

Survival Analysis - Sick-Sicker model

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. *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.

```
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", "gems", "flexsurv", "survHE", "ggplot2", "msm", "igraph", "mstate",
       "reshape2", "knitr")
# load (install if required) packages from GitHub
# install_github("DARTH-git/dampack", force = TRUE) Uncomment if there is a newer version
p_load_gh("DARTH-git/dampack")
```

02 Load functions

```
source(here("functions", "functions.R"))
```

03 Input model parameters

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

# Model structure
n_t <- 30 # time horizon, 30 cycles
c_l <- 1
n_i <- 100000 # number of simulated individuals
n_s <- length(v_n) # the number of health states
d_r <- 0.03 # discount rate of 3% per cycle
v_dw <- 1 / ((1 + d_r) ^ (0:n_t)) # discount weight
v_names_str <- c("no treatment", "treatment") # strategy names

# Event probabilities (per cycle)
# Annual transition probabilities
p_HS1 <- 0.15 # probability of becoming sick when healthy

# Annual probabilities of death
# load age dependent probability
p_mort <- read.csv(here("data", "mortProb_age.csv"))
# load age distribution
dist_Age <- read.csv(here("data", "MyPopulation-AgeDistribution.csv"))

# 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_Trtr   <- 0.95         # utility when sick(er) and being treated

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

```

04 Sample individual level characteristics

04.1 Static characteristics

```

set.seed(2019) # set the seed for the simulation of individual characteristics
v_x           <- runif(n_i, min = 0.95, max = 1.05) # treatment effect modifier at baseline

# sample from age distribution an initial age for every individual
v_age0        <- sample(x = dist_Age$age, prob = dist_Age$prop, size = n_i, replace = TRUE)

# store the information at baseline into a data frame.
df_X          <- data.frame(ID = 1:n_i, x = v_x, Age = v_age0)

```

Survival analysis component

```

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

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

# Create subsets for each transition
data_S1H <- subset(data_long, trans == 1)
data_S1S2 <- subset(data_long, trans == 2)
data_S1D <- subset(data_long, trans == 3)
data_S2D <- subset(data_long, trans == 4)

# fit independent models for each transition and pick the one with the lowest AIC
fit_S1H <- fit.fun(time = "time", status = "status", data = data_S1H, times = times,
  extrapolate = F)
fit_S1S2 <- fit.fun(time = "time", status = "status", data = data_S1S2, times = times,
  extrapolate = F)
fit_S1D <- fit.fun(time = "time", status = "status", data = data_S1D, times = times,
  extrapolate = F)
fit_S2D <- fit.fun(time = "time", status = "status", data = data_S2D, times = times,
  extrapolate = F)

best.fit_S1H <- fit_S1H [[which.min(fit_S1H$AIC)]]
best.fit_S1S2 <- fit_S1S2 [[which.min(fit_S1S2$AIC)]]
best.fit_S1D <- fit_S1D [[which.min(fit_S1D$AIC)]]
best.fit_S2D <- fit_S2D [[which.min(fit_S2D$AIC)]]

# Extract transition probabilities from the best fitting models

```

```
p_S1H <- flexsurvreg_prob(object = best.fit_S1H, t = times)
p_S1S2 <- flexsurvreg_prob(object = best.fit_S1S2, t = times)
p_S1D <- flexsurvreg_prob(object = best.fit_S1D, t = times)
p_S2D <- flexsurvreg_prob(object = best.fit_S2D, t = times)
```

04.2 Dynamic characteristics

```
# Specify the initial health state of the individuals
# everyone begins in the healthy state (in this example)
v_M_init <- rep("H", n_i) # a vector with the initial health state for all individuals
v_Ts1_init <- rep(0, n_i) # a vector with the time of being sick at the start of the model
v_Ts2_init <- rep(0, n_i) # a vector with the time of being sick at the start of the model
```

05 Define Simulation Functions

05.1 Probability function

The function that updates the transition probabilities of every cycle is shown below.

```
Probs <- function(M_t, df_X, v_Ts1, v_Ts2, t) {
  # Arguments:
  # M_t: health state occupie at cycle t (character variable)
  # v_Ts: time an individual is sick
  # t: current cycle
  # Returns:
  # transition probabilities for that cycle

  # create matrix of state transition probabilities
  m_p_t <- matrix(0, nrow = n_s, ncol = n_i)
  rownames(m_p_t) <- v_n # give the state names to the rows

  # lookup baseline probability and rate of dying based on individual characteristics
  p_HD_all <- inner_join(df_X, p_mort, by = c("Age"))
  p_HD <- p_HD_all[M_t == "H", "p_HD"]

  # update the v_p with the appropriate probabilities
  # transition probabilities when healthy
  m_p_t[, M_t == "H"] <- rbind(1 - p_HS1 - p_HD, p_HS1, 0, p_HD)
  # transition probabilities when sick
  m_p_t[, M_t == "S1"] <- rbind(p_S1H[v_Ts1], 1 - p_S1H[v_Ts1] - p_S1S2[v_Ts1] -
                                p_S1D[v_Ts1], p_S1S2[v_Ts1], p_S1D[v_Ts1])
  # transition probabilities when sicker
  m_p_t[, M_t == "S2"] <- rbind(0, 0, 1 - p_S2D[v_Ts2], p_S2D[v_Ts2])
  # transition probabilities when dead
  m_p_t[, M_t == "D"] <- rbind(0, 0, 0, 1)
  return(t(m_p_t))
}
```

05.2 Cost function

The Costs function estimates the costs at every cycle.

```
Costs <- function (M_t, Trt = FALSE) {  
  # M_t: health state occupied by individual i at cycle t (character variable)  
  # Trt: is the individual being treated? (default is FALSE)  
  
  c_t <- vector("numeric", n_i)      # create the cost variable  
  c_t[M_t == "H"] <- c_H              # update the cost if healthy  
  c_t[M_t == "S1"] <- c_S1 + c_Trtr * Trt # update the cost if sick conditional  
                                          # on treatment  
  c_t[M_t == "S2"] <- c_S2 + c_Trtr * Trt # update the cost if sicker conditional  
                                          # on treatment  
  c_t[M_t == "D"] <- c_D              # update the cost if dead  
  
  return(c_t)                        # return the costs  
}
```

05.3 Health outcome function

The Effs function to update the utilities at every cycle.

```
Effs <- function (M_t, df_X, Trt = FALSE, cl = 1) {  
  # M_t: health state occupied by individual i at cycle t (character variable)  
  # df_X: individual characteristics including Age, Sex and the effect modifier of  
  #       the treatment effect  
  # Trt: is the individual treated? (default is FALSE)  
  # cl:  cycle length (default is 1)  
  
  u_t <- 0 # by default the utility for everyone is zero  
  u_t[M_t == "H"] <- u_H # update the utility if healthy  
  u_t[M_t == "S1" & Trt == FALSE] <- u_S1 # update the utility if sick  
  # update the utility if sick but on treatment (adjust for individual effect modifier)  
  u_t[M_t == "S1" & Trt == TRUE] <- u_Trtr * df_X$x[M_t == "S1"]  
  u_t[M_t == "S2"] <- u_S2 # update the utility if sicker  
  u_t[M_t == "D"] <- u_D # update the utility if dead  
  
  QALYs <- u_t * cl # calculate the QALYs during cycle t  
  return(QALYs)    # return the QALYs  
}
```

06 Run Microsimulation

```
MicroSim <- function(n_i, df_X, Trt = FALSE, seed = 1) {  
  # Arguments:  
  # n_i:      number of individuals  
  # df_X:     data frame with individual data  
  # Trt:      is this the individual receiving treatment? (default is FALSE)  
  # seed:     default is 1  
}
```

```

set.seed(seed)      # set the seed

n_s <- length(v_n) # the number of health states

# create three matrices called m_M, m_C and m_E
# number of rows is equal to the n_i, the number of columns is equal to n_t
# (the initial state and all the n_t cycles)
# m_M is used to store the health state information over time for every individual
# m_C is used to store the costs information over time for every individual
# m_E is used to store the effects information over time for every individual

m_M <- m_C <- m_E <- m_Ts <- matrix(nrow = n_i, ncol = n_t + 1,
                                     dimnames = list(paste("ind" , 1:n_i, sep = " "),
                                                       paste("cycle", 0:n_t, sep = " ")))

m_M[, 1] <- v_M_init      # initial health state at cycle 0 for individual i
v_Ts1 <- v_Ts1_init      # initialize time since illness onset for individual i
v_Ts2 <- v_Ts2_init      # initialize time since illness onset for individual i

m_C[, 1] <- Costs(m_M[, 1], Trt)      # calculate costs per individual during cycle 0
m_E[, 1] <- Effs(m_M[, 1], df_X, Trt) # calculate QALYs per individual during cycle 0

# open a loop for time running cycles 1 to n_t
for (t in 1:n_t) {
  # calculate the transition probabilities for the cycle based on health state t
  m_p <- Probs(m_M[, t], df_X, v_Ts1, v_Ts2, t)
  # sample the current health state and store that state in matrix m_M
  m_M[, t + 1] <- samplev(m_p, 1)
  # calculate costs per individual during cycle t + 1
  m_C[, t + 1] <- Costs(m_M[, t + 1], Trt)
  # calculate QALYs per individual during cycle t + 1
  m_E[, t + 1] <- Effs(m_M[, t + 1], df_X, Trt)

  v_Ts1 <- if_else(m_M[, t + 1] == "S1", v_Ts1 + 1, 0)
  v_Ts2 <- if_else(m_M[, t + 1] == "S2", v_Ts2 + 1, 0)
  df_X$Age[m_M[, t + 1] != "D"] <- df_X$Age[m_M[, t + 1] != "D"] + 1

  # Display simulation progress
  if(t/(n_t/10) == round(t/(n_t/10), 0)) { # display progress every 10%
    cat('\r', paste(t/n_t * 100, "% done", sep = " "))
  }
} # close the loop for the time points

# calculate
tc <- m_C %>% v_dw      # total (discounted) cost per individual
te <- m_E %>% v_dw      # total (discounted) QALYs per individual
tc_hat <- mean(tc)      # average (discounted) cost
te_hat <- mean(te)      # average (discounted) QALYs

# store the results from the simulation in a list
results <- list(m_M = m_M, m_C = m_C, m_E = m_E, tc = tc , te = te, tc_hat = tc_hat, te_hat = te_hat)

```

```

return(results) # return the results

} # end of the MicroSim function

# By specifying all the arguments in the `MicroSim()` the simulation can be started
# In this example the outcomes are of the simulation are stored in the variables `outcomes_no_tr` and `

# Run the simulation for both no treatment and treatment options
outcomes_no_trt <- MicroSim(n_i, df_X, Trt = FALSE, seed = 1)
outcomes_trt    <- MicroSim(n_i, df_X, Trt = TRUE, seed = 1)

```

07 Visualize results

```

options(scipen = 999)

# No treatment
plot(density(outcomes_no_trt$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes_no_trt$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_m_TR(outcomes_no_trt$m_M) # health state trace

# Treatment
plot(density(outcomes_trt$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
plot(density(outcomes_trt$te), main = paste("Total QALYs per person"), xlab = "QALYs")
plot_m_TR(outcomes_trt$m_M)    # health state trace

```

08 Cost Effectiveness Analysis

```

# store the mean costs of each strategy in a new variable C (vector of costs)
v_C <- c(outcomes_no_trt$tc_hat, outcomes_trt$tc_hat)
# store the mean QALYs of each strategy in a new variable E (vector of effects)
v_E <- c(outcomes_no_trt$te_hat, outcomes_trt$te_hat)

# use dampack to calculate the ICER
calculate_icers(cost      = v_C,
                effect    = v_E,
                strategies = v_names_str)

```