Package 'OncoBayes2'

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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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LinkingTo StanHeaders (>= 2.18.0), rstan (>= 2.18.1), BH (>= 1.66.0), Rcpp (>= 0.12.0), RcppEigen (>= 0.3.3.3.0)

License GPL (>= 3)

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R topics documented:

`blrm_exnex` *Bayesian Logistic Regression Model for N-compounds with EXNEX*

Description

Bayesian Logistic Regression Model (BLRM) for N compounds using EXchangability and NonEXchangability (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 predictor

`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 $\boldsymbol{\mu}_i = (\mu_{\alpha i}, \mu_{\beta i})$ 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 heterogeniety parameter $\boldsymbol{\tau}_{si} = (\tau_{\alpha si}, \tau_{\beta si})$ 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 heterogeniety 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 $\boldsymbol{m}_{ij}$ and sd $\boldsymbol{s}_{ij} = \text{diag}(\boldsymbol{S}_{ij})$ 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 heterogeniety 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 `stan`.

`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 π 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 $\boldsymbol{\theta} = (\log\,\alpha, \log\,\beta)$ 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,

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

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

$$\pi_i(d_i) = \log\,\alpha_i + \beta_i\,t(d_i),$$

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

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

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 π on the logit scale as

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

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

Regression models can be again be specified for each π_i and γ_k, such as

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

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

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

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

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

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 schedules).

`blrm_exnex` provides tools for robust Bayesian hierarchical modeling to jointly model data from multiple sources. An additional index $j = 1,\ldots,J$ 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

$$\text{logit}\,\pi_j(d_1,\ldots,d_N) = \text{logit}\Big(1-\prod_{i=1}^{N}(1-\pi_{ij}(d_i))\Big) + \sum_{k=1}^{K}\gamma_{kj}(d_1,\ldots,d_N),$$

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

Thus, for $j = 1, \ldots, J$, we now have group-specific parameters $\boldsymbol{\theta}_{ij} = (\log \alpha_{ij}, \log \beta_{ij})$ and η_{kj} for each component $i = 1, \ldots, N$ and interaction $k = 1, \ldots, K$.

The structure of the prior on $(\boldsymbol{\theta}_{i1}, \ldots, \boldsymbol{\theta}_{iJ})$ and $(\eta_{k1}, \ldots, \eta_{kJ})$ 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

$$\boldsymbol{\theta}_{ij} \sim \mathrm{BVN}\big(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}_i\big),$$

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

$$\eta_{kj} \sim \mathrm{N}(\mu_{\eta k}, \tau^2_{\eta k})$$

  for groups $j = 1, \ldots, J$ and interactions $k = 1, \ldots, K$, and the prior on $\tau^2_{\eta k}$ captures the amount of heterogeneity expected in the interaction terms a-priori.

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

$$\boldsymbol{\theta}_{ij} \sim \mathrm{BVN}\big(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}_{ij}\big),$$

  where

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

  For the interactions, the model becomes

$$\eta_{kj} \sim \mathrm{N}(\mu_{\eta k}, \tau^2_{\eta s_j k}).$$

  Each stratum $s = 1, \ldots, S$ then corresponds to its own set of τ parameters. Independent priors are specified for the component parameters $\tau_{\alpha s i}$ and $\tau_{\beta s i}$ and for the interaction parameters $\tau_{\eta s k}$ for each stratum $s = 1, \ldots, S$. Inference for strata s where the prior is centered on larger values of the τ parameters will exhibit less shrinkage towards the the means, $\boldsymbol{\mu}_i$ and $\mu_{\eta,k}$ respectively.

- *EXNEX (Partial exchangeability):* Another mechansim 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

$$\boldsymbol{\theta}_{ij} \sim p_{ij}\, \mathrm{BVN}\big(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}_i\big) + (1 - p_{ij})\, \mathrm{BVN}\big(\boldsymbol{m}_{ij}, \boldsymbol{S}_{ij}\big)$$

  when applied to the treatment-component parameters, and

$$\eta_{kj} \sim p_{\eta kj}\, \mathrm{N}(\mu_{\eta k}, \tau^2_{\eta k}) + (1 - p_{\eta kj})\, \mathrm{N}(m_{\eta kj}, s^2_{\eta kj})$$

  when applied to the interaction parameters. The *exchangeability weights* p_{ij} and $p_{\eta kj}$ 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",
  DosesAdm1 = 400, DosesAdm2 = 800, DosesAdm3 = 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$Npat <- rep(3, nrow(newdata))
newdata$Ntox <- 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)
```

---

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

DosesAdm1 dose of Drug A

DosesAdm2 dose of Drug B

Npat number of patients

Ntox number of DLTs

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)

library(RBesT)
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(Ntox, Npat - Ntox) ~
      1 + I(log(DosesAdm1 / dref[1])) |
      1 + I(log(DosesAdm2 / dref[2])) |
      0 + I(DosesAdm1/dref[1] *DosesAdm2/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 *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 $j = 1, \ldots, 4$ representing each of the four sources of data mentioned above,

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

and

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

are logistic regressions for the single-agent toxicity of drugs A and B, respectively, when administered in group j. Conditional on the regression parameters $\boldsymbol{\theta}_{1j} = (\log\, \alpha_{1j}, \log\, \beta_{1j})$ and $\boldsymbol{\theta}_{2j} = (\log\, \alpha_{2j}, \log\, \beta_{2j})$, 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 $\boldsymbol{\theta}_{ij}$,

$$\boldsymbol{\theta}_{ij} \sim \text{BVN}(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}_i).$$

For the mean, a further prior is specified as

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

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

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

the specified priors are $\tau_{\alpha i} \sim$ Log-Normal$(\log\, 0.25, ((\log 4)/1.96)^2)$,

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

For the interaction parameters η_j in each group, the hierarchical model has

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

for $j = 1, \ldots, 4$, with $\mu_\eta \sim \text{N}(0, 1.121^2)$ and $\tau_\eta \sim$ 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)

library(RBesT)
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(Ntox, Npat - Ntox) ~
      1 + I(log(DosesAdm1 / dref[1])) |
      1 + I(log(DosesAdm2 / dref[2])) |
      0 + I(DosesAdm1/dref[1] *DosesAdm2/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-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 $j = 1, \ldots, 3$,

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

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

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

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

$$\boldsymbol{\theta}_{ij} \sim p_{ij}\text{BVN}(\boldsymbol{\mu}_i, \boldsymbol{\Sigma}_{ij}) + (1 - p_{ij})\text{BVN}(\boldsymbol{m}_{ij}, \boldsymbol{S}_{ij}),$$

where the exchangeability weights are all $p_{ij} = 0.9$. The NEX parameters are set to $\boldsymbol{m}_{ij} = (\text{logit}(1/3), \log\,1)$, $\boldsymbol{S}_{ij} = \text{diag}(2^2, 1^2)$ 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

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

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

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

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

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

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

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

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

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

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(RBesT)
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(Ntox, Npat-Ntox) ~
                          1 + I(log(DosesAdm1/dref[1])) |
                          1 + I(log(DosesAdm2/dref[2])) |
                          1 + I(log(DosesAdm3/dref[3])) |
                          0
                        + I(DosesAdm1/dref[1] * DosesAdm2/dref[2])
                        + I(DosesAdm1/dref[1] * DosesAdm3/dref[3])
                        + I(DosesAdm2/dref[2] * DosesAdm3/dref[3])
                        + I(DosesAdm1/dref[1] * DosesAdm2/dref[2] * DosesAdm3/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:

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

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

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

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

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

$$\boldsymbol{\mu} \sim \text{N}(\boldsymbol{m}, \boldsymbol{S}).$$

The arguments `prior_tau_dist` and `prior_EX_tau_mean_comp` as specified below ensure that the τ'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)

library(RBesT)

## 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(Ntox, Npat - Ntox) ~
    1 + log(DosesAdm1 / 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 *Dataset: historical data on two single-agents to inform a combination study*

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 data frame with 11 rows and 5 variables:

group_id study

DosesAdm1 dose of Drug A

DosesAdm2 dose of Drug B

Npat number of patients

Ntox number of DLTs

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-schedule data.

Usage

```
hist_combo3
```

Format

A data frame with 18 rows and 7 variables:

group_id study

DosesAdm1 dose of Drug A

DosesAdm2 dose of Drug B

DosesAdm3 dose of Drug C

Npat number of patients

Ntox 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(RBesT)
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(Ntox, Npat-Ntox) ~
                          1 + I(log(DosesAdm1/dref[1])) |
                          1 + I(log(DosesAdm2/dref[2])) |
                          1 + I(log(DosesAdm3/dref[3])) |
                          0
                        + I(DosesAdm1/dref[1] * DosesAdm2/dref[2])
                        + I(DosesAdm1/dref[1] * DosesAdm3/dref[3])
                        + I(DosesAdm2/dref[2] * DosesAdm3/dref[3])
                        + I(DosesAdm1/dref[1] * DosesAdm2/dref[2] * DosesAdm3/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

DosesAdm1 dose

Npat number of patients

Ntox 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)

library(RBesT)

## 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(Ntox, Npat - Ntox) ~
    1 + log(DosesAdm1 / 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)
```

`OncoBayes2` *OncoBayes2*

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`	`list(adapt_delta=0.99, stepsize=0.1)`	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.

`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-prob/2 and 0.5+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

`object`	fitted model object
`transform`	logical (defaults to `FALSE`) indicating if the linear predictor on the logit link scale is transformed with `inv_logit` to the 0-1 response scale.
`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 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, but first name
## rows of input data to obtain nice labels with bayesplot
trial_design <- hist_SA
row.names(trial_design) <- hist_SA$DosesAdm1
post_prob_dlt <- posterior_linpred(blrmfit, TRUE, newdata=trial_design)

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$Npat, "/")
```

```
library(bayesplot)
library(ggplot2)

## compare posterior predictive of the model for the response rates
## with observed data
with(hist_SA, ppc_intervals(Ntox / Npat, post_pred_rate, x=DosesAdm1, 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-prob/2 and 0.5+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` object as returned from `blrm_exnex` 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` analysis.

Value

Returns a list of class `prior_summary.blrmfit` 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` *Summarise model results*

Description

Provides model summaries for `blrm_exnex` 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 `inv_logit` to the 0-1 response scale.
`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.
`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 probabilites 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)
```

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