Markov Sick-Sicker model in R

The DARTH workgroup

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- 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

```r
rm(list = ls())        # clear memory (removes all the variables from the workspace)
```

01 Load packages

```r
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/dectree", force = TRUE) Uncomment if there is a newer version
p_load_gh("DARTH-git/dampack", "DARTH-git/dectree")
```

02 Load functions

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

03 Input model parameters

```r
# 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

# 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
```

```r
# 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

```r
# 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
```

```
##         H S1 S2  D
## cycle 0 NA NA NA NA
## cycle 1 NA NA NA NA
## cycle 2 NA NA NA NA
## cycle 3 NA NA NA NA
## cycle 4 NA NA NA NA
## cycle 5 NA NA NA NA
```

```r
# The cohort starts as healthy
m_M_notrt[1, ] <- m_M_trt[1, ] <- c(1, 0, 0, 0) # initiate first cycle of cohort trace
```

04.2 Transition probability matrix

```r
# 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
```

```
##    H S1 S2 D
## H  0  0  0 0
## S1 0  0  0 0
## S2 0  0  0 0
## D  0  0  0 0
```

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

# check rows add up to 1
rowSums(m_P_notrt)
```

```
##  H S1 S2  D
##  1  1  1  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
```

```
##                 H         S1         S2          D
## cycle 0 1.0000000 0.0000000 0.00000000 0.00000000
## cycle 1 0.8450000 0.1500000 0.00000000 0.00500000
```

```
## cycle 2 0.7890250 0.1837612 0.01575000 0.01146377
## cycle 3 0.7586067 0.1881968 0.03427491 0.01892157
## cycle 4 0.7351211 0.1853199 0.05235988 0.02719916
## cycle 5 0.7138373 0.1807036 0.06925860 0.03620055
```

06 Compute and Plot Epidemiological Outcomes

06.1 Cohort trace

```r
# 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")
```
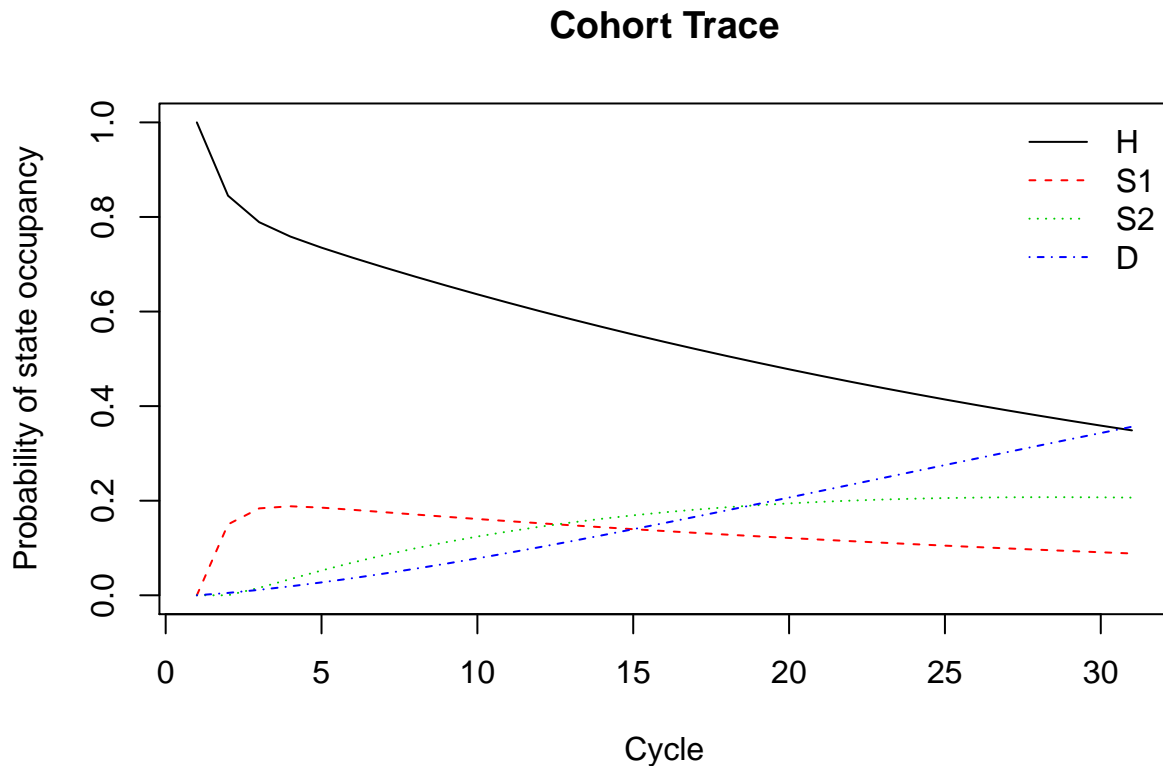

06.2 Overall Survival (OS)

```r
# 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
```

```r
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"),
     equilogs = TRUE)
```

Overall Survival
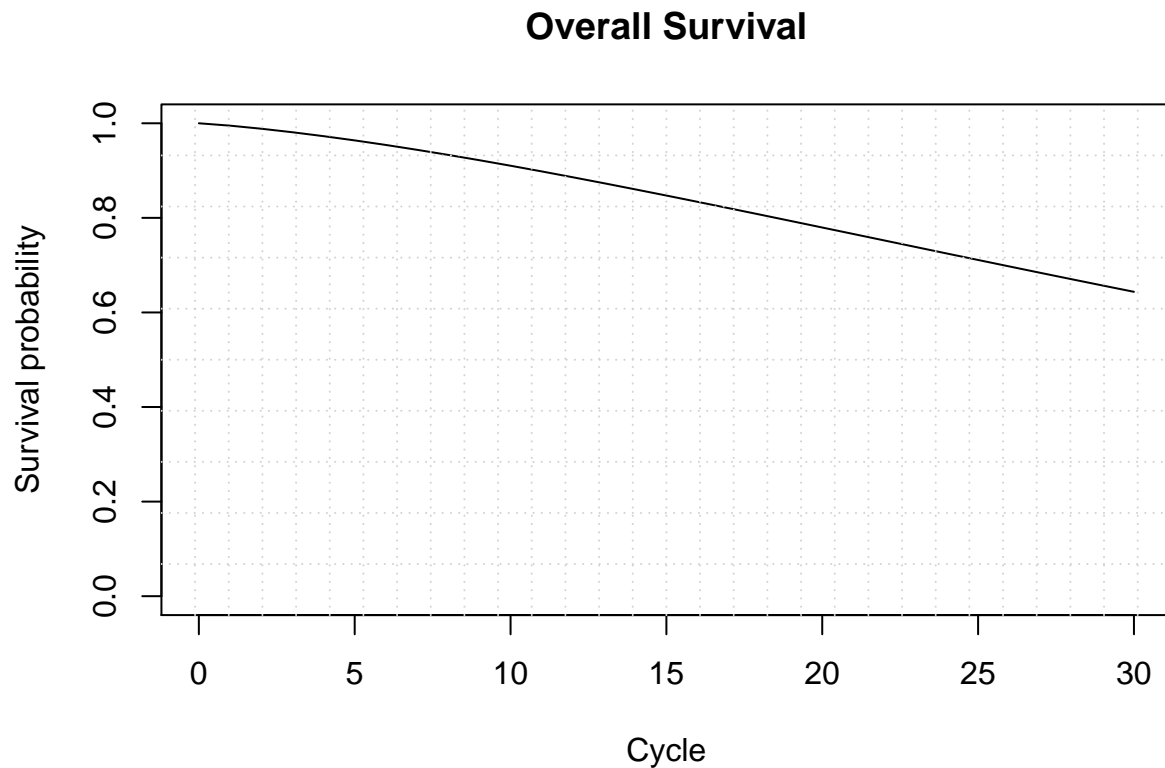
06.2.1 Life Expectancy (LE)

```r
v_le <- sum(v_os_notrt)      # summing probablity of OS over time  (i.e. life expectancy)
```
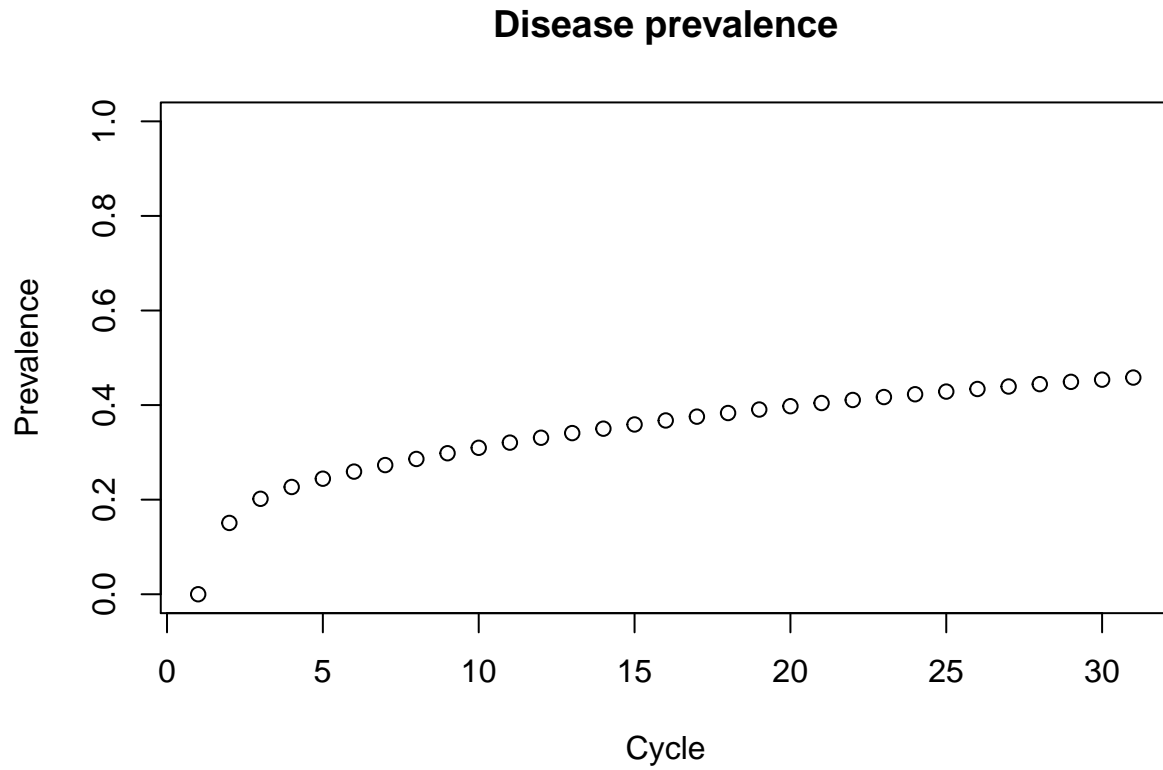
06.3 Disease prevalence

```r
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")
```
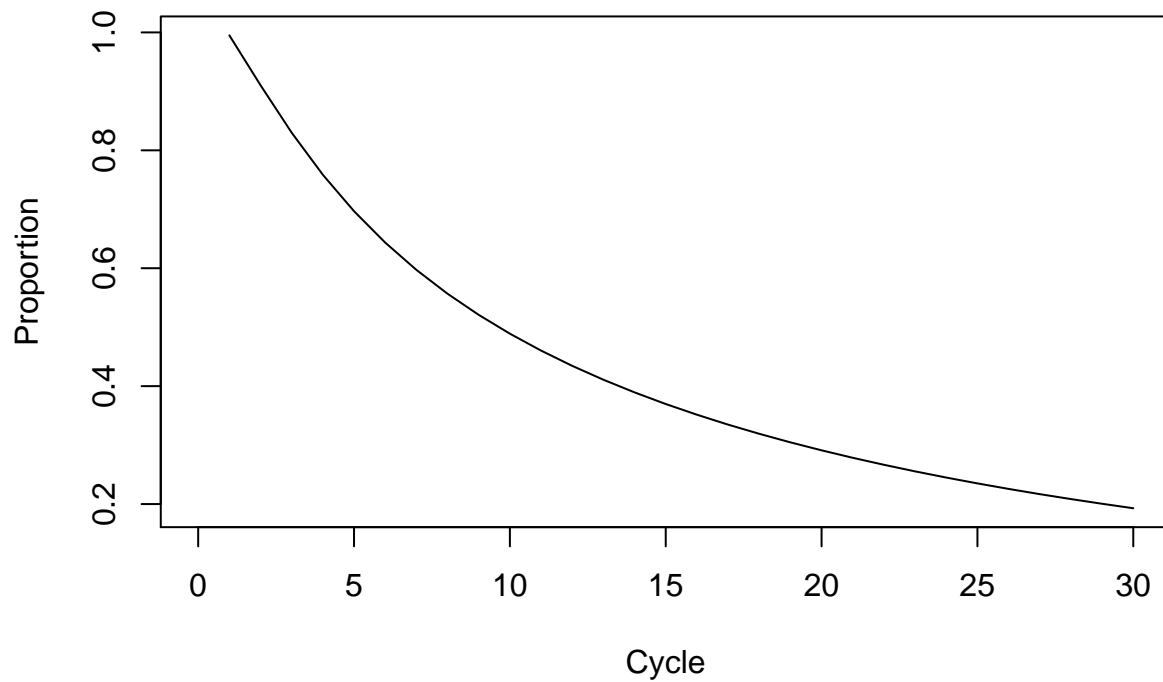
Disease prevalence

06.4 Proportion of sick in S1 state

```r
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")
```

Proportion of sick in S1 state

07 Compute Cost-Effectiveness Outcomes

```r
# 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

```r
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

```r
tu_d_notrt  <- t(v_tu_notrt)    %*%  v_dwe
tu_d_trt    <- t(v_tu_trt)      %*%  v_dwe
```

```r
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
```

```
##         Strategy       Cost    Effect
## 1 No Treatment   75976.15 15.83885
## 2    Treatment  141623.03 16.40041
```

07.3 Compute ICERs of the Markov model

```r
df_cea <- calculate_icers(cost       = df_ce$Cost,
                          effect     = df_ce$Effect,
                          strategies = df_ce$Strategy)
df_cea
```

```
##         Strategy       Cost    Effect Inc_Cost Inc_Effect      ICER Status
## 1 No Treatment   75976.15 15.83885       NA         NA        NA     ND
## 2    Treatment  141623.03 16.40041 65646.88  0.5615578 116901.4     ND
```

07.4 Plot frontier of the Markov model

```r
plot(df_cea, effect_units = "Quality of Life", xlim = c(15.6, 16.6))
```