Microsimulation Sick-Sicker model with time dependency with PSA

Includes individual characteristics: age, age dependent mortality probabilities, individual treatment effect modifyer, state-residence dependence for the sick (S1) state, increasing change of death in the first 6 year of sickness (tunnel)

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- Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. Med Decis Making. 2018;38(3):400–22. https://journals.sagepub.com/doi/abs/10.1177/0272989X18754513
- Krijkamp EM, Alarid-Escudero F, Enns E, Pechlivanoglou P, Hunink MM, Jalal H. A Multidimensional Array Representation of State-Transition Model Dynamics. Med Decis Making. 2020 Online first. https://doi.org/10.1177/0272989X19893973

Change `eval` to `TRUE` if you want to knit this document.

```
rm(list = ls())      # clear memory (removes all the variables from the workspace)
```

01 Load packages

```
if (!require('pacman')) install.packages('pacman'); library(pacman) # use this package to conveniently
# load (install if required) packages from CRAN
p_load("here", "dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "ggraph", "re
# load (install if required) packages from GitHub
# install_github("DARTH-git/dampack", force = TRUE) Uncomment if there is a newer version
# install_github("DARTH-git/dampack", force = TRUE) # Uncomment if there is a newer version
# install_github("DARTH-git/darthtools", force = TRUE) # Uncomment if there is a newer version
p_load_gh("DARTH-git/dampack", "DARTH-git/darthtools")
```

02 Load functions

```
# No functions needed
```

03 Input model parameters

```
set.seed(1)  # set the seed

# Model structure
n_t   <- 30                       # time horizon, 30 cycles
n_i   <- 100000                   # number of simulated individuals
v_n   <- c("H", "S1", "S2", "D")  # the model states names
n_states   <- length(v_n)              # the number of health states
d_r   <- 0.03                     # discount rate of 3% per cycle
v_dwe <- v_dwc <- 1 / ((1 + d_r) ^ (0:n_t))    # discount weight
v_names_str <- c("no treatment", "treatment")  # strategy names
n_str <- length(v_names_str)      # number of strategies

### Event probabilities (per cycle)
# Annual transition probabilities
p_HS1   <- 0.15                   # probability of becoming sick when healthy
p_S1H   <- 0.5                    # probability of recovering to healthy when sick
p_S1S2  <- 0.105                  # probability of becoming sicker when sick

# Annual probabilities of death
# load age dependent probability
p_mort   <- read.csv(here("data", "mortProb_age.csv"))
# load age distribution
dist_Age <- read.csv("MyPopulation-AgeDistribution.csv")
```

```r
# probability to die in S1 by cycle (is increasing)
p_S1D    <- c(0.0149, 0.018, 0.021, 0.026, 0.031, rep(0.037, n_t - 5))
#p_S1D    <- rep(0.0149, n_t)          # probability to die in S1 by cycle
p_S2D    <- 0.048           # probability to die in S2

# Cost inputs
c_H     <- 2000             # cost of one cycle in the healthy state
c_S1    <- 4000             # cost of one cycle in the sick state
c_S2    <- 15000            # cost of one cycle in the sicker state
c_D     <- 0                # cost of one cycle in the dead state
c_Trt   <- 12000            # cost of treatment (per cycle)

# Utility inputs
u_H     <- 1                # utility when healthy
u_S1    <- 0.75             # utility when sick
u_S2    <- 0.5              # utility when sicker
u_D     <- 0                # utility when dead
u_Trt   <- 0.95             # utility when sick and being treated
```

04 Sample individual level characteristics

04.1 Static characteristics

```r
v_x     <- runif(n_i, min = 0.95, max = 1.05) # treatment effect modifier at baseline
```

04.2 Dynamic characteristics

```r
# sample from age distribution an initial age for every individual
v_age0  <- sample(x = dist_Age$age, prob = dist_Age$prop, size = n_i, replace = TRUE)
# a vector with the time of being sick at the start of the model

# Specify the initial health state of the individuals
# everyone begins in the healthy state (in this example)
# a vector with the initial health state for all individuals
v_M_init  <- rep("H", n_i)
v_Ts_init <- rep(0, n_i)         # since all individuals start healthy this value is zero for everyone
```

04.3 Create a dataframe with the individual characteristics

```r
df_X    <- data.frame(ID = 1:n_i, x = v_x, Age = v_age0, n_ts = v_Ts_init) # create a dataframe with an
```

05 Define Simulation Functions

05.1 Probability function

The function that updates the transition probabilities of every cycle is shown below.

```
Probs <- function(M_t, df_X, t) {
  # Arguments:
    # M_t: health state occupied by individual i at cycle t (character variable)
    # df_X:     data frame with individual characteristics data
  # t:     current cycle
# Returns:
  #   transition probabilities for that cycle

  # create matrix of state transition probabilities
  m_p_t           <- matrix(0, nrow = n_states, ncol = n_i)
  rownames(m_p_t) <-  v_n  # give the state names to the rows

  # lookup baseline probability and rate of dying based on individual characteristics
  p_HD_all <- inner_join(df_X, p_mort, by = c("Age"))
  p_HD     <- p_HD_all[M_t == "H","p_HD"]

  # update the m_p with the appropriate probabilities
  # transition probabilities when healthy
  m_p_t[, M_t == "H"]  <- rbind(1 - p_HS1 - p_HD, p_HS1, 0, p_HD)
  # transition probabilities when sick
  m_p_t[, M_t == "S1"] <- rbind(p_S1H, 1 - p_S1H - p_S1S2 - p_S1D[df_X$n_ts], p_S1S2, p_S1D[df_X$n_ts])
  # transition probabilities when sicker
  m_p_t[, M_t == "S2"] <- rbind(0, 0, 1 - p_S2D, p_S2D)
  # transition probabilities when dead
  m_p_t[, M_t == "D"]  <- rbind(0, 0, 0, 1)

  return(t(m_p_t))
}
```

05.2 Cost function

The `Costs` function estimates the costs at every cycle.

```
Costs <- function (M_t, Trt = FALSE) {
  # M_t: health state occupied by individual i at cycle t (character variable)
  # Trt:  is the individual being treated? (default is FALSE)

  c_t <- 0                                  # by default the cost for everyone is zero
  c_t[M_t == "H"]  <- c_H                   # update the cost if healthy
  c_t[M_t == "S1"] <- c_S1 + c_Trt * Trt    # update the cost if sick conditional on treatment
  c_t[M_t == "S2"] <- c_S2 + c_Trt * Trt    # update the cost if sicker conditional on treatment
  c_t[M_t == "D"]  <- c_D                   # update the cost if dead

  return(c_t)                                   # return the costs
}
```

05.3 Health outcome function

The `Effs` function to update the utilities at every cycle.

```
Effs <- function (M_t, df_X, Trt = FALSE, cl = 1) {
  # M_t: health state occupied by individual i at cycle t (character variable)
  # df_X: data frame with individual characteristics data
  # Trt:  is the individual treated? (default is FALSE)
  # cl:   cycle length (default is 1)

  u_t <- 0                                # by default the utility for everyone is zero
  u_t[M_t == "H"]  <- u_H                 # update the utility if healthy
  u_t[M_t == "S1" & Trt == FALSE] <- u_S1  # update the utility if sick
  # update the utility if sick but on treatment (adjust for individual effect modifier)
  u_t[M_t == "S1" & Trt == TRUE]  <- u_Trt * df_X$x[M_t == "S1"]
  u_t[M_t == "S2"] <- u_S2                # update the utility if sicker
  u_t[M_t == "D"]  <- u_D                 # update the utility if dead

  QALYs <-  u_t * cl  # calculate the QALYs during cycle t
  return(QALYs)       # return the QALYs
}
```

06 Run Microsimulation

```
MicroSim <- function(n_i, df_X, Trt = FALSE, seed = 1) {
# Arguments:
  # n_i:     number of individuals
    # df_X     data frame with individual characteristics data
    # Trt:     is this the individual receiving treatment? (default is FALSE)
  # seed:    default is 1

  set.seed(seed) # set the seed

  n_states <- length(v_n) # the number of health states

  # create three matrices called m_M, m_C and m_E
  # number of rows is equal to the n_i, the number of columns is equal to n_t
  # (the initial state and all the n_t cycles)
  # m_M is used to store the health state information over time for every individual
  # m_C is used to store the costs information over time for every individual
  # m_E is used to store the effects information over time for every individual

  m_M <- m_C <- m_E <- m_Ts <-  matrix(nrow = n_i, ncol = n_t + 1,
                                       dimnames = list(paste("ind"  , 1:n_i, sep = " "),
                                                       paste("cycle", 0:n_t, sep = " ")))

    m_M [, 1] <- v_M_init    # initial health state at cycle 0 for individual i

    # calculate costs per individual during cycle 0
    m_C[, 1]  <- Costs(m_M[, 1], Trt)
    # calculate QALYs per individual during cycle 0
```

```
    m_E[, 1]  <- Effs (m_M[, 1], df_X, Trt)

    # open a loop for time running cycles 1 to n_t
    for (t in 1:n_t) {
      # calculate the transition probabilities for the cycle based on  health state t
      m_P <- Probs(m_M[, t], df_X, t)
      # sample the current health state and store that state in matrix m_M
      m_M[, t + 1]  <- samplev(m_P)
      # calculate costs per individual during cycle t + 1
      m_C[, t + 1]  <- Costs(m_M[, t + 1], Trt)
      # calculate QALYs per individual during cycle t + 1
      m_E[, t + 1]  <- Effs(m_M[, t + 1], df_X, Trt)

      # update time since illness onset for t + 1
      df_X$n_ts <- if_else(m_M[, t + 1] == "S1", df_X$n_ts + 1, 0)
      # update the age of individuals that are alive
      df_X$Age[m_M[, t + 1] != "D"]  <- df_X$Age[m_M[, t + 1] != "D"] + 1

      # Display simulation progress
      if(t/(n_t/10) == round(t/(n_t/10), 0)) { # display progress every 10%
        cat('\r', paste(t/n_t * 100, "% done", sep = " "))
      }

    } # close the loop for the time points

  # calculate
  tc <- m_C %*% v_dwc    # total (discounted) cost per individual
  te <- m_E %*% v_dwe    # total (discounted) QALYs per individual
  tc_hat <- mean(tc)     # average (discounted) cost
  te_hat <- mean(te)     # average (discounted) QALYs

  # store the results from the simulation in a list
  results <- list(m_M = m_M, m_C = m_C, m_E = m_E, tc = tc , te = te, tc_hat = tc_hat,
                  te_hat = te_hat)

  return(results)  # return the results

} # end of the MicroSim function

# By specifying all the arguments in the `MicroSim()` the simulation can be started
# In this example the outcomes are of the simulation are stored in the variables `outcomes_no_tr` and `

# Run the simulation for both no treatment and treatment options
outcomes_no_trt  <- MicroSim(n_i, df_X, Trt = FALSE, seed = 1)
outcomes_trt     <- MicroSim(n_i, df_X, Trt = TRUE,  seed = 1)
```

07 Visualize results

```
options(scipen = 999) # disabling scientific notation in R

# No treatment
```

```r
plot(density(outcomes_no_trt$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes_no_trt$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_m_TR(outcomes_no_trt$m_M)  # health state trace

# Treatment
plot(density(outcomes_trt$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes_trt$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_m_TR(outcomes_trt$m_M)     # health state trace
```

08 Cost-Effectiveness Analysis

```r
# store the mean costs of each strategy in a new variable C (vector of costs)
v_C <- c(outcomes_no_trt$tc_hat, outcomes_trt$tc_hat)
# store the mean QALYs of each strategy in a new variable E (vector of effects)
v_E <- c(outcomes_no_trt$te_hat, outcomes_trt$te_hat)

# use dampack to calculate the ICER
calculate_icers(cost       = v_C,
                effect     = v_E,
                strategies = v_names_str)
```

09 Probabilistic Sensitivity Analysis (PSA)

```r
# Function that generates random sample for PSA
gen_psa <- function(n_sim = 1000, seed = 071818){
  set.seed(seed) # set a seed to be able to reproduce the same results

  df_psa <- data.frame(
    # Transition probabilities (per cycle)
    # NOTE: this is just a small part of all the model parameters that should be considered for PSA
    p_HS1   = rbeta(n_sim, 30, 170),          # probability to become sick when healthy
    p_S1H   = rbeta(n_sim, 60, 60) ,          # probability to become healthy when sick
    p_S1S2  = rbeta(n_sim, 84, 716),          # probability to become sicker when sick
    p_S2D   = rbeta(n_sim, 22, 434),          # probability to die in S2

    # Cost vectors with length n_sim
    # cost of remaining one cycle in state H
    c_H     = rgamma(n_sim, shape = 100, scale = 20)    ,
    # cost of remaining one cycle in state S1
    c_S1    = rgamma(n_sim, shape = 177.8, scale = 22.5),
    # cost of remaining one cycle in state S2
    c_S2    = rgamma(n_sim, shape = 225, scale = 66.7)  ,
    # cost of treatment (per cycle)
    c_trt   = rgamma(n_sim, shape = 73.5, scale = 163.3),
    # cost of being in the death state
    c_D     = 0                                         ,

    # Utility vectors with length n_sim
```

```r
    u_H   = rbeta(n_sim, shape1 = 200, shape2 = 3),   # utility when healthy
    u_S1  = rbeta(n_sim, shape1 = 130, shape2 = 45),  # utility when sick
    u_S2  = rbeta(n_sim, shape1 = 230, shape2 = 230), # utility when sicker
    u_D   = 0                                       , # utility when dead
    u_Trt = rbeta(n_sim, shape1 = 300, shape2 = 15),  # utility when being treated
    lb_eff  = 0.95,                                 # lower bound of effect modifier
    ub_eff  = 1.05                                  # upper bound of effect modifier
    )

  return(df_psa)
}
# Try it
gen_psa(10)

# Decrease number of individuals since PSA takes a lot of time
n_i <- 100000

# update Sample individual level characteristics

# Dynamic characteristics
# Specify the initial health state of the individuals
# everyone begins in the healthy state (in this example)
v_M_init  <- rep("H", n_i)    # a vector with the initial health state for all individuals


# Number of PSA simulations
n_sim <- 100

# Generate PSA input dataset
df_psa_input <- gen_psa(n_sim = n_sim)
# First six observations
head(df_psa_input)

## Histogram of parameters
# Make sure the Plots window is large enough to plot all the histograms
ggplot(melt(df_psa_input, variable.name = "Parameter"), aes(x = value)) +
  facet_wrap(~Parameter, scales = "free") +
  geom_histogram(aes(y = ..density..)) +
  theme_bw(base_size = 16)

# Initialize dataframes with PSA output
# Dataframe of costs
df_c <- as.data.frame(matrix(0,
                             nrow = n_sim,
                             ncol = n_str))
colnames(df_c) <- v_names_str
# Dataframe of effectiveness
df_e <- as.data.frame(matrix(0,
                             nrow = n_sim,
                             ncol = n_str))
colnames(df_e) <- v_names_str
```

09.1 Load function of microsimulation model

```
source(here("functions", "Function_Microsim_Sick-Sicker_time.R"))
# Test microsimulation function
calculate_ce_out(df_psa_input[1,])
```

09.2 Run microsimulation model on each parameter set of PSA input dataset

```
start.time <-proc.time()
for(i in 1:n_sim){
  df_ce_psa <- calculate_ce_out(df_psa_input[i, ])
   df_c[i, ] <- df_ce_psa$Cost   # take the cost from the psa run and store in df_c
   df_e[i, ] <- df_ce_psa$Effect # take the cost from the psa run in store in a df_e
  # Display simulation progress
  if(i/(n_sim/10) == round(i/(n_sim/10),0)) { # display progress every 10%
    cat('\r', paste('            ', 'Overall progress: ', i/n_sim * 100, "% done",
                    sep = " "))
  }
}
elapsed.time <-proc.time()-start.time

### Creae PSA object for dampack
l_psa <- make_psa_obj(cost = df_c,
                      effectiveness = df_e,
                      parameters = df_psa_input,
                      strategies = v_names_str)
```

09.3 Cost Effectiveness Analysis

Vector with willingness-to-pay (WTP) thresholds your considering and would like to have in your plot.

```
v_wtp <- seq(0, 300000, by = 10000)
```

09.3.1 ICER

```
# use dampack to calculate the ICER
calculate_icers(cost       = df_ce_psa$Cost,
                effect     = df_ce_psa$Effect,
                strategies = df_ce_psa$Strategy)
```

09.3.2 Cost-Effectiveness Acceptability Curves (CEAC) and Frontier (CEAF)

```
out_ceaf <- ceac(v_wtp, l_psa)
plot(out_ceaf)
```

09.3.3 Cost-Effectiveness Scatter plot

```
plot(l_psa)
```

07.4.4 Expected value of perfect information (EVPI)

```
evpi <- calc_evpi(wtp = v_wtp, psa = l_psa)
# EVPI plot
plot(evpi, effect_units = "QALY")
```