial refer to [example-single-agent](#).

**Value**

The function returns a S3 object of type `blrmfit`.

**Methods (by generic)**

- `print`: print function.

**Combination of two treatments**

For a combination of two treatment components, the basic modeling framework is that the DLT rate  $\pi(d_1, d_2)$  is comprised of (1) a "no-interaction" baseline model  $\tilde{\pi}(d_1, d_2)$  driven by the single-agent toxicity of each component, and (2) optional interaction terms  $\gamma(d_1, d_2)$  representing synergy or antagonism between the drugs. On the log-odds scale,

$$\text{logit } \pi(d_1, d_2) = \text{logit } \tilde{\pi}(d_1, d_2) + \eta \gamma(d_1, d_2).$$

The "no interaction" part  $\tilde{\pi}(d_1, d_2)$  represents the probability of a DLT triggered by either treatment component acting *independently*. That is,

$$\tilde{\pi}(d_1, d_2) = 1 - (1 - \pi_1(d_1))(1 - \pi_2(d_2)).$$

In simple terms,  $P(\text{no DLT for combination}) = P(\text{no DLT for drug 1}) * P(\text{no DLT from drug 2})$ . To complete this part, the treatment components can then be modeled with monotone logistic regressions as before.

$$\text{logit } \pi_i(d_i) = \log \alpha_i + \beta_i t(d_i),$$

where  $t(d_i)$  is a monotone transformation of the doses, such as  $t(d_i) = \log(d_i/d_i^*)$ .

The inclusion of an interaction term  $\gamma(d_1, d_2)$  allows DLT rates above or below the "no-interaction" rate. The magnitude of the interaction term may also be made dependent on the doses (or other covariates) through regression. As an example, one could let

$$\gamma(d_1, d_2) = \frac{d_1}{d_1^*} \frac{d_2}{d_2^*}.$$

The specific functional form is specified in the usual notation for a design matrix. The interaction model must respect the constraint that whenever any dose approaches zero, then the interaction term must vanish as well. Therefore, the interaction model must not include an intercept term which would violate this consistency requirement. A dual combination example can be found in [example-combo2](#).

**General combinations**

The model is extended to general combination treatments consisting of  $N$  components by expressing the probability  $\pi$  on the logit scale as

$$\text{logit } \pi(d_1, \dots, d_N) = \text{logit} \left( 1 - \prod_{i=1}^N (1 - \pi_i(d_i)) \right) + \sum_{k=1}^K \eta_k \gamma_k(d_1, \dots, d_N),$$

Multiple drug-drug interactions among the  $N$  components are now possible, and are represented through the  $K$  interaction terms  $\gamma_k$ .

Regression models can be again be specified for each  $\pi_i$  and  $\gamma_k$ , such as

$$\text{logit } \pi_i(d_i) = \log \alpha_i + \beta_i t(d_i)$$

Interactions for some subset  $I(k) \subset \{1, \dots, N\}$  of the treatment components can be modeled with regression as well, for example on products of doses,

$$\gamma_k(d_1, \dots, d_N) = \prod_{i \in I(k)} \frac{d_i}{d_i^*}.$$

For example,  $I(k) = \{1, 2, 3\}$  results in the three-way interaction term

$$\frac{d_1}{d_1^*} \frac{d_2}{d_2^*} \frac{d_3}{d_3^*}$$

for drugs 1, 2, and 3.

For a triple combination example please refer to [example-combo3](#).

### Meta-analytic framework

Information on the toxicity of a drug may be available from multiple studies or sources. Furthermore, one may wish to stratify observations within a single study (for example into groups of patients corresponding to different geographic regions, or multiple dosing dose\_info corresponding to different schedules).

blrm\_exnex provides tools for robust Bayesian hierarchical modeling to jointly model data from multiple sources. An additional index  $j = 1, \dots, J$  on the parameters and observations denotes the  $J$  groups. The resulting model allows the DLT rate to differ across the groups. The general  $N$ -component model becomes

$$\text{logit } \pi_j(d_1, \dots, d_N) = \text{logit} \left( 1 - \prod_{i=1}^N (1 - \pi_{ij}(d_i)) \right) + \sum_{k=1}^K \eta_{kj} \gamma_k(d_1, \dots, d_N),$$

for groups  $j = 1, \dots, J$ . The component toxicities  $\pi_{ij}$  and interaction terms  $\gamma_k$  are modelled, as before, through regression. For example,  $\pi_{ij}$  could be a logistic regression on  $t(d_i) = \log(d_i/d_i^*)$  with intercept and log-slope  $\theta_{ij}$ , and  $\gamma_k$  regressed with coefficient  $\eta_{kj}$  on a product  $\prod_{i \in I(k)} (d_i/d_i^*)$  for some subset  $I(k)$  of components.

Thus, for  $j = 1, \dots, J$ , we now have group-specific parameters  $\theta_{ij} = (\log \alpha_{ij}, \log \beta_{ij})$  and  $\nu_j = (\eta_{1j}, \dots, \eta_{Kj})$  for each component  $i = 1, \dots, N$  and interaction  $k = 1, \dots, K$ .

The structure of the prior on  $(\theta_{i1}, \dots, \theta_{iJ})$  and  $(\nu_1, \dots, \nu_J)$  determines how much information will be shared across groups  $j$ . Several modeling choices are available in the function.



- *EX (Full exchangeability)*: One can assume the parameters are conditionally exchangeable given hyperparameters

$$\theta_{ij} \sim N(\mu_{\theta i}, \Sigma_{\theta i}),$$

independently across groups  $j = 1, \dots, J$  and treatment components  $i = 1, \dots, N$ . The covariance matrix  $\Sigma_{\theta i}$  captures the patterns of cross-group heterogeneity, and is parametrized with standard deviations  $\tau_{\theta i} = (\tau_{\alpha i}, \tau_{\beta i})$  and the correlation  $\rho_i$ . Similarly for the interactions, the fully-exchangeable model is

$$\nu_j \sim N(\mu_{\nu}, \Sigma_{\nu})$$

for groups  $j = 1, \dots, J$  and interactions  $k = 1, \dots, K$ , and the prior on the covariance matrix  $\Sigma_{\nu}$  captures the amount of heterogeneity expected in the interaction terms a-priori. The covariance is again parametrized with standard deviations  $(\tau_{\eta 1}, \dots, \tau_{\eta K})$  and its correlation matrix.

- *Differential discounting*: For one or more of the groups  $j = 1, \dots, J$ , larger deviations of  $\theta_{ij}$  may be expected from the mean  $\mu_i$ , or of the interactions  $\eta_{kj}$  from the mean  $\mu_{\eta, k}$ . Such differential heterogeneity can be modeled by mapping the groups  $j = 1, \dots, J$  to *strata* through  $s_j \in \{1, \dots, S\}$ , and modifying the model specification to

$$\theta_{ij} \sim N(\mu_{\theta i}, \Sigma_{\theta ij}),$$

where

$$\Sigma_{\theta ij} = \begin{pmatrix} \tau_{\alpha s_j i}^2 & \rho_i \tau_{\alpha s_j i} \tau_{\beta s_j i} \\ \rho_i \tau_{\alpha s_j i} \tau_{\beta s_j i} & \tau_{\beta s_j i}^2 \end{pmatrix}.$$

For the interactions, the model becomes

$$\nu_j \sim N(\mu_{\nu}, \Sigma_{\nu j}),$$

where the covariance matrix  $\Sigma_{\nu j}$  is modelled as stratum specific standard deviations  $(\tau_{\eta 1 s_j}, \dots, \tau_{\eta K s_j})$  and a stratum independent correlation matrix. Each stratum  $s = 1, \dots, S$  then corresponds to its own set of standard deviations  $\tau$  leading to different discounting per stratum. Independent priors are specified for the component parameters  $\tau_{\alpha si}$  and  $\tau_{\beta si}$  and for the interaction parameters  $\tau_{\eta sk}$  for each stratum  $s = 1, \dots, S$ . Inference for strata  $s$  where the prior is centered on larger values of the  $\tau$  parameters will exhibit less shrinkage towards the means,  $\mu_{\theta i}$  and  $\mu_{\nu}$  respectively.

- *EXNEX (Partial exchangeability)*: Another mechanism for increasing robustness is to introduce mixture priors for the group-specific parameters, where one mixture component is shared across groups, and the other is group-specific. The result, known as an EXchangeable-NonEXchangeable (EXNEX) type prior, has a form

$$\theta_{ij} \sim p_{\theta ij} N(\mu_{\theta i}, \Sigma_{\theta i}) + (1 - p_{\theta ij}) N(m_{\theta ij}, S_{\theta ij})$$

when applied to the treatment-component parameters, and

$$\nu_{kj} \sim p_{\nu kj} N(\mu_{\nu}, \Sigma_{\nu})_k + (1 - p_{\nu kj}) N(m_{\nu kj}, s_{\nu kj}^2)$$

when applied to the interaction parameters. The *exchangeability weights*  $p_{\theta ij}$  and  $p_{\nu kj}$  are fixed constants in the interval  $[0, 1]$  that control the degree to which inference for group  $j$  is informed by the exchangeable mixture components. Larger values for the weights correspond to greater exchange of information, while smaller values increase robustness in case of outlying observations in individual groups  $j$ .

## References

- Neuenschwander, B., Roychoudhury, S., & Schmidli, H. (2016). On the use of co-data in clinical trials. *Statistics in Biopharmaceutical Research*, 8(3), 345-354.
- Neuenschwander, B., Wandel, S., Roychoudhury, S., & Bailey, S. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharmaceutical statistics*, 15(2), 123-134.
- Neuenschwander, B., Branson, M., & Gsponer, T. (2008). Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in medicine*, 27(13), 2420-2439.
- Neuenschwander, B., Matano, A., Tang, Z., Roychoudhury, S., Wandel, S. Bailey, Stuart. (2014). A Bayesian Industry Approach to Phase I Combination Trials in Oncology. In *Statistical methods in drug combination studies* (Vol. 69). CRC Press.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

# fit an example model. See documentation for "combo3" example
example_model("combo3")

# print a summary of the prior
prior_summary(blrmfit, digits = 3)

# print a summary of the posterior (model parameters)
print(blrmfit)

# summary of posterior for DLT rate by dose for observed covariate levels
summ <- summary(blrmfit, interval_prob = c(0, 0.16, 0.33, 1))
print(cbind(hist_combo3, summ))

# summary of posterior for DLT rate by dose for new set of covariate levels
newdata <- expand.grid(
  stratum = "BID", group_id = "Combo",
  drug_A = 400, drug_B = 800, drug_C = c(320, 400, 600, 800),
  stringsAsFactors = FALSE
)
summ_pred <- summary(blrmfit, newdata = newdata, interval_prob = c(0, 0.16, 0.33, 1))
print(cbind(newdata, summ_pred))

# update the model after observing additional data
newdata$num_patients <- rep(3, nrow(newdata))
newdata$num_toxicities <- c(0, 1, 2, 2)
library(dplyr)
blrmfit_new <- update(blrmfit,
  data = rbind(hist_combo3, newdata) %>%
    arrange(stratum, group_id))

# updated posterior summary
summ_upd <- summary(blrmfit_new, newdata = newdata, interval_prob = c(0, 0.16, 0.33, 1))
print(cbind(newdata, summ_upd))
```

```
## Recover user set sampling defaults
options(.user_mc_options)
```

---

blrm\_formula\_linear     *Build a BLRM formula with linear interaction term in logit-space*

---

## Description

blrm\_formula\_linear is a convenience function for generating a formula for blrm\_trial and blrm\_exnex with an interaction of the form:

$$\eta \prod_{i=1}^N (d_i / d_i^*)$$

## Usage

```
blrm_formula_linear(ref_doses, max_interaction_level = 2)
```

## Arguments

ref\_doses            Numeric vector of reference doses with names corresponding to drug names

max\_interaction\_level  
                     Highest interaction order to consider [1 - Inf]. Default: 2

## Value

The function returns an object of class blrm\_formula.

## Examples

```
ref_doses <- c(drug_A=10, drug_B=20)

# can be used with blrm_trial
blrm_formula_linear(ref_doses)
```

---

blrm\_formula\_saturating

*Build a BLRM formula with saturating interaction term in logit-space*


---

### Description

blrm\_formula\_saturating is a convenience function for generating a formula for blrm\_trial and blrm\_exnex with an interaction of the form:

$$2\eta \frac{\prod_{i=1}^N (d_i/d_i^*)}{1 + \prod_{i=1}^N (d_i/d_i^*)}$$

### Usage

```
blrm_formula_saturating(ref_doses, max_interaction_level = 2)
```

### Arguments

ref\_doses            Numeric vector of reference doses with names corresponding to drug names  
max\_interaction\_level            Highest interaction order to consider [1 - Inf]. Default: 2

### Value

The function returns an object of class blrm\_formula.

### Examples

```
ref_doses <- c(drug_A=10, drug_B=20)

# can be used with blrm_trial
blrm_formula_saturating(ref_doses)
```

---

blrm\_trial

*Dose-Escalation Trials guided by Bayesian Logistic Regression Model*


---

### Description

blrm\_trial facilitates the conduct of dose escalation studies guided by Bayesian Logistic Regression Models (BLRM). While the blrm\_exnex only fits the BLRM model to data, the blrm\_trial function standardizes the specification of the entire trial design and provides various standardized functions for trial data accrual and derivation of model summaries needed for dose-escalation decisions.

**Usage**

```
blrm_trial(
  data,
  dose_info,
  drug_info,
  simplified_prior = FALSE,
  EXNEX_comp = TRUE,
  EX_prob_comp_hist = 1,
  EX_prob_comp_new = 0.8,
  EXNEX_inter = FALSE,
  EX_prob_inter = 0.8,
  formula_generator = blrm_formula_linear,
  interval_prob = c(0, 0.16, 0.33, 1),
  interval_max_mass = c(prob_underdose = 1, prob_target = 1, prob_overdose = 0.25),
  ...
)

## S3 method for class 'blrm_trial'
print(x, ...)
```

**Arguments**

data	dose-toxicity data available at design stage of trial
dose_info	specificaion of the dose levels as planned for the ongoing trial arms.
drug_info	specification of drugs used in trial arms.
simplified_prior	logical (defaults to FALSE) indicating whether a simplified prior should be employed based on the reference_p_dlt values provided in drug_info. <b>Warning:</b> The simplified prior will change between releases. Please read instructions below in the respective section for the simplified prior.
EXNEX_comp	logical (default to TRUE) indicating whether EXchangeable-NonEXchangeable priors should be employed for all component parameters
EX_prob_comp_hist	prior weight ([0, 1], default to 1) on exchangeability for the component parameters in groups representing historical data
EX_prob_comp_new	prior weight ([0, 1], default to 0.8) on exchangeability for the component parameters in groups representing new or concurrent data
EXNEX_inter	logical (default to FALSE) indicating whether EXchangeable-NonEXchangeable priors should be employed for all interaction parameters
EX_prob_inter	prior weight ([0, 1], defaults to 0.8) on exchangeability for the interaction parameters
formula_generator	formula generation function (see for example blrm_formula_linear or blrm_formula_saturating). The formula generator defines the employed interaction model.

`interval_prob` defines the interval probabilities reported in the standard outputs. Defaults to `c(0,0.16,0.33,1)`.

`interval_max_mass` named vector defining for each interval of the `interval_prob` vector a maximal admissible probability mass for a given dose level. Whenever the posterior probability mass in a given interval exceeds the threshold, then the Escalation With Overdose Control (EWOC) criterion is considered to be not fulfilled. Dose levels not fulfilling EWOC are ineligible for the next cohort of patients. The default restricts the overdose probability to less than 0.25.

`...` Additional arguments are forwarded to `blrm_exnex`, i.e. for the purpose of prior specification.

`x` `blrm_trial` object to print

## Details

`blrm_trial` constructs an object of class `blrm_trial` which stores the complete information about the study design of a dose-escalation trial. The study design is defined through the data sets (see sections below for a definition of the columns):

**data (historical data)** The data argument defines available dose-toxicity data at the design stage of the trial. Together with the prior of model (without any data) this defines the prior used for the trial conduct.

**dose\_info** Definition of the pre-specified dose levels explored in the ongoing trial arms. Thus, all dose-toxicity trial data added to the object is expected correspond to one of the dose levels in the pre-defined set of `dose_info`.

**drug\_info** Determines the drugs used in the trial, their units, reference dose level and optionally defines the expected probability for a toxicity at the reference dose.

Once the `blrm_trial` object is setup the complete trial design is specified and the model is fitted to the given data. This allows evaluation of the pre-specified dose levels of the trial design wrt. to safety, i.e. whether the starting dose of the trial fulfills the escalate with overdose criterion (EWOC) condition.

The `blrm_trial` trial can also be constructed in a 2-step process which allows for a more convenient specification of the prior since meta data like number of drugs and the like can be used. See the example section for details.

After setup of the initial `blrm_trial` object additional data is added through the use of the update method which has a `add_data` argument intended to add data from the ongoing trial. The summary function finally allows to extract various model summaries. In particular, the EWOC criterion can be calculated for the pre-defined dose levels of the trial.

## Value

The function returns an object of class `blrm_trial`.

## Methods (by generic)

- `print`: print function.

### Simplified prior

As a convenience for the user, a simplified prior can be specified whenever the `reference_p_dlt` column is present in the `drug_info` data set. However, the user is **warned** that the simplified prior will change in future releases of the package and thus **we strongly discourage the use of the simplified prior for setting up trial designs**. The functionality is intended to provide the user a quick start and as a starting point. The actually instantiated prior can be seen as demonstrated below in the examples.

### Input data

The data given to the `data` argument of `blrm_trial` is considered as the available at design stage of the trial. The collected input data thus does not necessarily need to have the same dose levels as the pre-specified `dose_info` for the ongoing trial(s). It's data columns must include, but are not limited to:

**group\_id** study

**stratum\_id** optional, only required for differential discounting of groups

**num\_patients** number of patients

**num\_toxicities** number of toxicities

**drug\_A** Columns for the dose of each treatment component, with column names matching the `drug_name` values specified in the `drug_info` argument of `blrm_trial`

### Drug info data

The drug information data-set defines drug properties. The fields included are:

**drug\_name** name of drug which is also used as column name for the dose

**dose\_ref** reference dose

**dose\_unit** units used for drug amounts

**reference\_p\_dlt** optional; if provided, allows setup of a simplified prior

### Dose info data

The `drug_info` data-set pre-specifies the dose levels of the ongoing trial. Thus, all data added to the `blrm_trial` through the `update` command must be consistent with the pre-defined dose levels as no other than those pre-specified ones can be explored in an ongoing trial.

**dose\_id** optional column which assigns a unique id to each `group_id`/dose combination. If not specified the column is internally generated.

**group\_id** study

**drug\_A** Columns for the dose of each treatment component, with column names matching the `drug_name` values specified in the `drug_info` argument of `blrm_trial`

## References

- Babb, J., Rogatko, A., & Zacks, S. (1998). Cancer phase I clinical trials: efficient dose escalation with overdose control. *Statistics in medicine*, 17(10), 1103-1120.
- Neuenschwander, B., Roychoudhury, S., & Schmidli, H. (2016). On the use of co-data in clinical trials. *Statistics in Biopharmaceutical Research*, 8(3), 345-354.

## See Also

Other blrm\_trial combo2 example: [dose\\_info\\_combo2](#), [drug\\_info\\_combo2](#), [example-combo2\\_trial](#)

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

# construct initial blrm_trial object from built-in example datasets
combo2_trial_setup <- blrm_trial(
  data = hist_combo2,
  dose_info = dose_info_combo2,
  drug_info = drug_info_combo2,
  simplified_prior = TRUE
)

# extract blrm_call to see setup of the prior as passed to blrm_exnex
summary(combo2_trial_setup, "blrm_exnex_call")

# Warning: The simplified prior will change between releases!
# please refer to the combo2_trial example for a complete
# example. You can obtain this example with
# ?example-combo2_trial
# or by running
# example_model("combo2_trial")

## Recover user set sampling defaults
options(.user_mc_options)
```

---

codata\_combo2

*Dataset: historical and concurrent data on a two-way combination*

---

## Description

One of two datasets from the application described in Neuenschwander et al (2016). In the study trial\_AB, the risk of DLT was studied as a function of dose for two drugs, drug A and drug B. Historical information on the toxicity profiles of these two drugs is available from single agent trials trial\_A and trial\_B. Another study IIT was run concurrently to trial\_AB, and studies the same combination. A second dataset hist\_combo2 is available from this example, which includes only the data from the single agent studies, prior to the initiation of trial\_AB and IIT.



**Usage**

```
codata_combo2
```

**Format**

A data frame with 20 rows and 5 variables:

**group\_id** study  
**drug\_A** dose of Drug A  
**drug\_B** dose of Drug B  
**num\_patients** number of patients  
**num\_toxicities** number of DLTs  
**cohort\_time** cohort number of patients

**References**

Neuenschwander, B., Roychoudhury, S., & Schmidli, H. (2016). On the use of co-data in clinical trials. *Statistics in Biopharmaceutical Research*, 8(3), 345-354.

**Examples**

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

dref <- c(300, 960)

num_comp <- 2 # two investigational drugs
num_inter <- 1 # one drug-drug interaction needs to be modeled
num_groups <- nlevels(codata_combo2$group_id) # no stratification needed
num_strata <- 1 # no stratification needed

blrmfit <- blrm_exnex(
  cbind(num_toxicities, num_patients - num_toxicities) ~
    1 + I(log(drug_A / dref[1])) |
    1 + I(log(drug_B / dref[2])) |
    0 + I(drug_A/dref[1] * drug_B/dref[2]) |
    group_id,
  data = codata_combo2,
  prior_EX_mu_mean_comp = matrix(
    c(logit(0.1), 0, # hyper-mean of (intercept, log-slope) for drug A
      logit(0.1), 0), # hyper-mean of (intercept, log-slope) for drug B
    nrow = num_comp,
    ncol = 2,
    byrow = TRUE
  ),
  prior_EX_mu_sd_comp = matrix(
    c(3.33, 1, # hyper-sd of mean mu for (intercept, log-slope) for drug A
      3.33, 1), # hyper-sd of mean mu for (intercept, log-slope) for drug B
    nrow = num_comp,
```

```

      ncol = 2,
      byrow = TRUE
    ),
    prior_EX_tau_mean_comp = matrix(
      c(log(0.25), log(0.125),
        log(0.25), log(0.125)),
      nrow = num_comp,
      ncol = 2,
      byrow = TRUE
    ),
    prior_EX_tau_sd_comp = matrix(
      c(log(4) / 1.96, log(4) / 1.96,
        log(4) / 1.96, log(4) / 1.96),
      nrow = num_comp,
      ncol = 2,
      byrow = TRUE
    ),
    prior_EX_mu_mean_inter = 0,
    prior_EX_mu_sd_inter = 1.121,
    prior_EX_tau_mean_inter = matrix(log(0.125), nrow = num_inter, ncol = num_strata),
    prior_EX_tau_sd_inter = matrix(log(4) / 1.96, nrow = num_inter, ncol = num_strata),
    prior_is_EXNEX_comp = rep(FALSE, num_comp),
    prior_is_EXNEX_inter = rep(FALSE, num_inter),
    prior_EX_prob_comp = matrix(1, nrow = num_groups, ncol = num_comp),
    prior_EX_prob_inter = matrix(1, nrow = num_groups, ncol = num_inter),
    prior_tau_dist = 1
  )
  ## Recover user set sampling defaults
  options(.user_mc_options)

```

---

dose\_info\_combo2

*Dataset: trial dose information for a dual-agent combination study*


---

## Description

The data set defines all pre-defined dose-levels which can be explored in the dual-agent example trial.

## Usage

```
dose_info_combo2
```

## Format

An object of class `tbl_df` (inherits from `tbl`, `data.frame`) with 33 rows and 4 columns.

**Details**

**group\_id** study

**drug\_A** drug A dose amount

**drug\_B** drug B dose amount

**dose\_id** unique id of record

**See Also**

Other blrm\_trial combo2 example: [blrm\\_trial\(\)](#), [drug\\_info\\_combo2](#), [example-combo2\\_trial](#)

---

drug\_info\_combo2

*Dataset: drug information for a dual-agent combination study*

---

**Description**

Data set describing the two drugs involved in the example for a dual-agent combination study.

**Usage**

```
drug_info_combo2
```

**Format**

A tibble with 2 rows (one per drug) and 4 columns:

**drug\_name** name of drug

**dose\_ref** reference dose

**dose\_unit** units used for drug amounts

**reference\_p\_dlt** a-priori probability for a DLT at the reference dose

**See Also**

Other blrm\_trial combo2 example: [blrm\\_trial\(\)](#), [dose\\_info\\_combo2](#), [example-combo2\\_trial](#)

example-combo2

*Two-drug combination example***Description**

Example using a combination of two experimental drugs.

**Details**

The following example is described in the reference Neuenschwander, B. et al (2016). The data are described in the help page for `codata_combo2`. In the study `trial_AB`, the risk of DLT was studied as a function of dose for two drugs, drug A and drug B. Historical information on the toxicity profiles of these two drugs was available from single agent trials `trial_A` and `trial_B`. Another study IIT was run concurrently to `trial_AB`, and studies the same combination.

The model described in Neuenschwander, et al (2016) is adapted as follows. For groups  $j = 1, \dots, 4$  representing each of the four sources of data mentioned above,

$$\text{logit } \pi_{1j}(d_1) = \log \alpha_{1j} + \beta_{1j} \log \left( \frac{d_1}{d_1^*} \right),$$

and

$$\text{logit } \pi_{2j}(d_2) = \log \alpha_{2j} + \beta_{2j} \log \left( \frac{d_2}{d_2^*} \right),$$

are logistic regressions for the single-agent toxicity of drugs A and B, respectively, when administered in group  $j$ . Conditional on the regression parameters  $\theta_{1j} = (\log \alpha_{1j}, \log \beta_{1j})$  and  $\theta_{2j} = (\log \alpha_{2j}, \log \beta_{2j})$ , the toxicity  $\pi_j(d_1, d_2)$  for the combination is modeled as the "no-interaction" DLT rate,

$$\tilde{\pi}_j(d_1, d_2) = 1 - (1 - \pi_{1j}(d_1))(1 - \pi_{2j}(d_2))$$

with a single interaction term added on the log odds scale,

$$\text{logit } \pi_j(d_1, d_2) = \text{logit } \tilde{\pi}_j(d_1, d_2) + \eta_j \frac{d_1}{d_1^*} \frac{d_2}{d_2^*}.$$

A hierarchical model across the four groups  $j$  allows dose-toxicity information to be shared through common hyperparameters.

For the component parameters  $\theta_{ij}$ ,

$$\theta_{ij} \sim \text{BVN}(\mu_i, \Sigma_i).$$

For the mean, a further prior is specified as

$$\mu_i = (\mu_{\alpha i}, \mu_{\beta i}) \sim \text{BVN}(\mathbf{m}_i, \mathbf{S}_i),$$

with  $\mathbf{m}_i = (\text{logit } 0.1, \text{logit } 1)$  and  $\mathbf{S}_i = \text{diag}(3.33^2, 1^2)$  for each  $i = 1, 2$ . For the standard deviations and correlation parameters in the covariance matrix,

$$\Sigma_i = \begin{pmatrix} \tau_{\alpha i}^2 & \rho_i \tau_{\alpha i} \tau_{\beta i} \\ \rho_i \tau_{\alpha i} \tau_{\beta i} & \tau_{\beta i}^2 \end{pmatrix},$$

the specified priors are  $\tau_{\alpha i} \sim \text{Log-Normal}(\log 0.25, ((\log 4)/1.96)^2)$ ,  
 $\tau_{\beta i} \sim \text{Log-Normal}(\log 0.125, ((\log 4)/1.96)^2)$ , and  $\rho_i \sim U(-1, 1)$  for  $i = 1, 2$ .  
 For the interaction parameters  $\eta_j$  in each group, the hierarchical model has

$$\eta_j \sim N(\mu_\eta, \tau_\eta^2),$$

for  $j = 1, \dots, 4$ , with  $\mu_\eta \sim N(0, 1.121^2)$  and  $\tau_\eta \sim \text{Log-Normal}(\log 0.125, ((\log 4)/1.96)^2)$ .

Below is the syntax for specifying this fully exchangeable model in `blrm_exnex`.

## References

Neuenschwander, B., Roychoudhury, S., & Schmidli, H. (2016). On the use of co-data in clinical trials. *Statistics in Biopharmaceutical Research*, 8(3), 345-354.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

dref <- c(300, 960)

num_comp <- 2 # two investigational drugs
num_inter <- 1 # one drug-drug interaction needs to be modeled
num_groups <- nlevels(codata_combo2$group_id) # no stratification needed
num_strata <- 1 # no stratification needed

blrmfit <- blrm_exnex(
  cbind(num_toxicities, num_patients - num_toxicities) ~
    1 + I(log(drug_A / dref[1])) |
    1 + I(log(drug_B / dref[2])) |
    0 + I(drug_A/dref[1] * drug_B/dref[2]) |
    group_id,
  data = codata_combo2,
  prior_EX_mu_mean_comp = matrix(
    c(logit(0.1), 0, # hyper-mean of (intercept, log-slope) for drug A
      logit(0.1), 0), # hyper-mean of (intercept, log-slope) for drug B
    nrow = num_comp,
    ncol = 2,
    byrow = TRUE
  ),
  prior_EX_mu_sd_comp = matrix(
    c(3.33, 1, # hyper-sd of mean mu for (intercept, log-slope) for drug A
      3.33, 1), # hyper-sd of mean mu for (intercept, log-slope) for drug B
    nrow = num_comp,
    ncol = 2,
    byrow = TRUE
  ),
  prior_EX_tau_mean_comp = matrix(
    c(log(0.25), log(0.125),
      log(0.25), log(0.125)),
```

```

      nrow = num_comp,
      ncol = 2,
      byrow = TRUE
    ),
    prior_EX_tau_sd_comp = matrix(
      c(log(4) / 1.96, log(4) / 1.96,
        log(4) / 1.96, log(4) / 1.96),
      nrow = num_comp,
      ncol = 2,
      byrow = TRUE
    ),
    prior_EX_mu_mean_inter = 0,
    prior_EX_mu_sd_inter = 1.121,
    prior_EX_tau_mean_inter = matrix(log(0.125), nrow = num_inter, ncol = num_strata),
    prior_EX_tau_sd_inter = matrix(log(4) / 1.96, nrow = num_inter, ncol = num_strata),
    prior_is_EXNEX_comp = rep(FALSE, num_comp),
    prior_is_EXNEX_inter = rep(FALSE, num_inter),
    prior_EX_prob_comp = matrix(1, nrow = num_groups, ncol = num_comp),
    prior_EX_prob_inter = matrix(1, nrow = num_groups, ncol = num_inter),
    prior_tau_dist = 1
  )
## Recover user set sampling defaults
options(.user_mc_options)

```

---

example-combo2\_trial    *Two-drug combination example using BLRM Trial*

---

## Description

Example using [blrm\\_trial](#) to guide the built-in two-drug combination study example.

## Details

[blrm\\_trial](#) is used to collect and store all relevant design information for the example. Subsequent use of the [update.blrm\\_trial](#) command allows convenient model fitting via [blrm\\_exnex](#). The [summary.blrm\\_trial](#) method allows exploration of the design and modeling results.

To run this example, use `example_model("combo2_trial")`. See [example\\_model](#).

## See Also

Other `blrm_trial` combo2 example: [blrm\\_trial\(\)](#), [dose\\_info\\_combo2](#), [drug\\_info\\_combo2](#)

## Examples

```

## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

```

```

library(tibble)
library(dplyr)
library(tidyr)

# Combo2 example using blrm_trial functionality

# construct initial blrm_trial object from built-in example datasets
combo2_trial_setup <- blrm_trial(
  data = hist_combo2,
  dose_info = dose_info_combo2,
  drug_info = drug_info_combo2,
  simplified_prior = FALSE
)

dims <- summary(combo2_trial_setup, "dimensionality")

# Fit the initial model with the historical data and fully specified prior
combo2_trial_start <- update(
  combo2_trial_setup,
  prior_EX_mu_mean_comp = matrix(
    c(logit(0.1), 0, # hyper-mean of (intercept, log-slope) for drug A
      logit(0.1), 0), # hyper-mean of (intercept, log-slope) for drug B
    nrow = dims$num_components,
    ncol = 2,
    byrow = TRUE
  ),
  prior_EX_mu_sd_comp = matrix(
    c(3.33, 1, # hyper-sd of mean mu for (intercept, log-slope) for drug A
      3.33, 1), # hyper-sd of mean mu for (intercept, log-slope) for drug B
    nrow = dims$num_components,
    ncol = 2,
    byrow = TRUE
  ),
  prior_EX_tau_mean_comp = matrix(
    c(log(0.25), log(0.125),
      log(0.25), log(0.125)),
    nrow = dims$num_components,
    ncol = 2,
    byrow = TRUE
  ),
  prior_EX_tau_sd_comp = matrix(
    c(log(4) / 1.96, log(4) / 1.96,
      log(4) / 1.96, log(4) / 1.96),
    nrow = dims$num_components,
    ncol = 2,
    byrow = TRUE
  ),
  prior_EX_mu_mean_inter = 0,
  prior_EX_mu_sd_inter = 1.121,
  prior_EX_tau_mean_inter = matrix(log(0.125),
                                     nrow = dims$num_interaction_terms,
                                     ncol = dims$num_strata),
  prior_EX_tau_sd_inter = matrix(log(4) / 1.96,

```

```

                                nrow = dims$num_interaction_terms,
                                ncol = dims$num_strata),
prior_is_EXNEX_comp = rep(FALSE, dims$num_components),
prior_is_EXNEX_inter = rep(FALSE, dims$num_interaction_terms),
prior_EX_prob_comp = matrix(1,
                                nrow = dims$num_groups,
                                ncol = dims$num_components),
prior_EX_prob_inter = matrix(1,
                                nrow = dims$num_groups,
                                ncol = dims$num_interaction_terms),
prior_tau_dist = 1
)

# print summary of prior specification
prior_summary(combo2_trial_start)

# summarize inference at observed dose levels
summary(combo2_trial_start, "data_prediction")

# summarize inference at specified dose levels
summary(combo2_trial_start, "dose_prediction")

# Update again with new data

# using update() with data argument supplied
# dem <- update(combo2_trial_start, data = codata_combo2)

# alternate way using update() with add_data argument for
# new observations only (those collected after the trial
# design stage).
new_data <- filter(codata_combo2, cohort_time > 0)

combo2_trial <- update(combo2_trial_start, add_data = new_data)

summary(combo2_trial, "data") # cohort_time is tracked
summary(combo2_trial, "data_prediction")
summary(combo2_trial, "dose_prediction")

rm(dims, new_data)

## Recover user set sampling defaults
options(.user_mc_options)

```

---

example-combo3

*Three-drug combination example*


---

## Description

Example using a combination of two experimental drugs, with EXNEX and differential discounting.



### Details

This dataset involves a hypothetical dose-escalation study of combination therapy with three treatment components. From two previous studies HistAgent1 and HistAgent2, historical data is available on each of the treatments as single-agents, as well as two of the two-way combinations. However, due to a difference in treatment schedule between the Combo study and the historical studies, a stratification (through stratum) is made between the groups to allow differential discounting of the alternate-schedule data. The association is as below.

group_id (j):	stratum (s_j):
Combo (1)	BID (1)
HistAgent1 (2)	QD (2)
HistAgent2 (3)	QD (2)

For additional robustness, EXNEX priors are used for all group-level treatment component and interaction parameters, to limit the amount of borrowing in case of significant heterogeneity across groups.

The complete model is as follows. As a function of doses  $d_1, d_2, d_3$ , the DLT rate in group  $j$  is, for  $j = 1, \dots, 3$ ,

$$\text{logit } \pi_j(d_1, d_2, d_3) = \text{logit} \left( 1 - \prod_{i=1}^3 (1 - \pi_{ij}(d_i)) \right) + \eta_j^{(12)} \frac{d_1}{d_1^*} \frac{d_2}{d_2^*} + \eta_j^{(13)} \frac{d_1}{d_1^*} \frac{d_3}{d_3^*} + \eta_j^{(23)} \frac{d_2}{d_2^*} \frac{d_3}{d_3^*} + \eta_j^{(123)} \frac{d_1}{d_1^*} \frac{d_2}{d_2^*} \frac{d_3}{d_3^*}.$$

In group  $j$  each treatment component  $i$  toxicity is modeled with logistic regression,

$$\text{logit } \pi_{ij}(d_i) = \log \alpha_{ij} + \beta_{ij} \log \left( \frac{d_i}{d_i^*} \right).$$

The intercept and log-slope parameters  $\theta_{ij} = (\log \alpha_{ij}, \log \beta_{ij})$  are given an EXNEX prior

$$\theta_{ij} \sim p_{ij} \text{BVN}(\mu_i, \Sigma_{ij}) + (1 - p_{ij}) \text{BVN}(\mathbf{m}_{ij}, \mathbf{S}_{ij}),$$

where the exchangeability weights are all  $p_{ij} = 0.9$ . The NEX parameters are set to  $\mathbf{m}_{ij} = (\text{logit}(1/3), \log 1)$ ,  $\mathbf{S}_{ij} = \text{diag}(2^2, 1^2)$  for all components  $i = 1, 2, 3$  and groups  $j = 1, 2, 3$ , and the EX parameters are modeled hierarchically. The mean of the exchangeable part has the distribution

$$\mu_i = (\mu_{\alpha i}, \mu_{\beta i}) \sim \text{BVN}(\mathbf{m}_i, \mathbf{S}_i),$$

with  $\mathbf{m}_i = (\text{logit}(1/3), \log 1)$  and  $\mathbf{S}_i = \text{diag}(2^2, 1^2)$  for each component  $i = 1, 2, 3$ . For differentially discounting data from each schedule (QD and BID), the covariance parameters for the exchangeable part

$$\Sigma_{ij} = \begin{pmatrix} \tau_{\alpha s_j i}^2 & \rho_i \tau_{\alpha s_j i} \tau_{\beta s_j i} \\ \rho_i \tau_{\alpha s_j i} \tau_{\beta s_j i} & \tau_{\beta s_j i}^2 \end{pmatrix}.$$

are allowed to vary across groups  $j$  depending on their mapping to strata  $s(j)$  as described above. For stratum  $s = 1$  (BID, which contains only the group  $j = 1$  (Combo)), the standard deviations are modeled as

$$\tau_{\alpha 1i} \sim \text{Log-Normal}(\log 0.25, (\log 4/1.96)^2)$$

$$\tau_{\beta 1i} \sim \text{Log-Normal}(\log 0.125, (\log 4/1.96)^2).$$

Whereas in stratum  $s = 2$  (QD, which contains the historical groups  $j = 2, 3$  (HistData1, HistData2)), the standard deviations are

$$\tau_{\alpha 2i} \sim \text{Log-Normal}(\log 0.5, (\log 4/1.96)^2)$$

$$\tau_{\beta 2i} \sim \text{Log-Normal}(\log 0.25, (\log 4/1.96)^2).$$

For all interaction parameters  $\eta_j^{(12)}$ ,  $\eta_j^{(13)}$ ,  $\eta_j^{(23)}$ , and  $\eta_j^{(123)}$  ( $j = 1, 2, 3$ ), the following prior is assumed:

$$\eta_j^{(\cdot)} \sim p_{\eta j}^{(\cdot)} \text{N}(\mu_{\eta}^{(\cdot)}, \tau_{\eta s_j}^{(\cdot)^2}) + (1 - p_{\eta j}^{(\cdot)}) \text{N}(m_{\eta j}^{(\cdot)}, s_{\eta j}^{(\cdot)^2}).$$

The exchangeability weights are  $p_{\eta j}^{(\cdot)} = 0.9$  for all interaction parameters and all groups. Here, for each  $\mu_{\eta}^{(12)}$ ,  $\mu_{\eta}^{(13)}$ ,  $\mu_{\eta}^{(23)}$ , and  $\mu_{\eta}^{(123)}$ , we take

$$\mu_{\eta}^{(\cdot)} \sim \text{N}(0, 1/2),$$

and for each  $\tau_{\eta s}^{(12)}$ ,  $\tau_{\eta s}^{(13)}$ ,  $\tau_{\eta s}^{(23)}$ , and  $\tau_{\eta s}^{(123)}$ ,

$$\tau_{\eta s}^{(\cdot)} \sim \text{Log-Normal}(\log(0.25), (\log 2/1.96)^2),$$

for both strata  $s = 1, 2$ . Furthermore,  $m_{\eta j}^{(\cdot)} = 0$  and  $s_{\eta j}^{(\cdot)^2} = 1/2$ , uniformly across all indices.

Below is the syntax for specifying this model in `blrm_exnex`.

## References

Neuenschwander, B., Roychoudhury, S., & Schmidli, H. (2016). On the use of co-data in clinical trials. *Statistics in Biopharmaceutical Research*, 8(3), 345-354.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## example combo3

library(abind)

dref <- c(500, 500, 1000)
num_comp <- 3
num_inter <- choose(3,2) + 1
num_strata <- nlevels(hist_combo3$stratum)
num_groups <- nlevels(hist_combo3$group_id)

blrmfit <- blrm_exnex(cbind(num_toxicities, num_patients-num_toxicities) ~
  1 + I(log(drug_A/dref[1])) |
  1 + I(log(drug_B/dref[2])) |
  1 + I(log(drug_C/dref[3])) |
  0
  + I(drug_A/dref[1] * drug_B/dref[2])
  + I(drug_A/dref[1] * drug_C/dref[3])
```

```

+ I(drug_B/dref[2] * drug_C/dref[3])
+ I(drug_A/dref[1] * drug_B/dref[2] * drug_C/dref[3]) |
stratum/group_id,
data=hist_combo3,
prior_EX_mu_mean_comp=matrix(c(logit(1/3), 0), nrow=num_comp, ncol=2, TRUE),
prior_EX_mu_sd_comp=matrix(c(2, 1), nrow=num_comp, ncol=2, TRUE),
prior_EX_tau_mean_comp=abind(matrix(log( c(0.25, 0.125))), nrow=num_comp, ncol=2, TRUE),
matrix(log(2*c(0.25, 0.125))), nrow=num_comp, ncol=2, TRUE),
along=0),
prior_EX_tau_sd_comp=abind(matrix(log(4)/1.96, nrow=num_comp, ncol=2, TRUE),
matrix(log(4)/1.96, nrow=num_comp, ncol=2, TRUE),
along=0),
prior_EX_mu_mean_inter=rep(0, num_inter),
prior_EX_mu_sd_inter=rep(sqrt(2)/2, num_inter),
prior_EX_tau_mean_inter=matrix(log(0.25) , nrow=num_strata, ncol=num_inter),
prior_EX_tau_sd_inter=matrix(log(2)/1.96, nrow=num_strata, ncol=num_inter),
prior_EX_prob_comp=matrix(0.9, nrow=num_groups, ncol=num_comp),
prior_EX_prob_inter=matrix(0.9, nrow=num_groups, ncol=num_inter),
## by default EXNEX is on for components and off for all interactions
prior_tau_dist=1,
prior_PD=FALSE
)
## Recover user set sampling defaults
options(.user_mc_options)

```

---

example-single-agent    *Single Agent Example*

---

## Description

Example using a single experimental drug.

## Details

The single agent example is described in the reference Neuenschwander, B. et al (2008). The data are described in the help page for `hist_SA`. In this case, the data come from only one study, with the treatment being only single agent. Hence the model specified does not involve a hierarchical prior for the intercept and log-slope parameters. The model described in Neuenschwander, et al (2008) is adapted as follows:

$$\text{logit } \pi(d) = \log \alpha + \beta \log \left( \frac{d}{d^*} \right),$$

where  $d^* = 250$ , and the prior for  $\theta = (\log \alpha, \log \beta)$  is

$$\theta \sim N(\mathbf{m}, \mathbf{S}),$$

and  $\mathbf{m} = (\text{logit } 0.5, \log 1)$  and  $\mathbf{S} = \text{diag}(2^2, 1^2)$  are constants.

In the `blrm_exnex` framework, in which the prior must be specified as a hierarchical model  $\theta \sim N(\mu, \Sigma)$  with additional priors on  $\mu$  and  $\Sigma$ , the simple prior distribution above is accomplished by fixing the diagonal elements  $\tau_\alpha^2$  and  $\tau_\beta^2$  of  $\Sigma$  to zero, and taking

$$\mu \sim N(m, S).$$

The arguments `prior_tau_dist` and `prior_EX_tau_mean_comp` as specified below ensure that the  $\tau$ 's are fixed at zero.

## References

Neuenschwander, B., Branson, M., & Gsponer, T. (2008). Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in medicine*, 27(13), 2420-2439.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## Example from Neuenschwander, B., et al. (2009). Stats in Medicine

num_comp <- 1 # one investigational drug
num_inter <- 0 # no drug-drug interactions need to be modeled
num_groups <- nlevels(hist_SA$group_id) # no stratification needed
num_strata <- 1 # no stratification needed

dref <- 50

## Since there is no prior information the hierarchical model
## is not used in this example by setting tau to (almost) 0.
blrmfit <- blrm_exnex(
  cbind(num_toxicities, num_patients - num_toxicities) ~
    1 + log(drug_A / dref) |
    0 |
    group_id,
  data = hist_SA,
  prior_EX_mu_mean_comp = matrix(
    c(logit(1/2), # mean of intercept on logit scale
      log(1)), # mean of log-slope on logit scale
    nrow = num_comp,
    ncol = 2
  ),
  prior_EX_mu_sd_comp = matrix(
    c(2, # sd of intercept
      1), # sd of log-slope
    nrow = num_comp,
    ncol = 2
  ),
  ## Here we take tau as known and as zero.
  ## This disables the hierarchical prior which is
```

```

## not required in this example as we analyze a
## single trial.
prior_EX_tau_mean_comp = matrix(
  c(0, 0),
  nrow = num_comp,
  ncol = 2
),
prior_EX_tau_sd_comp = matrix(
  c(1, 1),
  nrow = num_comp,
  ncol = 2
),
prior_EX_prob_comp = matrix(1, nrow = num_comp, ncol = 1),
prior_tau_dist = 0,
prior_PD = FALSE
)
## Recover user set sampling defaults
options(.user_mc_options)

```

---

example\_model

*Runs example models*


---

## Description

Runs example models

## Usage

```
example_model(topic, envir = parent.frame(), silent = FALSE)
```

## Arguments

topic	example to run
envir	environment which the example is loaded into. Defaults to the caller environment.
silent	logical controlling if execution is run silently (defaults to FALSE)

## Value

When topic is not specified a list of all possible topics is return. Whenever a valid topic is specified, the function inserts the example into the environment given and returns (invisibly) the updated environment.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## get a list of available examples
example_model()

## run 3 component example
example_model("combo3")

## Recover user set sampling defaults
options(.user_mc_options)
```

---

hist_combo2	<i>Dataset: historical data on two single-agents to inform a combination study</i>
-------------	--

---

## Description

One of two datasets from the application described in Neuenschwander et al (2016). The risk of DLT is to be studied as a function of dose for two drugs, drug A and drug B. Historical information on the toxicity profiles of these two drugs is available from single agent trials `trial_A` and `trial_B`. A second dataset `codata_combo2` is available from this application, which includes additional dose-toxicity data from `trial_AB` and IIT of the combination of Drugs A and B.

## Usage

```
hist_combo2
```

## Format

A tibble with 11 rows and 5 variables:

**group\_id** study  
**drug\_A** dose of Drug A  
**drug\_B** dose of Drug B  
**num\_patients** number of patients  
**num\_toxicities** number of DLTs  
**cohort\_time** cohort number of patients

## References

Neuenschwander, B., Roychoudhury, S., & Schmidli, H. (2016). On the use of co-data in clinical trials. *Statistics in Biopharmaceutical Research*, 8(3), 345-354.

hist\_combo3

*Dataset: historical and concurrent data on a three-way combination***Description**

This dataset involves a hypothetical dose-escalation study of combination therapy with three treatment components. From two previous studies HistAgent1 and HistAgent2, historical data is available on each of the treatments as single-agents, as well as two of the two-way combinations. However, due to a difference in treatment schedule between the Combo study and the historical studies, a stratification (through stratum) is made between the groups to allow differential discounting of the alternate-dose data.

**Usage**

hist\_combo3

**Format**

A data frame with 18 rows and 7 variables:

**group\_id** study  
**drug\_A** dose of Drug A  
**drug\_B** dose of Drug B  
**drug\_C** dose of Drug C  
**num\_patients** number of patients  
**num\_toxicities** number of DLTs  
**stratum** stratum for group\_id's used for differential discounting

**Examples**

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## example combo3

library(abind)

dref <- c(500, 500, 1000)
num_comp <- 3
num_inter <- choose(3,2) + 1
num_strata <- nlevels(hist_combo3$stratum)
num_groups <- nlevels(hist_combo3$group_id)

blrmfit <- blrm_exnex(cbind(num_toxicities, num_patients-num_toxicities) ~
  1 + I(log(drug_A/dref[1])) |
  1 + I(log(drug_B/dref[2])) |
```

```

      1 + I(log(drug_C/dref[3])) |
      0
    + I(drug_A/dref[1] * drug_B/dref[2])
    + I(drug_A/dref[1] * drug_C/dref[3])
    + I(drug_B/dref[2] * drug_C/dref[3])
    + I(drug_A/dref[1] * drug_B/dref[2] * drug_C/dref[3]) |
    stratum/group_id,
    data=hist_combo3,
    prior_EX_mu_mean_comp=matrix(c(logit(1/3), 0), nrow=num_comp, ncol=2, TRUE),
    prior_EX_mu_sd_comp=matrix(c(2, 1), nrow=num_comp, ncol=2, TRUE),
    prior_EX_tau_mean_comp=abind(matrix(log( c(0.25, 0.125)), nrow=num_comp, ncol=2, TRUE),
    matrix(log(2*c(0.25, 0.125)), nrow=num_comp, ncol=2, TRUE),
    along=0),
    prior_EX_tau_sd_comp=abind(matrix(log(4)/1.96, nrow=num_comp, ncol=2, TRUE),
    matrix(log(4)/1.96, nrow=num_comp, ncol=2, TRUE),
    along=0),
    prior_EX_mu_mean_inter=rep(0, num_inter),
    prior_EX_mu_sd_inter=rep(sqrt(2)/2, num_inter),
    prior_EX_tau_mean_inter=matrix(log(0.25) , nrow=num_strata, ncol=num_inter),
    prior_EX_tau_sd_inter=matrix(log(2)/1.96, nrow=num_strata, ncol=num_inter),
    prior_EX_prob_comp=matrix(0.9, nrow=num_groups, ncol=num_comp),
    prior_EX_prob_inter=matrix(0.9, nrow=num_groups, ncol=num_inter),
    ## by default EXNEX is on for components and off for all interactions
    prior_tau_dist=1,
    prior_PD=FALSE
  )
## Recover user set sampling defaults
options(.user_mc_options)

```

hist\_SA

*Single-agent example***Description**

Example data from the application in Neuenschwander, et. al. 2008, from an "open-label, multicenter, non-comparative, dose-escalation cancer trial to characterize the safety, tolerability, and pharmacokinetic profile of a drug and to determine its MTD."

**Usage**

```
hist_SA
```

**Format**

A data frame with 5 rows and 4 variables:

**group\_id** study

**drug\_A** dose

**num\_patients** number of patients

**num\_toxicities** number of events



## References

Neuenschwander, B., Branson, M., & Gsponer, T. (2008). Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in medicine*, 27(13), 2420-2439.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## Example from Neuenschwander, B., et al. (2009). Stats in Medicine

num_comp <- 1 # one investigational drug
num_inter <- 0 # no drug-drug interactions need to be modeled
num_groups <- nlevels(hist_SA$group_id) # no stratification needed
num_strata <- 1 # no stratification needed

dref <- 50

## Since there is no prior information the hierarchical model
## is not used in this example by setting tau to (almost) 0.
blrmfit <- blrm_exnex(
  cbind(num_toxicities, num_patients - num_toxicities) ~
    1 + log(drug_A / dref) |
    0 |
    group_id,
  data = hist_SA,
  prior_EX_mu_mean_comp = matrix(
    c(logit(1/2), # mean of intercept on logit scale
      log(1)), # mean of log-slope on logit scale
    nrow = num_comp,
    ncol = 2
  ),
  prior_EX_mu_sd_comp = matrix(
    c(2, # sd of intercept
      1), # sd of log-slope
    nrow = num_comp,
    ncol = 2
  ),
  ## Here we take tau as known and as zero.
  ## This disables the hierarchical prior which is
  ## not required in this example as we analyze a
  ## single trial.
  prior_EX_tau_mean_comp = matrix(
    c(0, 0),
    nrow = num_comp,
    ncol = 2
  ),
  prior_EX_tau_sd_comp = matrix(
    c(1, 1),
    nrow = num_comp,
```

```

      ncol = 2
    ),
    prior_EX_prob_comp = matrix(1, nrow = num_comp, ncol = 1),
    prior_tau_dist = 0,
    prior_PD = FALSE
  )
  ## Recover user set sampling defaults
  options(.user_mc_options)

```

---

lodds

*Logit (log-odds) and inverse-logit function.*


---

### Description

Calculates the logit (log-odds) and inverse-logit.

### Usage

```
logit(mu)
```

```
inv_logit(eta)
```

### Arguments

mu	A numeric object with probabilities, with values in the in the range [0,1]. Missing values (NAs) are allowed.
eta	A numeric object with log-odds values, with values in the range [-Inf,Inf]. Missing values (NAs) are allowed.

### Details

Values of mu equal to 0 or 1 will return -Inf or Inf respectively.

### Value

A numeric object of the same type as mu and eta containing the logits or inverse logit of the input values. The logit and inverse transformation equates to

$$\text{logit}(\mu) = \log(\mu/(1 - \mu))$$

$$\text{logit}^{-1}(\eta) = \exp(\eta)/(1 + \exp(\eta)).$$

### Examples

```

logit(0.2)
inv_logit(-1.386)

```

---

nsamples.blrmfit	<i>Return the number of posterior samples</i>
------------------	---

---

**Description**

Return the number of posterior samples

**Usage**

```
## S3 method for class 'blrmfit'
nsamples(object, ...)
```

**Arguments**

object	fitted model object
...	not used in this function

**Examples**

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## run single-agent analysis which defines blrmfit model object
example_model("single_agent")

nsamples(blrmfit)

## Recover user set sampling defaults
options(.user_mc_options)
```

---

OncoBayes2	<i>OncoBayes2</i>
------------	-------------------

---

**Description**

Bayesian logistic regression model with optional EXchangeability-NonEXchangeability parameter modelling for flexible borrowing from historical or concurrent data-sources. The safety model can guide dose-escalation decisions for adaptive Oncology phase I dose-escalation trials which involve an arbitrary number of drugs.

## Global Options

Option	Default	Description
OncoBayes2.MC.warmup	1000	MCMC warmup iterations
OncoBayes2.MC.iter	2000	total MCMC iterations
OncoBayes2.MC.chains	4	MCMC chains
OncoBayes2.MC.thin	1	MCMC thinning
OncoBayes2.MC.control	<code>list(adapt_delta=0.99, stepsize=0.1)</code>	sets control argument for Stan call
OncoBayes2.abbreviate.min	0	Minimal length of variable names when abbreviating variable names. The default 0 disables abbreviation.

## References

- Neuenschwander, B., Roychoudhury, S., & Schmidli, H. (2016). On the use of co-data in clinical trials. *Statistics in Biopharmaceutical Research*, 8(3), 345-354.
- Neuenschwander, B., Wandel, S., Roychoudhury, S., & Bailey, S. (2016). Robust exchangeability designs for early phase clinical trials with multiple strata. *Pharmaceutical statistics*, 15(2), 123-134.
- Neuenschwander, B., Branson, M., & Gsponer, T. (2008). Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in medicine*, 27(13), 2420-2439.
- Neuenschwander, B., Matano, A., Tang, Z., Roychoudhury, S., Wandel, S. Bailey, Stuart. (2014). A Bayesian Industry Approach to Phase I Combination Trials in Oncology. In *Statistical methods in drug combination studies* (Vol. 69). CRC Press.
- Stan Development Team (2019). RStan: the R interface to Stan. R package version 2.19.2. <https://mc-stan.org>

---

posterior\_interval.blrmfit

*Posterior intervals*

---

## Description

Posterior intervals of all model parameters.

## Usage

```
## S3 method for class 'blrmfit'
posterior_interval(object, prob = 0.95, ...)
```

**Arguments**

object	fitted model object
prob	central probability mass to report, i.e. the quantiles $0.5 - \text{prob}/2$ and $0.5 + \text{prob}/2$ are displayed. Multiple central widths can be specified.
...	not used in this function

**Details**

Reports the quantiles of posterior parameters which correspond to the central probability mass specified. The output includes the posterior of the hyper-parameters and the posterior of each group estimate.

**Value**

Matrix of two columns for the central probability interval prob for all parameters of the model.

**Examples**

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

example_model("single_agent")

posterior_interval(blrmfit)

## Recover user set sampling defaults
options(.user_mc_options)
```

---

posterior\_linpred.blrmfit

*Posterior of linear predictor*

---

**Description**

Calculates the posterior of the linear predictor.

**Usage**

```
## S3 method for class 'blrmfit'
posterior_linpred(object, transform = FALSE, newdata, draws, ...)
```

**Arguments**

<code>object</code>	fitted model object
<code>transform</code>	logical (defaults to FALSE) indicating if the linear predictor on the logit link scale is transformed with <code>inv_logit</code> to the 0-1 response scale.
<code>newdata</code>	optional data frame specifying for what to predict; if missing, then the data of the input model object is used
<code>draws</code>	number of returned posterior draws; by default the entire posterior is returned
<code>...</code>	not used in this function

**Details**

Simulates the posterior of the linear predictor of the model object for the specified data set.

**Value**

Matrix of dimensions `draws` by `nrow(newdata)` where row correspond to a draw of the posterior and each column corresponds to a row in `newdata`. The columns are labelled with the `row.names` of `newdata`.

**Group and strata definitions**

The groups and strata as defined when running the `blrm_exnex` analysis cannot be changed at a later stage. As a result no evaluations can be performed for groups which have not been present in the data set used for running the analysis. However, it is admissible to code the group (and/or stratum) column as a factor which contains empty levels. These groups are thus not contained in the fitting data set and they are assigned by default to the first stratum. In addition priors must be setup for these groups (and/or strata). These empty group (and/or strata) levels are then allowed in subsequent evaluations. This enables the evaluation of the hierarchical model in terms of representing a prior for future groups.

**Examples**

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## run single-agent analysis which defines blrmfit model object
example_model("single_agent")

## obtain posterior of linear prediction on 0-1 scale
post_prob_dlt <- posterior_linpred(blrmfit, TRUE, newdata=hist_SA)
## name columns to obtain nice bayesplot labels
colnames(post_prob_dlt) <- hist_SA$drug_A

library(bayesplot)
library(ggplot2)
mcmc_intervals(post_prob_dlt, prob=0.5, prob_outer=0.95) +
  coord_flip() +
```

```

vline_at(c(0.16, 0.33), linetype=2) +
ylab("Dose [mg]") +
ggtitle("Posterior Probability of a DLT") +
scale_x_continuous(breaks=c(0.1,0.16,0.33, 0.5, 0.75))

## Recover user set sampling defaults
options(.user_mc_options)

```

---

```
posterior_predict.blrmfit
```

*Posterior of predictive*

---

### Description

Simulation of the predictive distribution.

### Usage

```

## S3 method for class 'blrmfit'
posterior_predict(object, newdata, draws, ...)

```

### Arguments

object	fitted model object
newdata	optional data frame specifying for what to predict; if missing, then the data of the input model object is used
draws	number of returned posterior draws; by default the entire posterior is returned
...	not used in this function

### Details

Simulates the posterior predictive of the model object for the specified data set.

### Value

Matrix of dimensions draws by nrow(newdata) where row correspond to a draw of the posterior and each column corresponds to a row in newdata. The columns are labelled with the row.names of newdata.

### Group and strata definitions

The groups and strata as defined when running the blrm\_exnex analysis cannot be changed at a later stage. As a result no evaluations can be performed for groups which have not been present in the data set used for running the analysis. However, it is admissible to code the group (and/or stratum) column as a factor which contains empty levels. These groups are thus not contained in the fitting data set and they are assigned by default to the first stratum. In addition priors must be setup for

these groups (and/or strata). These empty group (and/or strata) levels are then allowed in subsequent evaluations. This enables the evaluation of the hierarchical model in terms of representing a prior for future groups.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

example_model("single_agent")

post_pred <- posterior_predict(blrmfit)
## turn DLT counts into DLT rates
post_pred_rate <- sweep(post_pred, 2, hist_SA$num_patients, "/")

library(bayesplot)
library(ggplot2)

## compare posterior predictive of the model for the response rates
## with observed data
with(hist_SA,
  ppc_intervals(num_toxicities / num_patients, post_pred_rate, x=drug_A, prob_outer=0.95)) +
  xlab("Dose [mg]")

## Recover user set sampling defaults
options(.user_mc_options)
```

---

predictive\_interval.blrmfit

*Posterior predictive intervals*

---

## Description

Posterior predictive intervals of the model.

## Usage

```
## S3 method for class 'blrmfit'
predictive_interval(object, prob = 0.95, newdata, ...)
```

## Arguments

object	fitted model object
prob	central probability mass to report, i.e. the quantiles $0.5 - \text{prob}/2$ and $0.5 + \text{prob}/2$ are displayed. Multiple central widths can be specified.



newdata	optional data frame specifying for what to predict; if missing, then the data of the input model object is used
...	not used in this function

## Details

Reports for each row of the input data set the predictive interval according to the fitted model.

## Value

Matrix with as many rows as the input data set and two columns which contain the lower and upper quantile corresponding to the central probability mass prob for the number of responses of the predictive distribution.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

example_model("single_agent")

predictive_interval(blrmfit)

## Recover user set sampling defaults
options(.user_mc_options)
```

---

prior\_summary.blrmfit *Summarise model prior*

---

## Description

Extracts a summary of the prior in a structured data format.

## Usage

```
## S3 method for class 'blrmfit'
prior_summary(object, digits = 2, ...)
```

## Arguments

object	blrmfit(blrm_trial) object as returned from <a href="#">blrm_exnex</a> (blrm_trial) analysis
digits	number of digits to show
...	ignored by the function

## Details

The summary of the prior creates a structured representation of the specified prior from a [blrm\\_exnex](#) ([blrm\\_trial](#)) analysis.

## Value

Returns an analysis specific list, which has it's own print function. The returned list contains arrays which represent the prior in a structured format.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

## run combo2 analysis which defines blrmfit model object
example_model("combo2")

prior_summary(blrmfit)

prior_sum <- prior_summary(blrmfit)
names(prior_sum)

## the entries of the prior list are labelled arrays
dimnames(prior_sum$EX_mu_log_beta)

## Recover user set sampling defaults
options(.user_mc_options)
```

---

summary.blrmfit	<i>Summarise model results</i>
-----------------	--------------------------------

---

## Description

Provides model summaries for [blrm\\_exnex](#) and [blrm\\_trial](#) analyses.

## Usage

```
## S3 method for class 'blrmfit'
summary(object, newdata, transform = TRUE, prob = 0.95, interval_prob, ...)
```

## Arguments

object	fitted model object
newdata	optional data frame specifying for what to predict; if missing, then the data of the input model object is used

transform	logical (defaults to FALSE) indicating if the linear predictor on the logit link scale is transformed with <code>inv_logit</code> to the 0-1 response scale.
prob	central probability mass to report, i.e. the quantiles $0.5 - \text{prob}/2$ and $0.5 + \text{prob}/2$ are displayed. Multiple central widths can be specified.
interval_prob	optional vector of sorted quantiles for which the interval probabilities are calculated
...	not used in this function

## Details

The calculated posterior summaries are returned as a `data.frame` and contain optional interval probabilities for the specified vector of sorted quantiles. These summaries are calculated on the response scale by default and can be obtained on the link scale when setting `transform=FALSE`.

## Value

Returns a `data.frame` of the key summaries of the posterior mean, standard deviation, central probability interval, median and optional interval probabilities. Each row of the `data.frame` corresponds to the respective input data which is by default the same data set as used for the `blrm_exnex` analysis or the data specified in the `newdata` argument.

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

example_model("single_agent")

## obtain underdosing (0-0.16), target dosing (0.16-0.33) and
## overdosing (0.33-1) probabilities
summary(blrmfit, interval_prob=c(0,0.16,0.33,1))

## Recover user set sampling defaults
options(.user_mc_options)
```

---

summary.blrm_trial	<i>Summarise trial</i>
--------------------	------------------------

---

## Description

Provides model summaries for `blrm_trial` analyses.

**Usage**

```
## S3 method for class 'blrm_trial'
summary(
  object,
  summarize = c("blrmfit", "blrm_exnex_call", "dose_info", "dose_prediction", "data",
    "data_prediction", "dimensionality"),
  ...
)
```

**Arguments**

object	blrm_trial object
summarize	one of the following options: <ul style="list-style-type: none"> <li>• blrmfit: summary of the underlying blrmfit object with further arguments</li> <li>• ...</li> <li>• blrm_exnex_call: blrm_exnex call used to create the blrmfit object</li> <li>• dose_info: dose_info that were defined</li> <li>• dose_prediction prediction for the defined dose_info</li> <li>• data: data that were observed</li> <li>• data_prediction: prediction for the observed data</li> <li>• dimensionality: numeric vector with entries "num_components", "num_interaction_terms", "num_groups", "num_strata"</li> </ul>
...	further arguments for summary.blrmfit

**Examples**

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

# construct initial blrm_trial object from built-in example datasets
combo2_trial_setup <- blrm_trial(
  data = hist_combo2,
  dose_info = dose_info_combo2,
  drug_info = drug_info_combo2,
  simplified_prior = TRUE
)

# extract blrm_call to see setup of the prior as passed to blrm_exnex
summary(combo2_trial_setup, "blrm_exnex_call")

## Recover user set sampling defaults
options(.user_mc_options)
```

---

update.blrmfit	<i>Update data of a BLRM analysis</i>
----------------	---------------------------------------

---

## Description

Adds data rows to a `blrm_exnex` or `blrm_trial` analysis object.

## Usage

```
## S3 method for class 'blrmfit'
update(object, ..., add_data)
```

## Arguments

<code>object</code>	blrmfit analysis object
<code>...</code>	<p>passed to default update command</p> <p>The data in <code>add_data</code> will be combined with data in <code>object</code> using <code>bind_rows</code>. The indices for groups and stratum (if defined) are matched between <code>add_data</code> and the data of the analysis object.</p> <p>Note that the <code>add_data</code> argument must be named explicitly as demonstrated in the example.</p>
<code>add_data</code>	additional data added to analysis data of object

## Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

example_model("single_agent")

library(tibble)
new_cohort <- tibble(group_id="trial_A", drug_A=50, num_patients=4, num_toxicities=1)

## this would fail, since add_data argument must be named
## new_blrmfit <- update(blrmfit, new_cohort)
new_blrmfit <- update(blrmfit, add_data=new_cohort)

## Recover user set sampling defaults
options(.user_mc_options)
```

---

update.blrm_trial	<i>Update data and/or prior of a BLRM trial</i>
-------------------	---

---

### Description

\* Adds data rows to a `blrm_trial` object (add\_data argument) \* Replaces data of a `blrm_trial` object (data argument) \* Sets the prior of a `blrm_trial` object (... argument will be passed to `blrm_exnex`)

### Usage

```
## S3 method for class 'blrm_trial'
update(object, ...)
```

### Arguments

object	blrm_trial object
...	passed to default update command of <code>blrm_exnex</code>

### Examples

```
## Setting up dummy sampling for fast execution of example
## Please use 4 chains and 100x more warmup & iter in practice
.user_mc_options <- options(OncoBayes2.MC.warmup=10, OncoBayes2.MC.iter=20, OncoBayes2.MC.chains=1)

# the combo2_trial example demonstrates the use of add_data of
# update.blrmfit
example_model("combo2_trial")

## Recover user set sampling defaults
options(.user_mc_options)
```

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