

# 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

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- 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 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", "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

```
# No functions needed
```

## 03 Input model parameters

```
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))
```

```

# 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

```

# 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

```

# 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.

```

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

```

```

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 illness 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

```

```

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

```

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

```

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)
```