

# Markov Sick-Sicker model in R

with dependency for time-since model start AND with state-residency 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*. 2020 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 functions needed
```

## 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

# Tunnels
n_tunnel_size <- n_t
# Sick state
v_Sick_tunnels <- paste("S1_", seq(1, n_tunnel_size), "Yr", sep = "")
### Create variables for time-dependent model
v_n_tunnels    <- c("H", v_Sick_tunnels, "S2", "D") # state names
n_states_tunnels <- length(v_n_tunnels)             # number of states

# Transition probabilities (per cycle) and hazard ratios
# Read age-specific mortality rates from csv file
lt_usa_2005 <- read.csv("HMD_USA_Mx_2015.csv")
```

```

v_r_HD <- lt_usa_2005 %>%
  filter(Age >= age & Age <= (max_age-1)) %>%
  select(Total) %>%
  as.matrix()

p_HD <- 1 - exp(- v_r_HD) # 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

# Weibull parameters
l <- 0.08 # scale
g <- 1.1 # shape
# Weibull function
p_S1S2 <- l*g*(1:n_tunnel_size)^(g-1) # probability to become sicker when sick
# (time-dependent)

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_states_tunnels,

```

```

dimnames = list(paste("cycle", 0:n_t, sep = " "), v_n_tunnels))

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

# The cohort starts as healthy
# initialize first cycle of Markov trace accounting for the tunnels
m_M_notrt[1, ] <- m_M_trt[1, ] <- c(1, rep(0, n_tunnel_size), 0, 0)

```

## 04.2 Transition probability array

```

# create the transition probability array for NO treatment
a_P_notrt <- array(0, # Create 3-D array
  dim = c(n_states_tunnels, n_states_tunnels, n_t),
  dimnames = list(v_n_tunnels, v_n_tunnels, 0:(n_t-1))) # name dimensions

```

Fill in the transition probability array:

```

# from Healthy
a_P_notrt["H", "H", ] <- (1 - p_HD) * (1 - p_HS1)
a_P_notrt["H", v_Sick_tunnels[1], ] <- (1 - p_HD) * p_HS1
a_P_notrt["H", "D", ] <- p_HD

# from Sick
for(i in 1:(n_tunnel_size - 1)){
  a_P_notrt[v_Sick_tunnels[i], "H", ] <- (1 - p_S1D) * p_S1H
  a_P_notrt[v_Sick_tunnels[i], v_Sick_tunnels[i + 1], ] <-
    (1 - p_S1D) * (1 - (p_S1H + p_S1S2[i]))
  a_P_notrt[v_Sick_tunnels[i], "S2", ] <- (1 - p_S1D) * p_S1S2[i]
  a_P_notrt[v_Sick_tunnels[i], "D", ] <- p_S1D
}
a_P_notrt[v_Sick_tunnels[n_tunnel_size], "H", ] <- (1 - p_S1D) * p_S1H
a_P_notrt[v_Sick_tunnels[n_tunnel_size], v_Sick_tunnels[n_tunnel_size], ] <-
  (1 - p_S1D) * (1 - (p_S1H + p_S1S2[n_tunnel_size]))
a_P_notrt[v_Sick_tunnels[n_tunnel_size], "S2", ] <- (1 - p_S1D) * p_S1S2[n_tunnel_size]
a_P_notrt[v_Sick_tunnels[n_tunnel_size], "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_tunnels, n_t = 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, ] <- t(m_M_notrt[t, ]) %*% a_P_notrt[ , , t] # estimate the Markov
                                                                # trace for cycle the
                                                                # next cycle (t + 1)

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

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

# create aggregated traces
m_M_td_notrt <- cbind(H = m_M_notrt[, "H"],
                     S1 = rowSums(m_M_notrt[, 2:(n_tunnel_size + 1)]),
                     S2 = m_M_notrt[, "S2"],
                     D = m_M_notrt[, "D"])
head(m_M_td_notrt)

m_M_td_trt <- cbind(H = m_M_trt[, "H"],
                  S1 = rowSums(m_M_trt[, 2:(n_tunnel_size + 1)]),
                  S2 = m_M_trt[, "S2"],
                  D = m_M_trt[, "D"])
head(m_M_td_trt)
```

## 06 Compute and Plot Epidemiological Outcomes

### 06.1 Cohort trace

```
# create a plot of the data
matplot(m_M_td_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_tunnels <- 1 - m_M_notrt[, "D"]
# alternative way of calculating the OS probability
v_os_notrt_tunnels <- rowSums(m_M_notrt[, 1:3])
# create a simple plot showing the OS
plot(age:max_age, v_os_notrt_tunnels, type = 'l',
```

```

ylim = c(0, 1),
ylab = "Survival probability",
xlab = "Age",
main = "Overall Survival Age-dependent with tunnels")
# 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_tunnels <- sum(v_os_notrt_tunnels) # summing probability of OS over time
# (i.e. life expectancy)

```

## 06.3 Disease prevalence

```

v_prev_tunnels <- rowSums(m_M_td_notrt[, c("S1", "S2")]) / v_os_notrt_tunnels
plot(v_prev_tunnels,
     ylim = c(0, 1),
     ylab = "Prevalence",
     xlab = "Cycle",
     main = "Disease prevalence")

```

### 06.4 ratio of sick(S1) vs sicker(S2)

```

v_ratio_S1S2_tunnels <- m_M_td_notrt[, "S1"] / m_M_td_notrt[, "S2"]
plot(0:n_t, v_ratio_S1S2_tunnels,
     xlab = "Cycle",
     ylab = "Ratio S1 vs S2",
     main = "Ratio of sick and sicker",
     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_td_notrt %*% v_u_notrt
v_tu_trt   <- m_M_td_trt   %*% v_u_trt

v_tc_notrt <- m_M_td_notrt %*% v_c_notrt
v_tc_trt   <- m_M_td_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)

# Store discounted costs and effectiveness for each strategy in a data frame
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

```

# Use the function calculate_icers() from the dampack package
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(17,18))

```