# B.1 Main WinBUGS Code

**##Required R packages**

library(MASS)

library(coda)

library(R2WinBUGS)

library(survival)

library(RBesT)

**##Main WinBUGS code**

MAC.Surv.WB <- function()

{

# tau.study: Between study variation (Half normal)

Prior.tau.study.prec <- pow(Prior.tau.study[2],-2)

for (t in 1:Nint) {

tau.study[t] ~ dnorm(Prior.tau.study[1], Prior.tau.study.prec) %\_% I(0, )

tau.study.prec[t] <- pow(tau.study[t],-2)

}

#tau.time: correlation for piecewise exponential pieces (log-normal)

Prior.tau.time.prec <- pow(Prior.tau.time[2],-2)

tau.time ~ dlnorm(Prior.tau.time[1], Prior.tau.time.prec)

tau.time.prec <- pow(tau.time,-2)

# priors for regression parameter: h covariates

for (h in 1:Ncov) {

prior.beta.prec[h] <- pow(Prior.beta[2,h],-2)

beta[h,1] ~ dnorm(Prior.beta[1,h],prior.beta.prec[h])

}

###########################

#EXNEX structure of mu

###########################

#EX structure for mu is 1st order NDLM

mu.prec.ex <- pow(Prior.mu.mean.ex[2],-2)

mu.mean.ex ~ dnorm(Prior.mu.mean.ex[1],mu.prec.ex)

mu1.ex ~ dnorm(mu.mean.ex,tau.time.prec)

mu.ex[1] <- mu1.ex

prec.rho.ex <- pow(Prior.rho.ex[2],-2)

for(t in 2:Nint){

mu.dlm.ex[t] <- mu.ex[t-1] + rho.ex[t-1]

#variance of mu: discount factor X tau.time.prec

mu.time.prec.ex[t] <- tau.time.prec/w.ex

mu.ex[t] ~ dnorm(mu.dlm.ex[t], mu.time.prec.ex[t])

rho.ex[t-1] ~ dnorm(Prior.rho.ex[1], prec.rho.ex)

}

w.ex ~dunif(w1,w2)

#NEX structure for mu: unrelated structure

for( s in 1:Nstudies){

for(t in 1:Nint) {

prior.mu.prec.nex[s,t] <- pow(prior.mu.sd.nex[s,t],-2)

mu.nex[s,t] ~ dnorm(prior.mu.mean.nex[s,t],prior.mu.prec.nex[s,t])

}

}

# hazard-base: for each study (+ population mean + prediction) and time-interval t, no covariates

for ( s in 1:Nstudies) {

for ( t in 1:Nint) {

RE[s,t] ~ dnorm(0,tau.study.prec[t])

Z[s,t] ~ dbin(p.exch[s,t],1)

#For ex

log.hazard.base.ex[s,t] <- mu.ex[t] + step(Nstudies-1.5)\*RE[s,t]

#For Nexch

log.hazard.base.nex[s,t] <- mu.nex[s,t]

log.hazard.base[s,t] <- Z[s,t]\*log.hazard.base.ex[s,t]+(1-Z[s,t])\*log.hazard.base.nex[s,t]

hazard.base[s,t] <- exp(log.hazard.base[s,t])

}

}

# likelihood: pick hazards according to study and time-invervals (int.low to int.high) for each

#observation j

# note: hazard is per unit time, not depending on length of interval t

for(j in 1:Nobs) {

for ( t in 1:Nint) {

# log.hazard for all time intervals

log(hazard.obs[j,t]) <- log.hazard.base[study[j],t] + inprod(X[j,1:Ncov],beta[1:Ncov,1])

}

#Poisson likelihood

alpha[j] <- (inprod(hazard.obs[j,int.low[j]:int.high[j]],int.length[int.low[j]:int.high[j]])

/sum(int.length[int.low[j]:int.high[j]]))\*exp.time[j]

n.events[j] ~ dpois(alpha[j])

n.events.pred[j] ~ dpois(alpha[j])

}

# outputs of interest (from covariate patterns in Xout)

for ( h in 1:Nout) {

for ( s in 1:Nstudies) {

# mean (index = Nstudies)

# surv: pattern x study x time

surv1[ h,s,1] <- 1

for ( t in 1:Nint) {

log(hazard[h,s,t]) <- log.hazard.base[s,t] + inprod(Xout[h,1:Ncov],beta[1:Ncov,1])

log.hazard[h,s,t] <- log(hazard.base[s,t])

surv1[h,s,t+1] <- surv1[h,s,t]\*exp(-hazard[h,s,t]\*int.length[t])

surv[h,s,t] <- surv1[h,s,t+1]

}

}

}

######### Prediction##########

for ( h in 1:Nout) {

for ( t in 1:Nint) {

hazard.pred[h,t] <- hazard[h,Nstudies,t]

log.hazard.pred[h,t] <- log(hazard[h,Nstudies,t]+pow(10,-6))

surv.pred[h,t] <- surv[h,Nstudies,t]

}

}

for (j in 1:Ncov) {

beta.ge.cutoffs[j] <- step(beta[j,1]-beta.cutoffs[j,1])

}

}

# B.2 R wrapper function for running the main WinBUGS code

**##Description of arguments of the function**

#Nobs = Total number of data points

#study = Study indicator

#Nstudies = Number of studies

#Nint = Number of intervals

#Ncov = Number of covariates

#int.low, int.high = Interval indicator

#int.length = Length of interval

#n.events = Number of events at each interval

#exp.time = Exposure time for each interval

#X = Important covariates

#Prior.mu.mean.ex = Mean and standard deviation for normal priors for exchangeability for the first interval

#Prior.rho.ex = Mean and standard deviation for normal priors for random gradient of 1st order NDLM

#w1, w2 = Upper and lower bound for uniform prior of the smoothing factor for 1st order NDLM model for exchangeability

#prior.mu.mean.nex = Mean of normal prior for non-exchangeability

#prior.mu.sd.nex = Standard deviation for normal prior of non-exchangeability

#p.exch = Prior probability of exchangeability

#Prior.beta = Mean and standard deviation for normal priors of regression coefficients

#beta.cutoffs = Cut-off for treatment effect

#Prior.tau.study = Scale parameter of half-normal prior for between trial heterogeneity

#Prior.tau.time = Mean and standard deviation for log-normal prior for variance compoment of 1st order NDLM

#MAP.Prior = If TRUE: derives MAP prior

#pars = Parameters to keep in each MCMC run

#bugs.directory = Directory path where WinBUGS14.exe file resides

#R.seed = Seed to generate initial value in R (requires for reprducibility)

#bugs.seed = WinBUGS seed (requires for reprducibility)

MAC.Surv.anal <- function(Nobs = NULL,

study = NULL,

Nstudies = NULL,

Nint = NULL,

Ncov = 1,

Nout = 1,

int.low = NULL,

int.high = NULL,

int.length = NULL,

n.events = NULL,

exp.time = NULL,

X = NULL,

Xout = matrix(0,1,1),

Prior.mu.mean.ex = NULL,

Prior.rho.ex = NULL,

w1 = 0,

w2 = 1,

prior.mu.mean.nex = NULL,

prior.mu.sd.nex = NULL,

p.exch = NULL,

Prior.beta = NULL,

beta.cutoffs = NULL,

Prior.tau.study = NULL,

Prior.tau.time = NULL,

MAP.prior = FALSE,

pars = c("tau.study","log.hazard","mu.ex", "hazard"),

bugs.directory = "C:/Program Files/WinBUGS14",

R.seed = 10,

bugs.seed = 12

)

{

set.seed(R.seed)

beta.cutoffs <- cbind(NULL,beta.cutoffs)

if(MAP.prior){Nstudies <- Nstudies+1}

#WinBUGS model

model <- MAC.Surv.WB

#Data for JAGS format

data = list("Nstudies", "Nint", "Ncov", "Nobs", "Nout","study","int.low","int.high","int.length",

"n.events","exp.time",

"X","Xout",

"Prior.mu.mean.ex","Prior.rho.ex",

"prior.mu.mean.nex","prior.mu.sd.nex",

"p.exch","w1","w2",

"Prior.beta",

"beta.cutoffs",

"Prior.tau.study","Prior.tau.time"

)

#Initial values

hazard0 = (sum(n.events)+0.5)/sum(exp.time)

initsfun = function(i)

list(

mu1.ex = rnorm(1,log(hazard0),0.25),

tau.study = rgamma(12,1,1),

tau.time = rgamma(1,1,1),

mu.mean.ex = rnorm(1,log(hazard0),0.1),

rho.ex = rnorm(Nint-1,0,0.05),

w.ex = runif(1,0,1),

beta=cbind(NULL,rnorm(Ncov,0,1))

)

inits <- lapply(rep(1,3),initsfun)

#WinBUGS run

fit = bugs(

data=data,

inits=inits,

par=pars,

model=model,

n.chains=3,n.burnin=8000,n.iter=16000,n.thin=1,

bugs.directory= bugs.directory,

bugs.seed= bugs.seed,

DIC= TRUE,

debug= FALSE

)

fit$sims.matrix = NULL

fit$sims.array = NULL

#WinBUGS summary

summary <- fit$summary

R2WB <- fit

output <- list(summary=summary,R2WB =R2WB)

return(output)

}

# B.3 FIOCCO Analysis

**##FIOCCO data set**

FIOCCO.n.events <- c(1, 3, 3, 4, 3, 0, 0, 2, 0, 6, 0, 0, 9, 1, 0, 10, 6, 6, 5, 9,

9, 3, 0, 0, 1, 3, 5, 7, 9, 4, 5, 10, 0, 0, 3, 7, 1, 2, 2, 4,

3, 1, 3, 0, 0, 0, 0, 0, 5, 3, 6, 2, 3, 3, 0, 2, 1, 1, 1, 0,

0, 6, 3, 12, 8, 2, 3, 2, 11, 1, 0, 10, 2, 2, 5, 3, 3, 3, 2, 3,

3, 0, 0, 0, 0, 1, 3, 4, 1, 1, 4, 1, 6, 0, 0, 0, 2, 0, 3, 1,

4, 0, 1, 1, 0, 0, 0, 0, 1, 5, 17, 0, 2, 7, 8, 4, 0, 6, 2, 0)

FIOCCO.exp.time <- c( 9.4, 8.8, 7.9, 7.0, 6.1, 5.8, 5.8, 7.3, 8.8, 7.6, 6.2, 10.0, 21.1,

19.9, 19.8, 18.5, 16.5, 15.0, 13.6, 15.7, 16.2, 13.6, 12.5, 20.1, 21.9, 21.4,

20.4, 18.9, 16.9, 15.2, 14.1, 16.2, 18.5, 18.3, 17.0, 24.5, 5.6, 5.2, 4.8,

4.0, 3.1, 2.6, 2.1, 2.3, 2.9, 2.9, 2.9, 4.7, 6.4, 5.4, 4.2, 3.2,

2.6, 1.9, 1.5, 1.7, 1.5, 1.0, 0.6, 0.7, 17.8, 17.0, 15.9, 14.0, 11.5,

10.2, 9.6, 11.9, 12.4, 9.9, 9.4, 12.1, 8.0, 7.5, 6.6, 5.6, 4.9, 4.1,

3.5, 3.8, 3.6, 2.9, 2.9, 4.7, 9.2, 9.1, 8.6, 7.8, 7.1, 6.9, 6.2,

7.4, 8.0, 6.7, 6.6, 10.7, 5.2, 5.0, 4.6, 4.1, 3.5, 3.0, 2.9, 3.5,

4.2, 4.2, 4.1, 6.7, 23.4, 22.6, 19.9, 17.8, 17.5, 16.4, 14.5, 17.2, 21.0,

19.7, 17.4, 27.5)

## B.3.1 Derivation of MAP Prior using First 9 Studies

FIOCCO.MAP.Prior <- MAC.Surv.anal(Nobs = 108,

study = sort(rep(1:9,12)),

Nstudies = 9,

Nint = 12,

Ncov = 1,

Nout = 1,

int.low = rep(1:12,9),

int.high = rep(1:12,9),

int.length = c(0.25, 0.25, 0.25, 0.25, 0.25, 0.25, 0.25,

0.33, 0.42, 0.42, 0.41, 0.67),

n.events = FIOCCO.n.events[1:108],

exp.time = FIOCCO.exp.time[1:108],

X = matrix(0,108,1),

Prior.mu.mean.ex = c(0, 10),

Prior.rho.ex = c(0,10),

prior.mu.mean.nex = matrix(rep(0,120), nrow=10, ncol=12),

prior.mu.sd.nex = matrix(rep(1,120), nrow=10, ncol=12),

p.exch = matrix(rep(1,120), nrow=10),

Prior.beta = matrix(c(0,10), nrow=2) ,

beta.cutoffs = 0,

Prior.tau.study = c(0, 0.5),

Prior.tau.time = c(-1.386294, 0.707293),

MAP.prior = TRUE,

pars = c("tau.study","log.hazard.pred"),

R.seed = 10,

bugs.seed = 12

)

print(FIOCCO.MAP.Prior$summary)

**#Calculation of Prior Effective ENE**

FIOCCO.MAP.ess <- NULL

for(l in 1:12){

prior.ss.int <- FIOCCO.MAP.Prior$R2WB$sims.list$log.hazard.pred[,,l]

prior.ss.int.mix <- RBesT::automixfit(prior.ss.int, type="norm")

FIOCCO.MAP.ess[l] <- RBesT::ess(prior.ss.int.mix, sigma=1)

}

#Prior ESS (mixture)

FIOCCO.ESS.nevent <- sum(FIOCCO.MAP.ess)

## B.3.2 MAC (EX) analysis of the FIOCCO data

FIOCCO.anal.1 <- MAC.Surv.anal(Nobs = 120,

study = sort(rep(1:10,12)),

Nstudies = 10,

Nint = 12,

Ncov = 1,

Nout = 1,

int.low = rep(1:12,10),

int.high = rep(1:12,10),

int.length = c(0.25, 0.25, 0.25, 0.25, 0.25, 0.25, 0.25,

0.33, 0.42, 0.42, 0.41, 0.67),

n.events = FIOCCO.n.events,

exp.time = FIOCCO.exp.time,

X = matrix(0,120,1),

Prior.mu.mean.ex = c(-1.1711, 1),

Prior.rho.ex = c(0,1),

prior.mu.mean.nex = matrix(rep(0,120), nrow=10, ncol=12),

prior.mu.sd.nex = matrix(rep(1,120), nrow=10, ncol=12),

p.exch = matrix(rep(1,120), nrow=10),

Prior.beta = matrix(c(0,10), nrow=2) ,

beta.cutoffs = 0,

Prior.tau.study = c(0, 0.5),

Prior.tau.time = c(-1.386294, 0.707293),

R.seed = 10,

bugs.seed = 12

)

print(FIOCCO.anal.1$summary)

## B.3.3 Robust MAC (EXNEX) analysis of the FIOCCO data

FIOCCO.anal.2 <- MAC.Surv.anal(Nobs = 120,

study = sort(rep(1:10,12)),

Nstudies = 10,

Nint = 12,

Ncov = 1,

Nout = 1,

int.low = rep(1:12,10),

int.high = rep(1:12,10),

int.length = c(0.25, 0.25, 0.25, 0.25, 0.25, 0.25, 0.25, 0.33,

0.42, 0.42, 0.41, 0.67),

n.events = FIOCCO.n.events,

exp.time = FIOCCO.exp.time,

X = matrix(0,120,1),

Prior.mu.mean.ex = c(-1.1711, 1),

Prior.rho.ex = c(0,1),

prior.mu.mean.nex = matrix(rep(c(-1.8625303, -1.6057708, -1.1242566,

-0.5940037, -0.5921193, -1.2484085,

-1.0011891, -0.9291769, -1.3337843,

-2.1254918, -2.9740698, -2.7570149),

10),

nrow=10, byrow = T),

prior.mu.sd.nex = matrix(rep(1,12\*10), nrow=10, byrow=T),

p.exch = rbind(matrix(rep(1,108), nrow=9), rep(0.5, 12)),

Prior.beta = matrix(c(0,10), nrow=2) ,

beta.cutoffs = 0,

Prior.tau.study = c(0, 0.5),

Prior.tau.time = c(-1.386294, 0.707293),

R.seed = 10,

bugs.seed = 12

)

print(FIOCCO.anal.2$summary)