

# 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*. 2020 Online first. <https://doi.org/10.1177/0272989X19893973>
- Alarid-Escudero, F., Krijkamp, E. M., Enns, E. A., Hunink, M. G. M., Pechlivanoglou, P., & Jalal, H. (2020). Cohort state-transition models in R: From conceptualization to implementation. *arXiv:2001.07824v1*, 1–31. <http://arxiv.org/abs/2001.07824>
- Alarid-Escudero, F., Enns, E. A., Kuntz, K. M., Michaud, T. L., & Jalal, H. (2019). “Time Traveling Is Just Too Dangerous” But Some Methods Are Worth Revisiting: The Advantages of Expected Loss Curves Over Cost-Effectiveness Acceptability Curves and Frontier. *Value in Health*, 22(5), 611–618. <https://doi.org/10.1016/j.jval.2019.02.008>

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```
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 install other packages  
# load (install if required) packages from CRAN  
p_load("here", "dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval",  
       "igraph", "truncnorm", "ggraph", "reshape2", "knitr", "stringr", "reshape2")  
# 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/dectree", force = TRUE) Uncomment if there is a newer version  
# install_github("annaheath/EVSI", force = TRUE) #Uncomment if there is a newer version  
p_load_gh("DARTH-git/dampack", "DARTH-git/dectree")  
p_load_gh("annaheath/EVSI")
```

## 02 Load functions

```
source("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)  
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 - START HERE

### 08.1 List of input parameters

Create list `l_params_all` with all input probabilities, cost and utilities.

```

l_params_all <- list(
  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_parms <- names(l_params_all)

```

## 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)

```
options(scipen = 999) # disabling scientific notation in R
# dataframe containing all parameters, their basecase values, and the min and
# max values of the parameters of interest
df_params_owsa <- data.frame(pars = c( , , , ), # SPECIFY PARAMETERS AND MIN MAX VALUES
                             min = c( , , , ), # min parameter values
                             max = c( , , , ) # max parameter values
                             )

owsa_nmb <- run_owsa_det(params_range = df_params_owsa, # dataframe with parameters for owsa
                        params_basecase = l_params_all, # list with 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

```
# YOUR TURN
```

### 08.3.2 Optimal strategy with OWSA

```
# YOUR TURN
```

### 08.3.3 Tornado plot

```
# YOUR TURN
```

## 08.4 Two-way sensitivity analysis (TWSA)

```
# dataframe containing all parameters, their basecase values, and the min and
# max values of the parameters of interest
df_params_twsa <- data.frame(pars = c( , ), # SPECIFY PARAMETERS AND MIN MAX VALUES
                             min = c( , ), # min parameter values
                             max = c( , ) # max parameter values
                             )

twsa_nmb <- run_twsa_det(params_range = df_params_twsa, # dataframe with parameters for twsa
                        params_basecase = l_params_all, # list with all parameters
                        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

*# YOUR TURN*

## 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 = # SPECIFY DISTRIBUTION , # probability to become sick when healthy
    p_S1H = # SPECIFY DISTRIBUTION , # probability to become healthy when sick
    p_S1S2 = # SPECIFY DISTRIBUTION , # probability to become sicker when sick
    p_HD = # SPECIFY DISTRIBUTION , # probability to die when healthy
    hr_S1 = # SPECIFY DISTRIBUTION , # rate ratio of death in S1 vs healthy
    hr_S2 = # SPECIFY DISTRIBUTION , # rate ratio of death in S2 vs healthy

    # State rewards
    # Costs
    c_H = # SPECIFY DISTRIBUTION , # cost of remaining one cycle in state H
    c_S1 = # SPECIFY DISTRIBUTION , # cost of remaining one cycle in state S1
    c_S2 = # SPECIFY DISTRIBUTION , # cost of remaining one cycle in state S2
    c_Trt = # SPECIFY DISTRIBUTION , # cost of treatment (per cycle)
    c_D = # SPECIFY DISTRIBUTION , # cost of being in the death state

    # Utilities
    u_H = # SPECIFY DISTRIBUTION , # utility when healthy
    u_S1 = # SPECIFY DISTRIBUTION , # utility when sick
    u_S2 = # SPECIFY DISTRIBUTION , # utility when sicker
    u_D = # SPECIFY DISTRIBUTION , # utility when dead
    u_Trt = # SPECIFY DISTRIBUTION , # utility when being treated
    d_e = # SPECIFY DISTRIBUTION , # discount factor for effectiveness
    d_c = # SPECIFY DISTRIBUTION , # discount factor for costs
  )
  return(df_psa)
}

# Try it
generate_psa_params(10)
```

```
# Number of simulations
n_sim <- 1000
```

```
# Generate PSA input dataset
# YOUR TURN
```

```
# First six observations
head(df_psa_input)
```

```
# Histogram of parameters
# YOUR TURN
```

```
# 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
# YOUR TURN

```

## 09.2 Create PSA object for dampack

```

# YOUR TURN

```

### 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

```

# YOUR TURN

```

## 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

*# YOUR TURN*

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

*# YOUR TURN*

#### 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.

*# YOUR TURN*

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

*# YOUR TURN*

#### 07.4.5 Expected value of partial perfect information (EVPPI)

```

evppi <- calc_evppi(psa = l_psa,
                  wtp = v_wtp,
                  params = c("p_S1S2"),
                  outcome = c("nmb"),
                  type = c("gam", "poly"),
                  poly.order = 2,
                  k = -1,
                  pop = 1
)
# EVPPI plot
dampack::plot.evppi(evppi)

```