

Package ‘blrm’

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Title Dose Escalation Design in Phase I Oncology Trial Using Bayesian Logistic Regression Modeling

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Description Plan dose escalation design using adaptive Bayesian logistic regression modeling in Phase I oncology trial.

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R topics documented:

blrm_mono_ss 1

Index 8

blrm_mono_ss	<i>Dose Escalation Design in Phase I Oncology Trial using Adaptive Bayesian Logistic Regression Modeling</i>
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Description

Provides dose escalation design in Phase I oncology trial using adaptive Bayesian Logistic Regression Modeling given prior and observed cohorts

Usage

```
blrm_mono_ss(prior, data, output_excel=FALSE, output_pdf=FALSE)
blrm_mono_ms(prior, data, output_excel=FALSE, output_pdf=FALSE)
blrm_combo_ss(prior, data, output_excel=FALSE, output_pdf=FALSE)
blrm_combo_ms(prior, data, output_excel=FALSE, output_pdf=FALSE)
```

Arguments

prior	mean, standard deviation, and correlation of parameters
data	parameters, including random number generating seeds, number of simulation samples, burn-in period, drug name, dose unit, provisional doses, reference dose, tested doses, number of patients, number of dose-limiting toxicities, category bounds, category names, escalation with overdose criterion
output_excel	output_excel = FALSE by default; if output_excel = TRUE, then the simulation output will be provided in excel file
output_pdf	output_pdf = FALSE by default; if output_pdf = TRUE, then visualization of simulation output, including interval probabilities by dose and posterior distribution of dose-limiting toxicity rate, will be provided in pdf file

Details

Model-based dose-escalation design is more flexible than traditional “3 + 3” design. Bayesian logistic regression model is a two-parameter statistical model to quantify the relationship between dose-limiting toxicity (DLT) rate and drug dose.

$$\log\left(\frac{\pi_d}{1 - \pi_d}\right) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right)$$

, where $\alpha > 0$, $\beta > 0$, π_d is the probability of toxicity at dose d , and d^* is the reference dose.

For more details, see Neuenschwander, et al. (2008).

Value

prob_posterior	interval probabilities by dose
para_posterior	posterior estimates of parameters
pi_posterior	posterior estimates of dose-limiting rates
next_dose	recommended next dose
current_summary	summary of simulation outputs
cohort_all	accumulated summary of each observed cohort

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References

Neuenschwander, B., Branson, M. and Gsponer, T. (2008). “Critical aspects of the Bayesian approach to phase I cancer trials”, *Statistics in Medicine*, 27(13), 2420-2439. doi: 10.1002/sim.3230.

Examples

```
## mono version
# prior for log(alpha) and log(beta)
mean <- c(-3.068, 0.564)
se <- c(2.706, 0.728)
corr <- -0.917
prior <- list(mean=mean, se=se, corr=corr)

# parameters
seeds <- 1:2
nsamples <- 10000
burn_in <- 0.5
drug_name <- "DRUG-X"
dose_unit <- "mg"
prov_dose <- c(360, 480, 720, 1080, 1440)
ref_dose <- 720
category_bound <- c(0.16, 0.33)
category_name <- c("under-dosing", "targeted-toxicity", "over-dosing")
ewoc <- 0.25

# observed cohorts
dose <- 480
n_pat <- 3
dlt <- 0

# combine prior, parameters, and observed cohorts to a list
data <- list(seeds=seeds, nsamples=nsamples, burn_in=burn_in, drug_name=drug_name,
            dose_unit=dose_unit, prov_dose=prov_dose, ref_dose=ref_dose,
            dose=dose, n_pat=n_pat, dlt=dlt, category_bound=category_bound,
            category_name=category_name, ewoc=ewoc)

# ready to go!
trial <- blrm_mono_ss(prior=prior, data=data, output_excel=FALSE, output_pdf=FALSE)
prob_posterior <- trial$prob_posterior
pi_posterior <- trial$pi_posterior

# visualization
## interval probabilities by dose
cols <- c("green", "red")[((prob_posterior[3,]) > ewoc)+1] # red: stop; green: pass
yrange <- function(max.y){
  yrange.final <- ifelse(rep((1.1*max.y <= 1), 2), c(0, 1.1*max.y), c(0, max.y))
}
layout(matrix(c(1,2,3), 3, 1, byrow=TRUE))
## e.g., (0.33, 1]
barplot(prob_posterior[3,],
        xlab=paste0("dose", "(", dose_unit, ")"), ylab="probability",
        ylim=yrange(max(prob_posterior[3,])), names.arg=paste(prov_dose),
```

```

        col=cols,
        main=paste0(category_name[3], ":", (" ", category_bound[2], " ", 1]),
        cex.main=1.3, font.main=4)
if(max(prob_posterior[3,]) >= ewoc){
  abline(h=ewoc, lty=2, col="red")
  text(x=0.4, y=1.15*ewoc, labels=paste0("EWOC=", ewoc),
       col="red", cex=1.2, font.main=4)
}else{
  text(x=0.8, y=max(prob_posterior[3,]), labels=paste0("EWOC=", ewoc),
       col="red", cex=1.2, font.main=4)
}
}
## e.g., (0.16, 0.33]
barplot(prob_posterior[2,],
        xlab=paste0("dose", "(" , dose_unit, ")"), ylab="probability",
        ylim=yrange(max(prob_posterior[2,])), names.arg=paste(prov_dose),
        col="green",
        main=paste0(category_name[2], ":", (" ", category_bound[1], " ", " ", category_bound[2], " ]")),
        cex.main=1.3, font.main=4)
## e.g., (0, 0.16]
barplot(prob_posterior[1,],
        xlab=paste0("dose", "(" , dose_unit, ")"), ylab="probability",
        ylim=yrange(max(prob_posterior[1,])), names.arg=paste(prov_dose),
        col="green", main=paste0(category_name[1], ":", (0, " ", category_bound[1], " ]")),
        cex.main=1.3, font.main=4)
## add a main title to the three barplots together
mtext("Interval Probabilities by Dose", side=3, outer=TRUE, line=-2,
      at=par("usr")[1]+0.035*diff(par("usr")[1:2]), cex=1.2, font=2)

## posterior distribution of DLT rate
par(mfrow=c(1,1))
plot(prov_dose, pi_posterior[4,], type="p", pch=20,
     xlab=paste0("dose", "(" , dose_unit, ")"), ylab="DLT rate",
     xlim=range(prov_dose), ylim=c(0, max(pi_posterior)),
     main="Posterior Distribution of DLT Rate", bty="n")
arrows(prov_dose, pi_posterior[3,], prov_dose, pi_posterior[5,],
       code=3, angle=90, length=0.1, lwd=1.5, col=1)
if(max(pi_posterior[5,]) >= category_bound[2]){
  abline(h=category_bound, lty=2, col=c(rgb(0,1,0,alpha=0.8), rgb(1,0,0,alpha=0.8)))
  legend("topleft", c(paste(category_bound), "median", "95 percent credible interval"),
        lty=c(2,2,NA,1), lwd=c(1,1,NA,1.5), pch=c(NA,NA,20,NA),
        col=c(rgb(0,1,0,alpha=0.8), rgb(1,0,0,alpha=0.8), 1, 1), bty="n")
}else if((max(pi_posterior[5,]) >= category_bound[1]) &&
        (max(pi_posterior[5,]) < category_bound[2])){
  abline(h=category_bound[1], lty=2, col=rgb(0,1,0,alpha=0.8))
  legend("topleft", c(paste(category_bound[1]), "median", "95 percent credible interval"),
        lty=c(2,NA,1), lwd=c(1,NA,1.5), pch=c(NA,20,NA),
        col=c(rgb(0,1,0,alpha=0.8), 1, 1), bty="n")
}else{
  legend("topleft", c("median", "95 percent credible interval"),
        lty=c(NA,1), lwd=c(NA,1.5), pch=c(20,NA), col=c(1,1), bty="n")
}
}

```

```
## combo version
# prior
## drug 1
mean1 <- c(-1.0989, -0.1674)
se1 <- c(1.2770, 0.5713)
corr1 <- 0.5224
prior1 <- list(mean=mean1, se=se1, corr=corr1)
## drug 2
mean2 <- c(-2.9444, 0)
se2 <- c(2, 1)
corr2 <- 0
prior2 <- list(mean=mean2, se=se2, corr=corr2)
## interaction between 2 drugs
prior3 <- list(mean=0, se=1.121)
## combine three sets of priors
prior <- list(prior1, prior2, prior3)

# parameters
seeds <- 1:2
nsamples <- 10000
burn_in <- 0.5

## drug 1
drug1_name <- "DRUG-X"
dose1_unit <- "mg"
ref_dose1 <- 10
prov_dose1 <- c(1, 2.5, 5, 10, 15, 20, 25, 30)

## drug 2
drug2_name <- "DRUG-Y"
dose2_unit <- "mg"
ref_dose2 <- 400
prov_dose2 <- c(200, 250, 300, 350, 400, 450, 500, 550)

dose1 <- c(1, 2.5, 5) # tested doses for drug 1
dose2 <- c(200, 200, 250) # tested doses for drug 2
n_pat <- c(3, 3, 4) # number of patients at each observed cohort
dlt <- c(0, 0, 1) # number of DLTs at each observed cohort

category_bound <- c(0.16, 0.33)
category_name <- c("under-dosing", "targeted-toxicity", "over-dosing")
ewoc <- 0.25

# combine to a list
data <- list(seeds=seeds, nsamples=nsamples, burn_in=burn_in,
            drug1_name=drug1_name, dose1_unit=dose1_unit,
            ref_dose1=ref_dose1, prov_dose1=prov_dose1,
            drug2_name=drug2_name, dose2_unit=dose2_unit,
            ref_dose2=ref_dose2, prov_dose2=prov_dose2,
            dose1=dose1, dose2=dose2, n_pat=n_pat, dlt=dlt,
            category_bound=category_bound, category_name=category_name,
            ewoc=ewoc)
```

```

# ready to go!
trial <- blrm_combo_ss(prior=prior, data=data, output_excel=FALSE, output_pdf=FALSE)
prob_posterior <- trial$prob_posterior
pi_posterior <- trial$pi_posterior

# visualization
## Interval Probabilities by Dose: `(0.33, 1]` is the target
### data manipulation
prov_dose <- expand.grid(prov_dose1, prov_dose2)
prob_posterior_3 <- cbind(prov_dose, prob_posterior[3,])
names(prob_posterior_3) <- c("drug1", "drug2", "probability")
prob_posterior_3 <- transform(prob_posterior_3,
                             level=ifelse(probability > ewoc, 1, 0))
prob_posterior_3_wide <- reshape2::dcast(prob_posterior_3[, -3],
                                       drug2 ~ drug1, value.var="level")
prob_posterior_3_wide <- prob_posterior_3_wide[, -1]
rownames(prob_posterior_3_wide) <- paste(prov_dose2)
colnames(prob_posterior_3_wide) <- paste(prov_dose1)
cols <- matrix(NA, nrow=length(prov_dose2), ncol=length(prov_dose1))
for(i in 1:nrow(prob_posterior_3_wide)){
  for(j in 1:ncol(prob_posterior_3_wide)){
    cols[i,j] <- ifelse(prob_posterior_3_wide[i,j]==1, "red", "green")
  }
}
### generate the plot
plot(NA, NA, type='n', xaxt='n', yaxt='n', cex.lab=1.5,
     cex.main=2,
     xlim=range(1:length(prov_dose1)),
     ylim=range(1:length(prov_dose2)),
     xlab=paste0(drug1_name, "(", dose1_unit, ")"),
     ylab=paste0(drug2_name, "(", dose2_unit, ")"),
     main="Dose Category")
abline(h=1:length(prov_dose2), v=1:length(prov_dose1),
       lty=2, lwd=1, col="gray")
axis(1, at=1:length(prov_dose1), labels=paste(prov_dose1))
axis(2, at=1:length(prov_dose2), labels=paste(prov_dose2), las=2)
# add dose level combinations
for(i in 1:length(prov_dose2)){
  for(j in 1:length(prov_dose1)){
    points(j, i, pch=19, col=cols[i,j], cex=4)
  }
}
legend("topright", c("<= EWOC", "> EWOC"), cex=1.1,
      pch=rep(19, 2), col=c("green", "red"), pt.cex=2,
      xpd=TRUE, horiz=TRUE, inset=c(0, -0.06), bty='n')

## Posterior Distribution of DLT Rate
par(mfrow=c(1,1))
labels <- apply(prov_dose, 1, paste, collapse=",")
plot(1:nrow(prov_dose), pi_posterior[4,], type="p", pch=20,
     xlab="drug combo", xaxt='n', cex.lab=1.5,
     ylab="DLT rate", ylim=c(0, max(pi_posterior)),

```

```

    main="Posterior Distribution of DLT Rate", cex.main=2.0, bty='n')
axis(1, at=1:nrow(prov_dose), labels=FALSE)
text(x=1:nrow(prov_dose), par("usr")[3]-0.03, labels=labels,
     srt=90, pos=1, xpd=TRUE, cex=0.5)
arrows(1:nrow(prov_dose), pi_posterior[3,],
       1:nrow(prov_dose), pi_posterior[5,],
       code=3, angle=90, length=0.1, lwd=1.5, col=1)
if(max(pi_posterior[5,]) >= category_bound[2]){
  abline(h=category_bound, lty=2,
        col=c(rgb(0,1,0,alpha=0.8), rgb(1,0,0,alpha=0.8)))
  legend("top",
        c(paste(category_bound), "median", "95 percent credible interval"),
        lty=c(2,2,NA,1), lwd=c(1,1,NA,1.5), pch=c(NA,NA,20,NA),
        col=c(rgb(0,1,0,alpha=0.8), rgb(1,0,0,alpha=0.8), 1, 1),
        xpd=TRUE, horiz=TRUE, inset=c(0, -0.035), bty='n')
}else if((max(pi_posterior[5,]) >= category_bound[1]) &&
        (max(pi_posterior[5,]) < category_bound[2])){
  abline(h=category_bound[1], lty=2, col=rgb(0,1,0,alpha=0.8))
  legend("top", c(paste(category_bound[1]), "median", "95 percent credible interval"),
        lty=c(2,NA,1), lwd=c(1,NA,1.5), pch=c(NA,20,NA),
        col=c(rgb(0,1,0,alpha=0.8), 1, 1), bty='n',
        xpd=TRUE, horiz=TRUE, inset=c(0, -0.035))
}else{
  legend("top", c("median", "95 percent credible interval"),
        lty=c(NA,1), lwd=c(NA,1.5), pch=c(20,NA), col=c(1,1),
        xpd=TRUE, horiz=TRUE, inset=c(0, -0.035), bty='n')
}
# end of visualization

```

Index

*Topic **Bayesian statistics**

blrm_mono_ss, 1

*Topic **clinical trial**

blrm_mono_ss, 1

*Topic **dose escalation**

blrm_mono_ss, 1

*Topic **logistic regression**

blrm_mono_ss, 1

blrm_combo_ms (blrm_mono_ss), 1

blrm_combo_ss (blrm_mono_ss), 1

blrm_mono_ms (blrm_mono_ss), 1

blrm_mono_ss, 1