

Microsimulation Sick-Sicker model with time dependency

Includes individual characteristics: age, age dependent mortality, individual treatment effect modifier, state-residency for the sick (S1) state, increasing change of death in the first 6 year of sickness

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)

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

Please cite our publications when using this code:

- Jalal H, Pechlivanoglou P, Krijkamp E, Alarid-Escudero F, Enns E, Hunink MG. An Overview of R in Health Decision Sciences. *Med Decis Making*. 2017; 37(3): 735-746. <https://journals.sagepub.com/doi/abs/10.1177/0272989X16686559>
- 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 EA, et al. A Multidimensional Array Representation of State-Transition Model Dynamics. *Med Decis Mak*. <https://doi.org/10.1177/0272989X19893973>

Copyright 2017, THE HOSPITAL FOR SICK CHILDREN AND THE COLLABORATING INSTITUTIONS. All rights reserved in Canada, the United States and worldwide. Copyright, trademarks, trade names and any and all associated intellectual property are exclusively owned by THE HOSPITAL FOR SICK CHILDREN and the collaborating institutions. These materials may be used, reproduced, modified, distributed and adapted with proper attribution.

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

01 Load packages

```
if (!require('pacman')) install.packages('pacman'); library(pacman)
# load (install if required) packages from CRAN
p_load("devtools", "dplyr", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "truncnorm", "ggraph")
# 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

```
# No functions needed
```

03 Input model parameters

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

# Strategy names
v_names_str <- c("no treatment", "treatment") # strategy names
n_str       <- length(v_names_str)           # number of strategies

# Model structure
v_names_states <- c("H", "S1", "S2", "D") # the model states names
n_states <- length(v_names_states)        # the number of health states

# Model parameters
n_t <- 30 # time horizon, 30 cycles
n_i <- 100000 # number of simulated individuals
d_r <- 0.03 # discount rate of 3% per cycle
v_dwe <- v_dwc <- 1 / ((1 + d_r) ^ (0:n_t)) # discount weight

# Event probabilities (per cycle)
# Annual transition probabilities
# (all non-probabilities are conditional on survival)
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("../data/mortProb_age.csv")
# load age distribution
dist_Age <- read.csv("../data/MyPopulation-AgeDistribution.csv")
```

```

# 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_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

```

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)

```

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", times = n_i)
v_Ts_init <- rep(0, n_i) # a vector with the time of being sick at the start of the model

```

04.3 Create a dataframe with the individual characteristics

```

# create a data frame with each individual's
# ID number, treatment effect modifier, age and initial time in sick state
df_X <- data.frame(ID = 1:n_i, x = v_x, Age = v_age0, n_ts = v_Ts_init, M_init = v_M_init)
head(df_X) # print the first rows of the dataframe

```

05 Define Simulation Functions

05.1 Probability function

The Probs function 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_names_states # 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
  # (all non-death probabilities are conditional on survival)
  # 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[df_X$n_ts]) * p_S1H,
                                (1 - p_S1D[df_X$n_ts]) * (1 - (p_S1H + p_S1S2)),
                                (1 - 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) {
  # Arguments:
  # M_t: health state occupied by individual i 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_Trtrt * Trt # update the cost if sick conditional on treatment
  c_t[M_t == "S2"] <- c_S2 + c_Trtrt * 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.

```

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
}

```

05.4 The Microsimulation function

```

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: seed for the random number generator, default is 1
  # Returns:
  # results: data frame with total cost and QALYs

  set.seed(seed) # set the seed

  n_states <- length(v_names_states) # 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 <- 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] <- as.character(df_X$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] <- Efs (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)
  # 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
  ## NOTE: to make this function work n_states = n_i in a Microsimulation
  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] <- Efs(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) QALY
# 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 `
```

06 Run Microsimulation

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

07 Visualize results

```
# 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
# 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

```
# 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
df_cea <- calculate_icers(cost      = v_C,
                        effect     = v_E,
                        strategies = v_names_str)

df_cea
```