

# 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

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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>

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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)
# load (install if required) packages from CRAN
p_load("here", "devtools", "dplyr", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "truncnorm", "
# 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

```
# 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
# (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("mortProb_age.csv")
# load age distribution
dist_Age <- read.csv("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_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
  # (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)
}

```

### 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)
}

```

### 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_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 <- 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] <- Effe (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
  check_sum_of_transition_array(m_P, n_states = n_i, n_t = n_t, verbose = TRUE)
  # 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] <- Effe(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 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

```
options(scipen = 999) # disable scientific notation in R
# No treatment
plot(density(outcomes_no_trt$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes_no_trt$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_m_TR(outcomes_no_trt$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

```
# 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
```