

# Survival Analysis - Sick-Sicker model

The DARTH workgroup

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Please cite our publications when using this code:

- 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. *BioRxiv* 670612 2019.<https://www.biorxiv.org/content/10.1101/670612v1>

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Change `eval` to `TRUE` if you want to knit this document.

## 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", "gems", "flexsurv", "survHE", "ggplot2", "msm", "igraph", "mstate",
# 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

```
set.seed(1) # set the seed
v_names_states <- c("S1", "S2", "D") # the model states names

# Model structure
n_t <- 30 # time horizon, 30 cycles
c_l <- 1
d_r <- 0.015 # discount rate of 1.5% per cycle

p_S2D <- 0.2 # probability of dying in sicker state

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

# Cost inputs
c_H <- 2000 # cost of one cycle in the healthy state
c_S1 <- 4000 # cost of one cycle in the sick state
c_S2 <- 15000 # cost of one cycle in the sicker state
c_D <- 0 # cost of one cycle in the dead state
c_Trt <- 12000 # cost of treatment (per cycle)

# Utility inputs
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_Trtrt <- 0.95          # utility when sick(er) and being treated

v_dw      <- 1 / ((1 + d_r) ^ (0:n_t))      # discount weight
n_states  <- length(v_names_states)         # the number of health states
v_names_str <- c("no treatment", "treatment") # strategy names

times      <- seq(0, n_t, c_l)              # the cycles in years

```

Survival analysis component

```

# Load the Sicker data
data_long <- read.csv("data_long_Sicker.csv", row.names = 1)
head(data_long)

# Models can be fitted independently for each transition. This is more flexible!

# Create subsets for each transition
data_S1S2 <- data_long[data_long$from == "S1" & data_long$to == "S2",]
data_S1D  <- data_long[data_long$from == "S1" & data_long$to == "D" ,]

# Fit independent models for each transition and pick one that fits best
fit_S1S2 <- fit.fun(time = "time", status = "status", data = data_S1S2, times = times)
fit_S1D  <- fit.fun(time = "time", status = "status", data = data_S1D,  times = times)

# Find the best-fitting models based on AIC
fit_S1S2$AIC
fit_S1D$AIC
best_S1S2 <- fit_S1S2$model.objects$models$log-Logistic
best_S1D  <- fit_S1D$model.objects$models$Exponential

# Calculate the transition probabilities from the best-fitting survival models
p_S1S2 <- trans_prob(surv_prob(best_S1S2))
p_S1D  <- trans_prob(surv_prob(best_S1D))

```

## 04 Define and initialize matrices and vectors

### 04.1 Cohort trace

```

# create the cohort trace
m_M <- matrix(NA,
              nrow = n_t + 1, # create Markov trace (n.t + 1 because R doesn't
                              # understand cycle 0)
              ncol = n_states,
              dimnames = list(0:n_t, v_names_states))

m_M[1, ] <- v_init # initialize first cycle of Markov trace

```

## 04.2 Transition probability array

```
# create the transition probability array
a_P <- 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 the dimensions of the
```

Fill in the transition probability array:

```
# from Sick
a_P["S1", "S1", ] <- (1 - p_S1D) * (1 - p_S1S2)
a_P["S1", "S2", ] <- (1 - p_S1D) * p_S1S2
a_P["S1", "D", ] <- p_S1D

# from Sicker
a_P["S2", "S2", ] <- 1 - p_S2D
a_P["S2", "D", ] <- p_S2D

# from Dead
a_P["D", "D", ] <- 1
```

## 04.3 Check if transition array and probabilities are valid

```
# Check that transition probabilities are in [0, 1]
check_transition_probability(a_P, verbose = TRUE)
# Check that all rows sum to 1
check_sum_of_transition_array(a_P, n_rows = n_states, n_cycles = n_t, verbose = TRUE)
```

## 05 Run Markov model

```
for (t in 1:n_t){ # t<-1                                # loop through the number of cycles
  m_M[t + 1, ] <- m_M[t, ] %*% a_P[, , t]                # estimate the Markov trace for cycle t + 1
                                                         # using the t-th matrix from the
                                                         # probability array
}
head(m_M) # print the first lines of the matrix
matplot(m_M, type = 'l')
```

## 07 Compute Cost-Effectiveness Outcomes

```
# Vectors with costs and utilities by treatment
v_u_notrt <- c(u_S1, u_S2, u_D)
v_u_trt <- c(u_Trt, u_S2, u_D)

v_c_notrt <- c(c_S1, c_S2, c_D)
v_c_trt <- c(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 %>% v_u_notrt
v_tu_trt   <- m_M %>% v_u_trt

v_tc_notrt <- m_M %>% v_c_notrt
v_tc_trt   <- m_M %>% v_c_trt
```

## 07.2 Discounted Mean Costs and QALYs

```
tu_d_notrt <- t(v_tu_notrt) %>% v_dw
tu_d_trt   <- t(v_tu_trt)   %>% v_dw

tc_d_notrt <- t(v_tc_notrt) %>% v_dw
tc_d_trt   <- t(v_tc_trt)   %>% v_dw

# 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")
```