library(survival)

N.pop <- 1000000

# Size of super-population.

hr.target <- 0.80

# Target population marginal hazard ratio for treatment.

tolerance <- 0.001

# How close to the target hazard ratio should the empirical marginal hazard

# ratio be.

set.seed(12072022)

# Set random number seed for reproducibility.

lambda <- 0.00002

nu <- 2

# Parameters for Weibull distribution for event times.

# These can be modified to change characteristics of the event-time

# distribution. See Bender et al. for parameterization of distribution.

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

# Generate 10 baseline covariates for each subject in the super-population.

# The first five are from independent standard normal distibutions.

# The last five are from independent Bernoulli distributions with parameter 0.5.

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

x1 <- rnorm(N.pop,0,1)

x2 <- rnorm(N.pop,0,1)

x3 <- rnorm(N.pop,0,1)

x4 <- rnorm(N.pop,0,1)

x5 <- rnorm(N.pop,0,1)

x6 <- rbinom(N.pop,1,0.5)

x7 <- rbinom(N.pop,1,0.5)

x8 <- rbinom(N.pop,1,0.5)

x9 <- rbinom(N.pop,1,0.5)

x10 <- rbinom(N.pop,1,0.5)

X <- cbind(1,x1,x2,x3,x4,x5,x6,x7,x8,x9,x10)

# Add a column for an intercept to the matrix of baseline covariates.

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

# Generate a binary treatment variable with the given prevalence of treatment.

# We use the intercept estimated in a previous example.

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

B.treat <- c(log(1.1),log(2),log(3),log(1.5),log(1.5),

log(1.1),log(2),log(3),log(1.5),log(1.5))

# Regression coefficients for treatment-selection model.

beta.0.treat <- -3.31749

# Intercept for treatment-selection model determined in earlier an example.

beta.treat <- c(beta.0.treat,B.treat)

# Set the intercept of the treat model to the given value.

XB.treat <- X %\*% beta.treat

p.treat <- exp(XB.treat)/(1 + exp(XB.treat))

treat <- rbinom(N.pop,1,p.treat)

# treat is binary treatment status variable.

remove(B.treat,beta.0.treat,beta.treat,XB.treat,p.treat)

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

# Define regression coefficients for the proportional hazards model.

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

B.outcome <- c(log(1.25),log(1.5),log(1.75),log(2),log(2.5),

log(1.25),log(1.5),log(1.75),log(2),log(2.5))

# Regression coefficients for the outcome model.

X <- X[,-1]

# Remove intercept from the design matrix since the proportional hazards

# model does not use an intercept.

XB.outcome <- X %\*% B.outcome

# Compute linear predictor for baseline covariates for the Cox model.

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

# Use a bisection approach to determine the log-hazard ratio that results in

# the desired marginal hazard ratio.

# We use a data-generating process for time-to-event outcomes described by

# Bender (Stat Med 2005).

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

int.low <- -10

int.high <- 10

iter <- 1

hr.empirical <- 1

# Initial value of marginal hazard ratio.

while(abs(hr.empirical - hr.target) > tolerance){

set.seed(iter)

int.mid <- (int.low + int.high)/2

ranu <- runif(N.pop,min=0,max=1)

# Generate outcome for each subject under control (untreated).

# We do not induce censoring.

linpred0 <- XB.outcome

time0 <- (-(log(ranu))/(lambda\*exp(linpred0)) )^(1/nu)

status0 <- rep(1,N.pop)

treat0 <- rep(0,N.pop)

# Generate outcome for each subject under treatment.

# We do not induce censoring.

linpred1 <- linpred0 + log(int.mid)

time1 <- (-(log(ranu))/(lambda\*exp(linpred1)) )^(1/nu)

status1 <- rep(1,N.pop)

treat1 <- rep(1,N.pop)

time.long <- c(time0,time1)

status.long <- c(status0,status1)

treat.long <- c(treat0,treat1)

cox.marginal <- coxph(Surv(time.long,status.long) ~ treat.long)

hr.empirical <- exp(cox.marginal$coeff)

if (hr.empirical < hr.target) int.low <- int.mid else

int.high <- int.mid

cat(iter,hr.target,int.mid,hr.empirical,file="Table4.txt",fill=T,append=T)

iter <- iter + 1

remove(ranu,linpred0,treat0,linpred1,treat1,time.long,status.long,

treat.long,cox.marginal)

}

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

# Generate an outcome for each subject.

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

event.time <- treat\*time1 + (1-treat)\*time0

status <- treat\*status1 + (1-treat)\*status0

remove(time0,time1,status0,status1,hr.empirical,B.outcome,int.low,int.mid,

int.high,iter,X,XB.outcome)