

# 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("dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "truncnorm", "ggraph")
# 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

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

## 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_states <- length(v_n)  # number of health states
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
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_e <- d_c <- 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_e) ^ (0:n_t)
# calculate discount weights for effectiveness for each cycle based on discount rate d_e
v_dwe <- 1 / (1 + d_c) ^ (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, ] <- v_init # initiate first cycle of cohort trace

```

## 04.2 Transition probability matrix

```

# create the transition probability matrix for NO treatment
m_P_notrt <- 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_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

# 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_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))
```