

# SA: Markov Sick-Sicker model in R

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*. Feb;40(2):242-248. <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
p_load_gh("DARTH-git/dampack", "DARTH-git/darthtools")
```

## 02 Load functions

```
# No function needed
```

## 03 Input model parameters

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

# 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)

v_init <- c("H" = 1,
           "S1" = 0,
           "S2" = 0,
           "D" = 0)      # initial cohort distribution (everyone allocated to the "healthy"

# Transition probabilities (per cycle)
p_HD    <- 0.005        # probability to die when healthy
p_HS1   <- 0.15         # probability to become sick when healthy, conditional on surviving
p_S1H   <- 0.5          # probability to become healthy when sick, conditional on surviving
p_S1S2  <- 0.105        # probability to become sicker when sick, conditional on surviving
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
d_e      <- d_c <- 0.03  # discount rate per cycle equal discount of costs and QALYs by 3%

n_str     <- length(v_names_str) # Number of strategies
n_states  <- length(v_n)        # number of states

# Discount weights for costs and effects
v_dwc <- 1 / (1 + d_c) ^ (0:n_t)
v_dwe <- 1 / (1 + d_e) ^ (0:n_t)

```

Create a state-transition diagram of the cohort model

```

m_P_diag <- matrix(0, nrow = n_states, ncol = n_states, dimnames = list(v_n, v_n))
m_P_diag["H" , "S1"] = ""
m_P_diag["H" , "D" ] = ""
m_P_diag["H" , "H" ] = ""
m_P_diag["S1", "H" ] = ""
m_P_diag["S1", "S2"] = ""
m_P_diag["S1", "D" ] = ""
m_P_diag["S1", "S1"] = ""
m_P_diag["S2", "D" ] = ""
m_P_diag["S2", "S2"] = ""
m_P_diag["D" , "D" ] = ""
layout.fig <- c(3, 1)

plotmat(t(m_P_diag), t(layout.fig), self.cex = 0.5, curve = 0, arr.pos = 0.7,
        latex = T, arr.type = "curved", relsize = 0.9, box.prop = 0.8,
        cex = 0.8, box.cex = 0.9, lwd = 1)

```

## 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_states,
                                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 both treatment arms
m_P_notrt <- m_P_trt <- matrix(0,
                                nrow = n_states,
                                ncol = n_states,
                                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_HD) * (1 - p_HS1)
m_P_notrt["H", "S1"] <- (1 - p_HD) * p_HS1
m_P_notrt["H", "D"] <- p_HD
# from Sick
m_P_notrt["S1", "H"] <- (1 - p_S1D) * p_S1H
m_P_notrt["S1", "S1"] <- (1 - p_S1D) * (1 - (p_S1H + p_S1S2))
m_P_notrt["S1", "S2"] <- (1 - p_S1D) * 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 that transition probabilities are in [0, 1]
check_transition_probability(m_P_notrt, verbose = TRUE)
# Check that all rows sum to 1
check_sum_of_transition_array(m_P_notrt, n_states = n_states, n_cycles = n_t, verbose = TRUE)

# Overwrite the transition probability matrix for treatment with the no treatment values as they are the same
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_states, lty = 1:n_states, 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"),
     equilog = 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 = "QALYs", 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, conditional on surviving
  p_S1H   = 0.5,   # probability to become healthy when sick, conditional on surviving
  p_S1S2  = 0.105, # probability to become sicker when sick, conditional on surviving
  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 <- names(l_params_all)
```

## 08.2 Load Sick-Sicker Markov model function

```
source("Functions_markov_sick-sicker_sol.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("p_S1S2", "c_trt", "u_S1", "u_trt"),
                             min = c(0.05, 6000, 0.65, 0.80), # min parameter values
                             max = c(0.155, 18000, 0.85, 0.98) # 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

```
plot(owsa_nmb, txtsize = 10, n_x_ticks = 4,
     facet_scales = "free") +
  theme(legend.position = "bottom")
```

### 08.3.2 Optimal strategy with OWSA

```
owsa_opt_strat(owsa = owsa_nmb, txtsize = 10)
```

### 08.3.3 Tornado plot

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

## 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("c_trt", "u_trt"),
                             min = c(6000, 0.80), # min parameter values
                             max = c(18000, 0.98) # 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

```

l ## 08.4.1 Plot TWSA

```
plot(twsa_nmb)
```

## 09 Probabilistic Sensitivity Analysis (PSA)

```

# Function to generate PSA input dataset
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)
    p_HS1 = rbeta(n_sim, shape1 = 30, shape2 = 170), # probability to become sick when healthy
    p_S1H = rbeta(n_sim, shape1 = 60, shape2 = 60),  # probability to become healthy when sick
    p_S1S2 = rbeta(n_sim, shape1 = 84, shape2 = 716), # probability to become sicker when sick
    p_HD   = rbeta(n_sim, shape1 = 10, shape2 = 1990), # probability to die when healthy
    hr_S1  = rlnorm(n_sim, meanlog = log(3), sdlog = 0.01), # rate ratio of death in S1 vs healthy
    hr_S2  = rlnorm(n_sim, meanlog = log(10), sdlog = 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
gen_psa(10)

# Number of simulations
n_sim <- 1000

# Generate PSA input dataset
df_psa_input <- gen_psa(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..)) +
  scale_x_continuous(breaks = scales::pretty_breaks(n = 3)) +
  theme_bw(base_size = 16) +
  theme(axis.text = element_text(size=6))

# 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")
```