

# 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*. 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 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(1, 0, 0, 0) # initial cohort distribution

# 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)

```

## 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_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)

# 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 <- 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)

```

# your turn

```

### 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)

```
# your turn
```

### 08.4.1 Plot TWSA

```
# your turn
```

## 09 Probabilistic Sensitivity Analysis (PSA)

```
# Function to generate PSA input dataset  
gen_psa <-
```

### 09.1 Conduct probabilistic sensitivity analysis

```
# your turn
```

### 09.2 Create PSA object for dampack

```
# your turn
```

#### 09.2.1 Save PSA objects

```
# your turn
```

### 09.3 Create probabilistic analysis graphs

```
# your turn
```

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



*# your turn*

### 09.3.1 Cost-Effectiveness Scatter plot

*# your turn*

## 09.4 Conduct CEA with probabilistic output

*# your turn*

### 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)

*# your turn*

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

*# your turn*