Microsimulation Sick-Sicker model

Includes individual characteristics: age, age dependent mortality probabilities, individual treatment effect modifyer

The DARTH workgroup

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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.

01 Load packages

```r
if (!require('pacman')) install.packages('pacman'); library(pacman) # use this package to conveniently
# load (install if required) packages from CRAN
p_load("dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "ggraph", "reshape2",
# load (install if required) packages from GitHub
# install_github("DARTH-git/darthtools", force = TRUE) # Uncomment if there is a newer version
p_load_gh("DARTH-git/darthtools")
```

02 Load functions

```r
# No functions needed
```

03 Input model parameters

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

# Model structure
n_t      <- 30                      # time horizon, 30 cycles
n_i      <- 100000                  # number of simulated individuals
v_names_states <- c("H", "S1", "S2", "D")  # the model states names
n_states <- length(v_names_states)  # 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("mortProb_age.csv")
# load age distribution
dist_Age <- read.csv("MyPopulation-AgeDistribution.csv")

p_S1D    <- 0.0149  # 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(er) and being treated
```

04 Sample individual level characteristics

04.1 Static characteristics

```
v_x      <- runif(n_i, min = 0.95, max = 1.05) # treatment effect modifier at baseline
# 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)
df_X     <- data.frame(ID = 1:n_i, x = v_x, Age = v_age0)
```

04.2 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
```

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) {
  # 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_names_states  # give the state names to the rows
```

```r
  # 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_HD) * (1 - p_HS1),
                                (1 - p_HD) *      p_HS1 ,
                                                      0,
                                   p_HD              )
  # transition probabilities when sick
  m_p_t[, M_t == "S1"] <- rbind((1 - p_S1D) *       p_S1H            ,
                                (1 - p_S1D) * (1 - p_S1H - p_S1S2),
                                (1 - p_S1D) *                p_S1S2 ,
                                   p_S1D                         )
  # 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.

```r
Costs <- function (M_t, Trt = FALSE) {
  # Arguments:
    # M_t: health state occupied at cycle t (character variable)
    # Trt: is the individual being treated? (default is FALSE)
  # Returns:
    # costs accrued in this cycle

  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 costs accrued this cycle
}
```

05.3 Health outcome function

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

```r
Effs <- function (M_t, df_X, Trt = FALSE, cl = 1) {
  # Arguments:
    # 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)
  # Returns:
    # QALYs accrued this cycle
  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 accrued this cycle
}
```

06 Run Microsimulation

```r
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

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

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

```r
      # calculate the transition probabilities for the cycle based on health state t
      m_P <- Probs(m_M[, t], df_X)
      # check if transition probabilities are between 0 and 1
      check_transition_probability(m_P, verbose = TRUE)
      # check if checks if each of the rows of the transition probabilities matrix sum to one
      check_sum_of_transition_array(m_P, n_rows = n_i, n_cycles = n_t, verbose = TRUE)
      # sample the current health state and store that state in matrix m_M
      m_M[, t + 1]  <- samplev(m_P, 1)
      # 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 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

```r
# No treatment
plot(density(outcomes_no_trt$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes_no_trt$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_trace_microsim(outcomes_no_trt$m_M)  # health state trace
```

```r
# Treatment
plot(density(outcomes_trt$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes_trt$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_trace_microsim(outcomes_trt$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)
```