

# PSA: Markov Sick-Sicker model in R

with age-specific mortality

The DARTH workgroup

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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",
       "reshape2", "knitr")
# load (install if required) packages from GitHub
# install_github("DARTH-git/dampack", force = TRUE) Uncomment if there is a newer version
p_load_gh("DARTH-git/dampack")
```

## 02 Load functions

```
source(here("functions", "Functions.R"))
```

## 03 Input model parameters

```
# Strategy names
v_names_str <- c("No Treatment", "Treatment")

# Number of strategies
n_str <- length(v_names_str)

# Markov model parameters
age      <- 25                # age at baseline
max_age  <- 55                # maximum age of follow up
n_t      <- max_age - age     # time horizon, number of cycles
v_n      <- c("H", "S1", "S2", "D") # the 4 states of the model: Healthy (H), Sick (S1),
                                   # Sicker (S2), Dead (D)
n_s      <- length(v_n)      # number of health states

# Transition probabilities (per cycle) and hazard ratios
# Read age-specific mortality rates from csv file
lt_usa_2005 <- read.csv(here("data", "HMD_USA_Mx_2015.csv"))
v_r_HD <- lt_usa_2005 %>%
  filter(Age >= age & Age <= (max_age-1)) %>%
  select(Total) %>%
  as.matrix()

p_HD      <- 1 - exp(- v_r_HD) # probability to die when healthy
p_HS1     <- 0.15             # probability to become sick when healthy
p_S1H     <- 0.5              # probability to become healthy when sick
```

```

p_S1S2 <- 0.105          # probability to become sicker when sick
hr_S1  <- 3              # hazard ratio of death in sick vs healthy
hr_S2  <- 10             # hazard ratio of death in sicker vs healthy
r_HD   <- -log(1 - p_HD)  # rate of death in healthy
r_S1D  <- hr_S1 * r_HD    # rate of death in sick
r_S2D  <- hr_S2 * r_HD    # rate of death in sicker
p_S1D  <- 1 - exp(-r_S1D) # probability to die in sick
p_S2D  <- 1 - exp(-r_S2D) # probability to die in sicker

# Cost and utility inputs
c_H    <- 2000           # cost of remaining one cycle in the healthy state
c_S1   <- 4000           # cost of remaining one cycle in the sick state
c_S2   <- 15000          # cost of remaining one cycle in the sicker state
c_trt  <- 12000          # cost of treatment(per cycle)
c_D    <- 0              # cost of being in the death state
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 being treated

# Discounting factor
d_r    <- 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_r) ^ (0:n_t)
# calculate discount weights for effectiveness for each cycle based on discount rate d_e
v_dwe  <- 1 / (1 + d_r) ^ (0:n_t)

```

## 04 Define and initialize matrices and vectors

### 04.1 Cohort trace

```

# create the markov trace matrix M capturing the proportion of the cohort in each state
# at each cycle
m_M_notrt <- m_M_trt <- matrix(NA,
                                nrow = n_t + 1, ncol = n_s,
                                dimnames = list(paste("cycle", 0:n_t, sep = " "), v_n))

head(m_M_notrt) # show first 6 rows of the matrix

# The cohort starts as healthy
m_M_notrt[1, ] <- m_M_trt[1, ] <- c(1, 0, 0, 0) # initiate first cycle of cohort trace

```

### 04.2 Transition probability array

```

# create transition probability array for NO treatment
a_P_notrt <- array(0,                                     # Create 3-D array
                  dim = c(n_s, n_s, n_t),
                  dimnames = list(v_n, v_n, 0:(n_t-1))) # name dimensions of the array

```

Fill in the transition probability array:

```
# from Healthy
a_P_notrt["H", "H", ] <- 1 - (p_HS1 + p_HD)
a_P_notrt["H", "S1", ] <- p_HS1
a_P_notrt["H", "D", ] <- p_HD
# from Sick
a_P_notrt["S1", "H", ] <- p_S1H
a_P_notrt["S1", "S1", ] <- 1 - (p_S1H + p_S1S2 + p_S1D)
a_P_notrt["S1", "S2", ] <- p_S1S2
a_P_notrt["S1", "D", ] <- p_S1D
# from Sicker
a_P_notrt["S2", "S2", ] <- 1 - p_S2D
a_P_notrt["S2", "D", ] <- p_S2D
# from Dead
a_P_notrt["D", "D", ] <- 1

### Check if transition matrix is valid (i.e., each row should add up to 1)
valid <- apply(a_P_notrt, 3, function(x) sum(rowSums(x))==n_s)
if (!isTRUE(all.equal(as.numeric(sum(valid)), as.numeric(n_t)))) {
  stop("This is not a valid transition Matrix")
}

### create transition probability matrix for treatment same as NO treatment
a_P_trt <- a_P_notrt
```

## 05 Run Markov model

```
for (t in 1:n_t){      # loop through the number of cycles
  m_M_notrt[t + 1, ] <- t(m_M_notrt[t, ]) %*% a_P_notrt[, , t]  # estimate the Markov
                                                                # trace for cycle the
                                                                # next cycle (t + 1)

  m_M_trt[t + 1, ]    <- t(m_M_trt[t, ]) %*% a_P_trt[, , t]      # estimate the Markov
                                                                # trace for cycle the
                                                                # next cycle (t + 1)
} # close the loop

head(m_M_notrt) # show the first 6 lines of the matrix
```

## 06 Compute and Plot Epidemiological Outcomes

### 06.1 Cohort trace

```
# create a plot of the data
matplot(m_M_notrt, type = 'l',
        ylab = "Probability of state occupancy",
        xlab = "Cycle",
```

```

    main = "Cohort Trace")
# add a legend to the graph
legend("topright", v_n, col = 1:n_s, lty = 1:n_s, bty = "n")

```

## 06.2 Overall Survival (OS)

```

# calculate the overall survival (OS) probability for no treatment
v_os_notrt_td <- 1 - m_M_notrt[, "D"]
# alternative way of calculating the OS probability
v_os_notrt_td <- rowSums(m_M_notrt[, 1:3])
# create a simple plot showing the OS
plot(age:max_age, v_os_notrt_td, type = 'l',
     ylim = c(0, 1),
     ylab = "Survival probability",
     xlab = "Age",
     main = "Overall Survival Age-Dependent")
# add grid
grid(nx = n_t, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"),
     equilogs = TRUE)

```

### 06.2.1 Life Expectancy (LE)

```

v_le_td <- sum(v_os_notrt_td) # summing probability of OS over time (i.e. life expectancy)

```

## 06.3 Disease prevalence

```

v_prev_td <- rowSums(m_M_notrt[, c("S1", "S2")])/v_os_notrt_td
plot(v_prev_td,
     ylim = c(0, 1),
     ylab = "Prevalence",
     xlab = "Cycle",
     main = "Disease prevalence")

```

### 06.4 ratio of sick(S1) vs sicker(S2)

```

v_ratio_S1S2_td <- m_M_notrt[, "S1"] / m_M_notrt[, "S2"]
plot(0:n_t, v_ratio_S1S2_td,
     xlab = "Cycle",
     ylab = "Ratio S1 vs S2",
     main = "Ratio of sick and sicker",
     col = "black", type = "l")

```

## 07 Compute Cost-Effectiveness Outcomes

```
# Vectors with costs and utilities by treatment
v_u_notrt <- c(u_H, u_S1, u_S2, u_D)
v_u_trt   <- c(u_H, u_trt, u_S2, u_D)

v_c_notrt <- c(c_H, c_S1, c_S2, c_D)
v_c_trt   <- c(c_H, c_S1 + c_trt, c_S2 + c_trt, c_D)
```

### 07.1 Mean Costs and QALYs for Treatment and NO Treatment

```
v_tu_notrt <- m_M_notrt %>% v_u_notrt
v_tu_trt   <- m_M_trt   %>% v_u_trt

v_tc_notrt <- m_M_notrt %>% v_c_notrt
v_tc_trt   <- m_M_trt   %>% v_c_trt
```

### 07.2 Discounted Mean Costs and QALYs

```
tu_d_notrt <- t(v_tu_notrt) %>% v_dwe
tu_d_trt   <- t(v_tu_trt)   %>% v_dwe

tc_d_notrt <- t(v_tc_notrt) %>% v_dwc
tc_d_trt   <- t(v_tc_trt)   %>% v_dwc

# store them into a vector
v_tc_d <- c(tc_d_notrt, tc_d_trt)
v_tu_d <- c(tu_d_notrt, tu_d_trt)

# Dataframe with discounted costs and effectiveness
df_ce <- data.frame(Strategy = v_names_str,
                    Cost      = v_tc_d,
                    Effect    = v_tu_d)

df_ce
```

### 07.3 Compute ICERs of the Markov model

```
df_cea <- calculate_icers(cost      = df_ce$Cost,
                          effect    = df_ce$Effect,
                          strategies = df_ce$Strategy)
```

### 07.4 Plot frontier of the Markov model

```
plot(df_cea, effect_units = "Quality of Life", xlim=c(16.8,17.8))
```

## 08 Deterministic Sensitivity Analysis

### 08.1 List of input parameters

Create list “l\_params\_all” with all input probabilities, cost and utilities.

```
l_params_all <- as.list(data.frame(
  p_HS1 = 0.15,          # probability to become sick when healthy
  p_S1H = 0.5,           # probability to become healthy when sick
  p_S1S2 = 0.105,       # probability to become sicker when sick
  hr_S1 = 3,             # hazard ratio of death in sick vs healthy
  hr_S2 = 10,            # hazard ratio of death in sicker vs healthy
  c_H = 2000,            # cost of remaining one cycle in the healthy state
  c_S1 = 4000,           # cost of remaining one cycle in the sick state
  c_S2 = 15000,          # cost of remaining one cycle in the sicker state
  c_trt = 12000,         # cost of treatment(per cycle)
  c_D = 0,               # cost of being in the death state
  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 treated
  d_e = 0.03,            # discount factor for effectiveness
  d_c = 0.03             # discount factor for costs
))

# store the parameter names into a vector
v_names_params <- c('p_HS1', 'p_S1H', 'p_S1S2', 'hr_S1', 'hr_S2', 'c_H', 'c_S1', 'c_S2', 'c_trt', 'c_D',
  'u_S1', 'u_S2', 'u_D', 'u_trt', 'd_e', 'd_c')
```

### 08.2 Load Sick-Sicker Markov model function

```
source(here("functions", "Functions_markov_sick-sicker_time.R"))
# Test function
calculate_ce_out(l_params_all)
```

### 08.3 One-way sensitivity analysis (OWSA)

```
v_params_owsa <-c("p_S1S2", "c_trt", "u_S1", "u_trt") # vector of names of parameters of interest

# dataframe containing all parameters, their basecase values, and the min and max values of the parameters
params_all_owsa <- data.frame(pars = v_names_params, basecase = as.numeric(l_params_all), min = rep(NA,
  length(v_names_params)), max = rep(NA, length(v_names_params)))
params_all_owsa$min[params_all_owsa$pars %in% v_params_owsa] <- c(0.05, 6000, 0.65, 0.80) # min values
params_all_owsa$max[params_all_owsa$pars %in% v_params_owsa] <- c(0.155, 18000, 0.85, 0.98) # max values
```

```

# list of all parameters with their basecase values
params_basecase_owsa <- as.list(params_all_owsa$basecase)
names(params_basecase_owsa) <- as.character(params_all_owsa$pars)

# dataframe containing name, min and max of parameters of interest
df_params_owsa <- params_all_owsa[params_all_owsa$pars %in% v_params_owsa, !colnames(params_all_owsa) %

owsa_nmb <- run_owsa_det(params_range = df_params_owsa, # parameters of interest
                        params_basecase = params_basecase_owsa, # dataframe containing all parameters
                        nsamp = 100, # number of parameter values
                        FUN = calculate_ce_out, # function to compute outputs
                        outcomes = c("NMB"), # output to do the OWSA on
                        strategies = v_names_str, # names of the strategies
                        n_wtp = 120000) # extra argument to pass to FUN

```

### 08.3.1 Plot OWSA

```

plot(owsa_nmb, txtsize = 16, n_x_ticks = 5,
     facet_scales = "free") +
  theme(legend.position = "bottom")

```

### 08.3.2 Optimal strategy with OWSA

```
owsa_opt_strat(owsa = owsa_nmb)
```

### 08.3.3 Tornado plot

```
owsa_tornado(owsa = owsa_nmb)
```

## 08.4 Two-way sensitivity analysis (TWSA)

```

v_params_twsa <- c("c_trt", "u_trt") # parameters of interest for TWSA
# dataframe containing all parameters, their basecase values, and the min and max values of the parameters
params_all_twsa <- data.frame(pars = v_names_params,
                              basecase = as.numeric(l_params_all),
                              min = rep(NA, length(v_names_params)),
                              max = rep(NA, length(v_names_params)))
params_all_twsa$min[params_all_twsa$pars %in% v_params_twsa] <- c( 6000, 0.80) # min parameter values
params_all_twsa$max[params_all_twsa$pars %in% v_params_twsa] <- c(18000, 0.98) # max parameter values

# list of all parameters with their basecase values
params_basecase_twsa <- as.list(params_all_twsa$basecase)
names(params_basecase_twsa) <- as.character(params_all_twsa$pars)

```



```

# dataframe containing name, min and max of parameters of interest
df_params_twsa <- params_all_twsa[params_all_twsa$pars %in% v_params_twsa, !colnames(params_all_twsa) %

twsa_nmb <- run_twsa_det(params_range = df_params_twsa, # parameters of interest
                        params_basecase = params_basecase_twsa, # dataframe containing all parameter b
                        nsamp = 40, # number of parameter values
                        FUN = calculate_ce_out, # function to compute outputs
                        outcomes = c("NMB"), # output to do the twsa on
                        strategies = v_names_str, # names of the strategies
                        n_wtp = 120000) # extra argument to pass to FUN

```

### 08.4.1 Plot TWSA

```
plot(twsa_nmb)
```

## 09 Probabilistic Sensitivity Analysis (PSA)

```

# Function to generate PSA input dataset
generate_psa_params <- 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)
    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
    hr_S1 = rlnorm(n_sim, log(3), 0.01), # rate ratio of death in S1 vs healthy
    hr_S2 = rlnorm(n_sim, log(10), 0.02), # rate ratio of death in S2 vs healthy

    # State rewards
    # Costs
    c_H = rgamma(n_sim, shape = 100, scale = 20), # cost of remaining one cycle in state H
    c_S1 = rgamma(n_sim, shape = 177.8, scale = 22.5), # cost of remaining one cycle in state S1
    c_S2 = rgamma(n_sim, shape = 225, scale = 66.7), # cost of remaining one cycle in state S2
    c_Trt = rgamma(n_sim, shape = 73.5, scale = 163.3), # cost of treatment (per cycle)
    c_D = 0, # cost of being in the death state

    # Utilities
    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
    d_e = 0.03, # discount factor for effectiveness
    d_c = 0.03 # discount factor for costs
  )
  return(df_psa)
}
# Try it

```

```

generate_psa_params(10)

# Number of simulations
n_sim <- 1000

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

# Histogram of parameters
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 matrices 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 Conduct probabilistic sensitivity analysis

```

# Run Markov model on each parameter set of PSA input dataset
for(i in 1:n_sim){
  l_out_temp <- calculate_ce_out(df_psa_input[i, ])
  df_c[i, ] <- l_out_temp$Cost
  df_e[i, ] <- l_out_temp$Effect
  # Display simulation progress
  if(i/(n_sim/10) == round(i/(n_sim/10),0)) { # display progress every 10%
    cat('\r', paste(i/n_sim * 100, "% done", sep = " "))
  }
}

```

## 09.2 Create PSA object for dampack

```

l_psa <- make_psa_obj(cost      = df_c,
                     effectiveness = df_e,
                     parameters  = df_psa_input,
                     strategies  = v_names_str)

```

### 09.2.1 Save PSA objects

```
save(df_psa_input, df_c, df_e, v_names_str, n_str,
     l_psa,
     file = here("output", "markov_sick-sicker_time_PSA_dataset.RData"))
```

## 09.3 Create probabilistic analysis graphs

```
load(file = here("output", "markov_sick-sicker_time_PSA_dataset.RData"))
```

Vector with willingness-to-pay (WTP) thresholds.

```
v_wtp <- seq(0, 200000, by = 10000)
```

### 09.3.1 Cost-Effectiveness Scatter plot

```
plot(l_psa)
```

## 09.4 Conduct CEA with probabilistic output

```
# Compute expected costs and effects for each strategy from the PSA
df_out_ce_psa <- summary(l_psa)

# Calculate incremental cost-effectiveness ratios (ICERs)
df_cea_psa <- calculate_icers(cost      = df_out_ce_psa$meanCost,
                             effect    = df_out_ce_psa$meanEffect,
                             strategies = df_out_ce_psa$Strategy)

df_cea_psa

# Save CEA table with ICERs
# As .RData
save(df_cea_psa,
     file = here("tables",
                  "markov_sick-sicker_time_probabilistic_CEA_results.RData"))

# As .csv
write.csv(df_cea_psa,
          file = here("tables",
                       "markov_sick-sicker_time_probabilistic_CEA_results.csv"))
```

### 09.4.1 Plot cost-effectiveness frontier

```
plot(df_cea_psa)
```

### 09.4.2 Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)

```
ceac_obj <- ceac(wtp = v_wtp, psa = l_psa)
# Regions of highest probability of cost-effectiveness for each strategy
summary(ceac_obj)
# CEAC & CEAF plot
plot(ceac_obj)
```

### 09.4.3 Expected Loss Curves (ELCs)

```
elc_obj <- calc_exp_loss(wtp = v_wtp, psa = l_psa)
elc_obj
# ELC plot
plot(elc_obj, log_y = FALSE)
```

### 09.4.4 Expected value of perfect information (EVPI)

```
evpi <- calc_evpi(wtp = v_wtp, psa = l_psa)
# EVPI plot
plot(evpi, effect_units = "QALY")
```