Markov Sick-Sicker model in R

with "OpenTree"

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

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

```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", "devtools", "scales", "ellipse", "lazyeval", "igraph", "truncnorm", "ggraph", "reshape2"
# load (install if required) packages from GitHub
# install_github("DARTH-git/darthtools", force = TRUE) Uncomment if there is a newer version
p_load_gh("DARTH-git/darthtools", "DARTH-git/OpenTree")
```

02 Load functions

```r
# all functions are in the darthtools package so no need for additional functions
```

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, conditional on surviving
p_S1H    <- 0.5                         # probability to become healthy when sick, conditional on surviving
p_S1S2   <- 0.105                       # probability to become sicker when sick, conditional on surviving
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 Create model in OpenTree

```
open_tree(file_name = "OpenTree_sick_sicker", dir_name = getwd())
```

04.1 Extract and initialize matrices and vectors from OpenTree

```
# extract the transition probability matrix and the initial state vector
l_markov  <- evaluate_model("OpenTree_sick_sicker", n_payoffs = 2)
m_P_notrt <- l_markov$m_P
v_s_init  <- l_markov$v_s_init

# create transition probability matrix for treatment (same as no treatment)
m_P_trt <- m_P_notrt
```

04.2 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_s_init # initiate first cycle of cohort trace
```

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)

```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
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)
```

06.2.1 Life Expectancy (LE)

```r
v_le <- sum(v_os_notrt)  # summing probability 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")
```

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")
```

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

```
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))
```