

# PSA: Markov Sick-Sicker model in R

The DARTH workgroup

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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 E, Pechlivanoglou P, Hunink MM, Jalal H. A Multidimensional Array Representation of State-Transition Model Dynamics. *Med Decis Making*. 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", "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

```
# 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)
p_HD     <- 0.005             # 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 matrix

```

# create the transition probability matrix for NO treatment (notrt)
m_P_notrt <- matrix(0,
                    nrow = n_s,
                    ncol = n_s,
                    dimnames = list(v_n, v_n)) # name the columns and rows of the matrix

m_P_notrt

```

Fill in the transition probability matrix:

```

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

# check rows add up to 1
rowSums(m_P_notrt)

# create transition probability matrix for treatment same as no treatment
m_P_trt <- m_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, ]) %*% m_P_notrt      # estimate the Markov trace
                                                                # for the next cycle (t + 1)
  m_M_trt[t + 1, ]    <- t(m_M_trt[t, ]) %*% m_P_trt         # estimate the Markov trace
                                                                # for 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 <- 1 - m_M_notrt[, "D"]
# alternative way of calculating the OS probability
v_os_notrt <- rowSums(m_M_notrt[, 1:3])
# create a simple plot showing the OS
plot(0:n_t, v_os_notrt, type = 'l',
     ylim = c(0, 1),
     ylab = "Survival probability",
     xlab = "Cycle",
     main = "Overall Survival")
# 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 <- sum(v_os_notrt) # summing probability of OS over time (i.e. life expectancy)
```

## 06.3 Disease prevalence

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

### 06.4 Proportion of sick in S1 state

```
v_prop_S1 <- m_M_notrt[, "S1"] / v_prev
plot(0:n_t, v_prop_S1,
     xlab = "Cycle",
     ylab = "Proportion",
     main = "Proportion of sick in S1 state",
     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)

df_cea
```

## 07.4 Plot frontier of the Markov model

```
plot(df_cea, effect_units = "Quality of Life", xlim = c(15.6, 16.6))
```

## 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_HD    = 0.005, # 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
  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_HD', 'p_HS1', 'p_S1H', 'p_S1S2',
  'hr_S1', 'hr_S2', 'c_H', 'c_S1', 'c_S2', 'c_trt', 'c_D',
  'u_H', 'u_S1', 'u_S2', 'u_D', 'u_trt', 'd_e', 'd_c')
```

### 08.2 Load Sick-Sicker Markov model function

```
source("Functions_markov_sick-sicker.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 pa
params_all_owsa$max[params_all_owsa$pars %in% v_params_owsa] <- c(0.155, 18000 , 0.85, 0.98) # max pa

# 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
    p_HD = rbeta(n_sim, 10, 1990), # probability to die when healthy
    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 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 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 = "markov_sick-sicker_PSA_dataset.RData")
```

## 09.3 Create probabilistic analysis graphs

```
load(file = "markov_sick-sicker_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 = "markov_sick-sicker_probabilistic_CEA_results.RData")  
# As .csv  
write.csv(df_cea_psa,  
          file = "markov_sick-sicker_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)

The expected loss is the the quantification of the foregone benefits when choosing a suboptimal strategy given current evidence.

```
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")
```