Example 5 using R

Drawing time to event from hazards with time-dependent covariates following random paths

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Code function

This document presents the code corresponding to the fifth example presented in the "A Fast Nonparametric Sampling (NPS) Method for Time-to-Event in Individual-Level Simulation Models." manuscript, all of them using R.

```
# 01 Initial Setup ------------------------------------------------------

## 01.01 Clean environment ----------------------------------------------
remove(list = ls())

#* Refresh environment memory
gc()

# 01.02 Load libraries -------------------------------------------------
library(dplyr)
library(ggplot2)
library(tidyr)
library(tibble)
library(data.table)
library(flexsurv)
library(LambertW)
library(reshape2)
```

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```r
library(microbenchmark)

# Load function to implement multivariate categorical sampling
source(file = "../R/nps_nhppp.R")
```

```r
# 02 Define general parameters ------------------------------------------

# Parameters for time-varying covariates
alpha_0 <- 0
alpha_1 <- 1
# When beta <- 0 the time-varying covariate is deactivated
beta    <- log(1.005)


# Define parameters for the Weibull baseline hazard
n_weib_shape <- 1.3
n_weib_scale <- 30.1

n_ind    <-  1000 # Number of simulated individuals
n_cycles <-  100  # Number of cycles
ourDrift <-  0.5

#* Number of iterations for microbenchmarking in time-dependent covariates
#* examples
n_iter_time_var_cov <- 100

# Seed for reproducibility in random number generation
n_seed <- 10242022
```

```r
# 03 Define required functions ------------------------------------------

# Define random path function
create_time_varying_covariate <- function(n_ind    = 100,
                                          n_cycles = 100,
                                          ourDrift = 0.005){

  m_random_paths <- matrix(nrow = n_ind, ncol = n_cycles)
  m_random_paths[, 1] <- 1

  for (cycle in 2:n_cycles) {

    v_next_step = rnorm(n = n_ind, mean = 0, sd = ourDrift)
```

```
    m_random_paths[, cycle] <- round(pmax(m_random_paths[, cycle - 1] +
                                            v_next_step, 0))
  }

  dtb_paths_individuals <- as.data.table(
    reshape2::melt(data       = m_random_paths,
                   varnames   = c("id", "Time"),
                   value.name = "Covariate"))

  setorder(dtb_paths_individuals, id, Time)

  return(dtb_paths_individuals)
}

## Function to apply the time-varying covariate to a baseline hazard
compute_time_varying_hazard_linear_3 <- function(hazard0,
                                                 alpha_0,
                                                 alpha_1,
                                                 beta,
                                                 time_var_cov){

  # This specification gets the full matrix of values as output
  hazard <- hazard0 %*% exp(beta*(alpha_0 + alpha_1*time_var_cov))

  return(hazard)
}
```

```
# 04 Draw time to events ------------------------------------------------

# Set seed for reproducibility
set.seed(n_seed)

# Sample from Weibull baseline hazard (h_0)
hazard0 <- matrix(flexsurv::hweibull(x     = 1:n_cycles,
                                     shape = n_weib_shape,
                                     scale = n_weib_scale),
                  ncol = 1)


# Compute values of the hazard based on a range of covariate values
weibull_hazard <- compute_time_varying_hazard_linear_3(
  hazard0      = hazard0,
```

```
  alpha_0      = alpha_0,
  alpha_1      = alpha_1,
  beta         = beta,
  time_var_cov = seq(0:n_cycles))

# Convert to long format
df_weibull_hazard_long <- reshape2::melt(data       = weibull_hazard,
                                         varnames   = c("Time", "Covariate"),
                                         value.name = "h(t)")

dt_weibull_hazard_long <- as.data.table(df_weibull_hazard_long)

# Correct covariate id
dt_weibull_hazard_long[, Covariate := Covariate - 1]

#* Set key for efficient binary search
#* Check `vignette("datatable-keys-fast-subset") `
setkey(dt_weibull_hazard_long, Time, Covariate)

# Create time varying covariate, y_i(t)
dtb_paths_individuals <- create_time_varying_covariate(n_ind    = n_ind,
                                                       n_cycles = n_cycles,
                                                       ourDrift = ourDrift)




# Obtain time-dependent hazards from indvidual-specific random paths
dtb_paths_individuals[, `h(t)` := dt_weibull_hazard_long[
  .(dtb_paths_individuals$Time, dtb_paths_individuals$Covariate),  `h(t)`]]


# Steps to get time-specific probability of event occurrence
# H(t) - Cumulative hazard
dtb_paths_individuals[, H := cumsum(`h(t)`),  by = id]
# F(t) - Cumulative probability
dtb_paths_individuals[, `F` := 1 - exp(-H)]
# f(t) - Instantaneous probability
dtb_paths_individuals[, f := c(`F`[1], diff(`F`)), by = id]

# Generate data set to sample time to event
dt_paths_individuals_wide <- data.table::dcast(data = dtb_paths_individuals,
```

```
                                                value.var = "f",
                                                formula = id ~ Time)

# Generate last cycle to sum probability up to 1
dt_paths_individuals_wide[
  , `101` := 1 - dtb_paths_individuals[Time == 100, `F`]]

# Sample time to event for all individuals
out_nps <- nps_nhppp(
  m_probs = as.matrix(dt_paths_individuals_wide[, `1`:`101`]),
  v_categories = seq(0, 100),
  correction = "none")

# Measure mean execution time
l_mbench_random_path <- microbenchmark::microbenchmark(
  nps_nhppp(m_probs    = as.matrix(dt_paths_individuals_wide[, 2:102]),
            correction = "uniform"),
  times = n_iter_time_var_cov,
  unit = "ms")

# Remove seed
set.seed(NULL)
```