

# Markov Sick-Sicker model in R

with age-dependency

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("dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "truncnorm", "ggraph")
# load (install if required) packages from GitHub
# install_github("DARTH-git/darthtools", force = TRUE) Uncomment if there is a newer version
p_load_gh("DARTH-git/darthtools")
```

## 02 Load functions

```
# all functions are in the darthtools package
```

## 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_names_states <- 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" state)

# Transition probabilities (per cycle) and hazard ratios
# Read age-specific mortality rates from csv file for the age 25 - 54
lt_usa_2015 <- read.csv("../data/HMD_USA_Mx_2015.csv")
v_r_HD <- lt_usa_2015 %>%
  filter(Age >= age & Age <= (max_age - 1)) %>%
  select(Total) %>%
  as.matrix()

# Transition probabilities (per cycle)
p_HD      <- rate_to_prob(r = v_r_HD, t = 1) # probability to die when healthy (vector)
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_S1D <- hr_S1 * v_r_HD # rate of death in sick (vector)
r_S2D <- hr_S2 * v_r_HD # rate of death in sicker (vector)
p_S1D <- rate_to_prob(r = r_S1D, t = 1) # probability to die in sick (vector)
p_S2D <- rate_to_prob(r = r_S2D, t = 1) # probability to die in sicker (vector)

# 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_names_states) # 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_names_states, v_names_states))
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_names_states))

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

# The cohort starts as healthy
m_M_notrt[1, ] <- m_M_trt[1, ] <- v_init # initiate first cycle of cohort trace
```

## 04.2 Transition probability matrix

```
# create the transition probability matrix for NO treatment
a_P_notrt <- a_P_trt <- array(0,                                     # Create 3-D array
                              dim = c(n_states, n_states, n_t),
                              dimnames = list(v_names_states, v_names_states, 0:(n_t-1))) # name and rows of the m
a_P_notrt[, , 1:3]
a_P_trt[, , 1:3]
```

Fill in the transition probability matrix:

```
# from Healthy
a_P_notrt["H", "H", ] <- (1 - p_HD) * (1 - p_HS1)
a_P_notrt["H", "S1", ] <- (1 - p_HD) *      p_HS1
a_P_notrt["H", "D", ] <- p_HD
# from Sick
a_P_notrt["S1", "H", ] <- (1 - p_S1D) * p_S1H
a_P_notrt["S1", "S1", ] <- (1 - p_S1D) * (1 - (p_S1H + p_S1S2))
a_P_notrt["S1", "S2", ] <- (1 - p_S1D) * 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 that transition probabilities are in [0, 1]
check_transition_probability(a_P_notrt, verbose = TRUE)
# Check that all rows sum to 1
check_sum_of_transition_array(a_P_notrt, n_states = n_states, n_cycles = n_t, verbose = TRUE)

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

The transition probabilities are similar in both strategies. Therefore, the cohort trace figure applies to both strategies.

```
# 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_names_states, 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(min(df_cea$Effect) - 0.5,
                max(df_cea$Effect) + 0.5))

```