

# Microsimulation Sick-Sicker model with time dependency with PSA

Includes individual characteristics: age, age dependent mortality probabilities, individual treatment effect modifier, 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>

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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) # 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")
```

```

# 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

```

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

```

### 04.2 Dynamic characteristics

```

# 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

```

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_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 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_Trtr * 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('\n', 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

```

```

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
calculate_icers(cost      = v_C,
                effect    = v_E,
                strategies = v_names_str)

```

## 09 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)
    # 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

```

```

    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")
```