Simple 3-state microsimulation model with PSA

Includes sex specific probability of dying when healthy and state occupation: probability of dying when sick depends on the time of being sick

The DARTH workgroup

Developed by the Decision Analysis in R for Technologies in Health (DARTH) workgroup:

Fernando Alarid-Escudero, PhD (1)

Eva A. Enns, MS, PhD (2)

M.G. Myriam Hunink, MD, PhD (3,4)

Hawre J. Jalal, MD, PhD (5)

Eline M. Krijkamp, MSc (3)

Petros Pechlivanoglou, PhD (6,7)

Alan Yang, MSc (7)

In collaboration of:

1. Drug Policy Program, Center for Research and Teaching in Economics (CIDE) - CONACyT, Aguascalientes, Mexico
2. University of Minnesota School of Public Health, Minneapolis, MN, USA
3. Erasmus MC, Rotterdam, The Netherlands
4. Harvard T.H. Chan School of Public Health, Boston, USA
5. University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA, USA
6. University of Toronto, Toronto ON, Canada
7. The Hospital for Sick Children, Toronto ON, Canada

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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.

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

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("here", "dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "ggraph", "r
 # 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/darthtools", force = TRUE) # Uncomment if there is a newer version
p_load_gh("DARTH-git/dampack", "DARTH-git/darthtools")
```

02 Load functions

```r
# No functions needed
```

03 Input model parameters

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

# Model structure
v_n   <- c("healthy", "sick", "dead")        # vector with state names
n_s   <- length(v_n)                         # number of states
n_t   <- 60                                  # number of cycles
n_i   <- 10000                               # number of individuals
d_e <- d_c <- 0.03                           # equal discount of costs and QALYs by 3%

# calculate discount weights for costs for each cycle based on discount rate d_c
v_dwc <- 1 / (1 + d_e) ^ (0:n_t)
# calculate discount weights for effectiveness for each cycle based on discount rate d_e
v_dwe <- 1 / (1 + d_c) ^ (0:n_t)

#### Deterministic analysis ####

# Transition probabilities
p_HS <- 0.05            # probability healthy -> sick
p_HD_female <- 0.0382   # probability health -> dead when female
p_HD_male   <- 0.0463   # probability health -> dead when male
m_p_HD      <- data.frame(Sex = c("Female", "Male"), p_HD = c(p_HD_female, p_HD_male))

# probability to die in sick state by cycle of being sick
p_SD <- c(0.1, 0.2, 0.3, 0.4, 0.5, rep(0.7, n_t - 5))
```

```r
# Costs inputs
c_H  <- 1500      # cost of one cycle in healthy state
c_S  <- 5000      # cost of one cycle in sick state
c_D  <- 0

# utility inputs
u_H  <- 1         # utility when healthy
u_S  <- 0.85      # utility when sick
u_D  <- 0         # utility when dead
```

04 Sample individual level characteristics

04.1 Static characteristics

```r
# randomly sample the sex of an individual (50% female)
v_sex <- sample(x = c("Female", "Male"), prob = c(0.5, 0.5), size = n_i, replace = TRUE)
df_X  <- data.frame(ID = 1:n_i, Sex = v_sex)
```

04.2 Dynamic characteristics

```r
# Specify the initial health state of the individuals
# everyone begins in the healthy state (in this example)
v_M_init  <- rep("healthy", times = n_i)
v_Ts_init <- rep(0, n_i)  # a vector with the time of being sick at the start of the model
```

05 Define Simulation Functions

05.1 Probability function

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

```r
Probs <- function(M_t, df_X, v_Ts) {
  # Arguments:
    # M_t: health state occupied  at cycle t (character variable)
    # df_X: data frame with individual characteristics data
    # v_Ts: vector with the duration of being sick
  # Returns:
    # transition probabilities for that cycle

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

  # lookup baseline probability and rate of dying based on individual characteristics
  p_HD_all <- inner_join(df_X, m_p_HD, by = c("Sex") )
```

```
  p_HD       <- p_HD_all[M_t == "healthy", "p_HD"]

  # update m_p_t with the appropriate probabilities
  # transition probabilities when healthy
  m_p_t[, M_t == "healthy"] <- rbind(1 - p_HD - p_HS, p_HS, p_HD)
  # transition probabilities when sick
  m_p_t[, M_t == "sick"]    <- rbind(0, 1 - p_SD[v_Ts], p_SD[v_Ts])
  # transition probabilities when dead
  m_p_t[, M_t == "dead"]    <- rbind(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) {
  # M_t: current health state
  c_t <- c()
  c_t[M_t == "dead"]    <- c_D    # costs at dead state
  c_t[M_t == "healthy"] <- c_H    # costs accrued by being healthy this cycle
  c_t[M_t == "sick"]    <- c_S    # costs accrued by being sick this cycle

  return(c_t)  # return costs accrued this cycle
}
```

05.3 Health outcome function

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

```
Effs <- function (M_t) {
  # M_t: current health state
  q_t <- c()
  q_t[M_t == "dead"]    <- u_D    # QALYs at dead state
  q_t[M_t == "healthy"] <- u_H    # QALYs accrued by being healthy this cycle
  q_t[M_t == "sick"]    <- u_S    # QALYs accrued by being sick this cycle

  return(q_t)  # return the QALYs accrued this cycle
}
```

06 Run Microsimulation

```
MicroSim <- function(n_i, df_X, seed = 1) {
  # Arguments:
    # n_i:    number of individuals
    # df_X    data frame with individual data
  # seed: default is 1
```

```r
  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 = " ")))

  m_M[, 1] <- v_M_init       # initial health state
  v_Ts     <- v_Ts_init      # initialize time since illnes onset
  m_C[, 1] <- Costs(m_M[, 1])  # costs accrued  during cycle 0
  m_E[, 1] <- Effs(m_M[, 1])   # QALYs accrued  during cycle 0

  # 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, v_Ts)
    # 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])
    # calculate QALYs per individual during cycle t + 1
    m_E[, t + 1]  <- Effs (m_M[, t + 1])

    # update time since illness onset for t + 1
    v_Ts <- if_else(m_M[, t + 1] == "sick", v_Ts + 1, 0)

    # 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

# Run the simulation model
outcomes <- MicroSim(n_i, df_X, seed = 1)

# Show results
results  <- data.frame("Total Cost" = outcomes$tc_hat, "Total QALYs" = outcomes$te_hat)
results
```

07 Visualize results

```
options(scipen = 999)
plot(density(outcomes$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_m_TR(outcomes$m_M)    # health state trace
```

08 Probabilistic Sensitivity Analysis (PSA)

```
# 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)
    # probability to become sick when healthy
    p_HS    = rbeta(n_sim, 24, 450)                        ,

    # Cost vectors with length n_sim
    # cost of remaining one cycle in state H
    c_H     = rgamma(n_sim, shape = 225, scale = 6.65)    ,
    # cost of remaining one cycle in state S1
    c_S     = rgamma(n_sim, shape = 625, scale = 8)       ,
    # cost of being in the death state
    c_D     = 0                                            ,

    # Utility vectors with length n_sim
    # utility when healthy
    u_H     = rbeta(n_sim, 9, 0.009)                      ,
    # utility when sick
    u_S     = rbeta(n_sim, 10, 1.75)                      ,
    # utility when dead
    u_D     = 0
  )
  return(df_psa)
}
gen_psa(n_sim = 10) # try it

# Decrease number of individuals since PSA takes a lot of time
```

```r
n_i <- 1000

# Dynamic characteristics
# Specify the initial health state of the individuals
# everyone begins in the healthy state (in this example)
v_M_init <- rep("healthy", times = n_i)
v_Ts_init <- rep(0, n_i) # a vector with the time of being sick at the start of the model

# Number of PSA simulations
n_sim <- 500

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

# Histogram of PSA parameters
# Make your 'Plots' window large in order to see the graphs!
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 and effectiveness
df_c <- df_e <- as.data.frame(matrix(0,
                             nrow = n_sim,
                             ncol = 1))
colnames(df_c) <- "Cost"
colnames(df_e) <- "Effectiveness"
```

08.1 Load function of microsimulation model

```r
source("Function_Microsim_3-state_time.R")
# Test microsimulation function
calculate_ce_out(df_psa_input[1, ], n_wtp = 10000)
```

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

```r
for(i in 1:n_sim){
  df_out_temp <- calculate_ce_out(df_psa_input[i, ], n_wtp = 10000)
  df_c[i, ] <- df_out_temp$Cost
  df_e[i, ] <- df_out_temp$Effect
  # 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 = " "))
  }
}
```

08.3 Cost Effectiveness Analysis

```
# make an PSA object using dampack
out_psa  <- make_psa_obj(df_c, df_e, df_psa_input, strategies = NULL, "$")
# Total cost and effectiveness
results  <- data.frame("Total Cost" = mean(out_psa$cost[, 1]),
                       "Total QALYs" = mean(out_psa$effectiveness[, 1]))
results

# Cost-Effectiveness Scatter plot
plot(out_psa)
```