3-state Markov model in R

with age 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
- Alarid-Escudero F, Krijkamp EM, Enns EA, Yang A, Hunink MGM Pechlivanoglou P, Jalal H. Cohort State-Transition Models in R: A Tutorial. arXiv:200107824v2. 2020:1-48. http://arxiv.org/abs/2001.07824
- 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 Mak. 2020;40(2):242-248. https://doi.org/10.1177/0272989X19893973

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("diagram", "dampack")
# install_github("DARTH-git/darthtools", force = TRUE) Uncomment if there is a newer version
p_load_gh("DARTH-git/darthtools")
```

02 Load functions

```
# No functions needed
```

03 Input model parameters

```
## General setup
n_cycles        <- 60                             # number of cycles
v_names_cycles  <- paste("cycle", 0:n_cycles)     # cycle names
v_names_states  <- c("Healthy", "Sick", "Dead")   # state names
n_states        <- length(v_names_states)         # number of health states

# Discounting factors
d_c             <- 0.03                           # discount rate for costs
d_e             <- 0.03                           # discount rate for QALYs

# Strategy names
v_names_str     <- c("Standard of Care",          # store the strategy names
                     "Treatment A",
                     "Treatment B")
n_str           <- length(v_names_str)            # number of strategies

## Transition probabilities
p_HS_SoC  <- 0.05  # probability of becoming sick when healthy, conditional on surviving, under standar
p_HS_trtA <- 0.04  # probability of becoming sick when healthy, conditional on surviving, under treatme
p_HS_trtB <- 0.02  # probability of becoming sick when healthy, conditional on surviving, under treatme
p_SD      <- 0.1   # probability of dying
p_HD_min  <- 0.003 # probability of dying when healthy at t = 0
p_HD_max  <- 0.01  # probability of dying when healthy at t = n_cycles
# probabilities of dying when healthy (age-dependent) - this is now a sequence of numbers
v_p_HD    <- seq(p_HD_min, p_HD_max, length.out = n_cycles)

## State rewards
```

```r
# Costs and utilities
c_H       <- 400   # cost of one cycle in healthy state
c_S       <- 1000  # cost of one cycle in sick state
c_D       <- 0     # cost of one cycle in dead state
c_trtA    <- 800   # cost of treatment A (per cycle) in healthy state
c_trtB    <- 1500  # cost of treatment B (per cycle) in healthy state
u_H       <- 1     # utility when healthy
u_S       <- 0.5   # utility when sick
u_D       <- 0     # utility when dead
d_e       <- 0.03  # discount rate per cycle equal discount of costs and QALYs by 3%
d_c       <- 0.03  # discount rate per cycle equal discount of costs and QAL

# Discount weight (equal discounting is assumed for costs and effects)
v_dwc <- 1 / (1 + d_c) ^ (0:n_cycles)
v_dwe <- 1 / (1 + d_e) ^ (0:n_cycles)
```

04 Define and initialize matrices and vectors

04.1 Cohort trace

```r
## Initial state vector
# All starting healthy
v_s_init <- c("Healthy" = 1, "Sick" = 0, "Dead" = 0)
v_s_init
```

```
## Healthy    Sick    Dead
##       1       0       0
```

```r
## Initialize cohort trace for cSTM for all strategies
m_M_SoC <- matrix(0,
                  nrow = (n_cycles + 1), ncol = n_states,
                  dimnames = list(v_names_cycles, v_names_states))
# Store the initial state vector in the first row of the cohort trace
m_M_SoC[1, ] <- v_s_init
## Initialize cohort traces
m_M_trtA <- m_M_trtB <- m_M_SoC # structure and initial states remain the same
```

04.2 Transition probability array

```r
## Initialize transition probability array
# all transitions to a non-death state are assumed to be conditional on survival
a_P_SoC <- array(0,  # Create 3-D array
                 dim = c(n_states, n_states, n_cycles),
                 dimnames = list(v_names_states, v_names_states,
                                 v_names_cycles[-length(v_names_cycles)])) # name the dimensions of the
```

Fill in the transition probability array:

```
## Standard of Care
# from Healthy
a_P_SoC["Healthy", "Healthy", ] <- (1 - v_p_HD) * (1 - p_HS_SoC)
a_P_SoC["Healthy", "Sick",    ] <- (1 - v_p_HD) * p_HS_SoC
a_P_SoC["Healthy", "Dead",    ] <-  v_p_HD

# from Sick
a_P_SoC["Sick", "Sick", ] <- 1 - p_SD
a_P_SoC["Sick", "Dead", ] <- p_SD

# from Dead
a_P_SoC["Dead", "Dead", ] <- 1

## Treatment A
a_P_trtA <- a_P_SoC
a_P_trtA["Healthy", "Healthy", ] <- (1 - v_p_HD) * (1 - p_HS_trtA)
a_P_trtA["Healthy", "Sick",    ] <- (1 - v_p_HD) * p_HS_trtA

## Treatment B
a_P_trtB <- a_P_SoC
a_P_trtB["Healthy", "Healthy", ] <- (1 - v_p_HD) * (1 - p_HS_trtB)
a_P_trtB["Healthy", "Sick",    ] <- (1 - v_p_HD) * p_HS_trtB
```

Check if transition array and probabilities are valid.

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

05 Run Markov model

```
for (t in 1:n_cycles){  # loop through the number of cycles
  # estimate the cohort trace for cycle t + 1 using the t-th matrix from the probability array
  m_M_SoC [t + 1, ] <- m_M_SoC [t, ] %*% a_P_SoC [, , t]
  m_M_trtA[t + 1, ] <- m_M_trtA[t, ] %*% a_P_trtA[, , t]
  m_M_trtB[t + 1, ] <- m_M_trtB[t, ] %*% a_P_trtB[, , t]
}
head(m_M_SoC)  # print the first few lines of the matrix
```

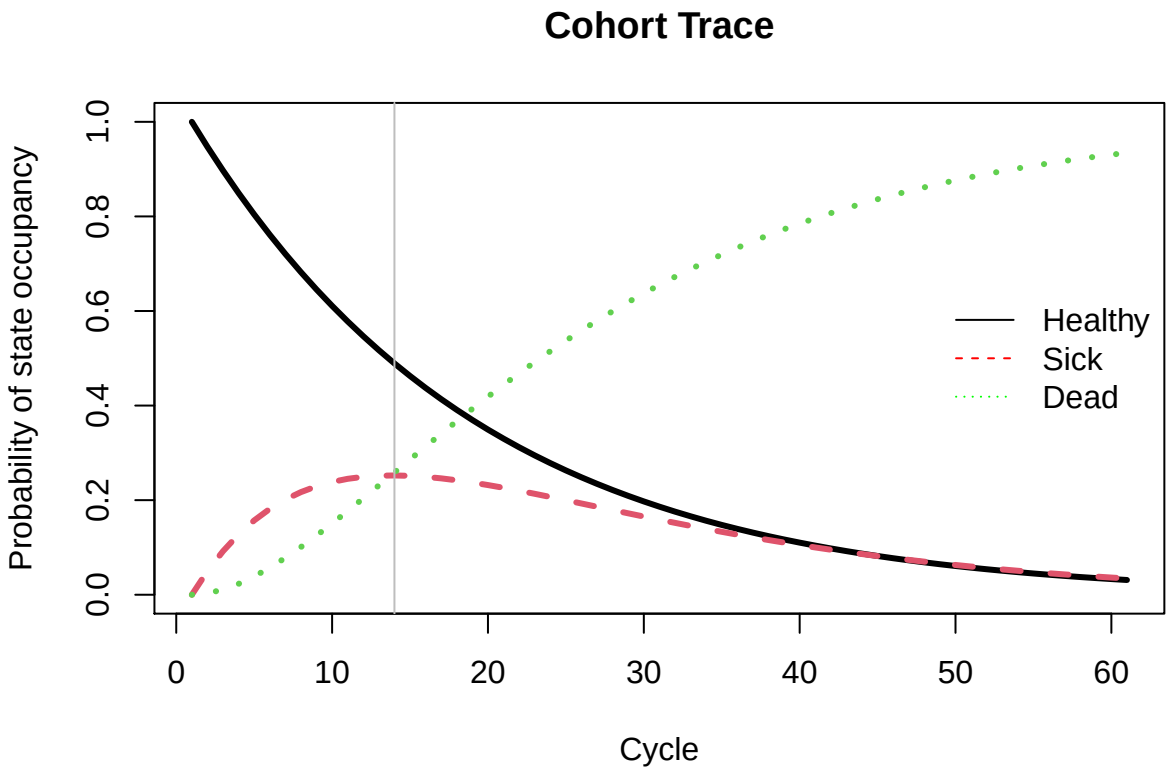
```
##           Healthy       Sick       Dead
## cycle 0 1.0000000 0.00000000 0.00000000
## cycle 1 0.9471500 0.04985000 0.00300000
## cycle 2 0.8969864 0.09207481 0.01093882
## cycle 3 0.8493784 0.12757146 0.02305011
## cycle 4 0.8042016 0.15714071 0.03865771
## cycle 5 0.7613370 0.18149700 0.05716604
```

06 Compute and Plot Epidemiological Outcomes

06.1 Cohort trace

```
matplot(m_M_SoC, type = 'l',
        ylab = "Probability of state occupancy",
        xlab = "Cycle",
        main = "Cohort Trace", lwd = 3)  # create a plot of the data
legend("right", v_names_states, col = c("black", "red", "green"),
       lty = 1:3, bty = "n")  # add a legend to the graph

# plot a vertical line that helps identifying at which cycle the prevalence of sick is highest
abline(v = which.max(m_M_SoC[, "Sick"]), col = "gray")
```

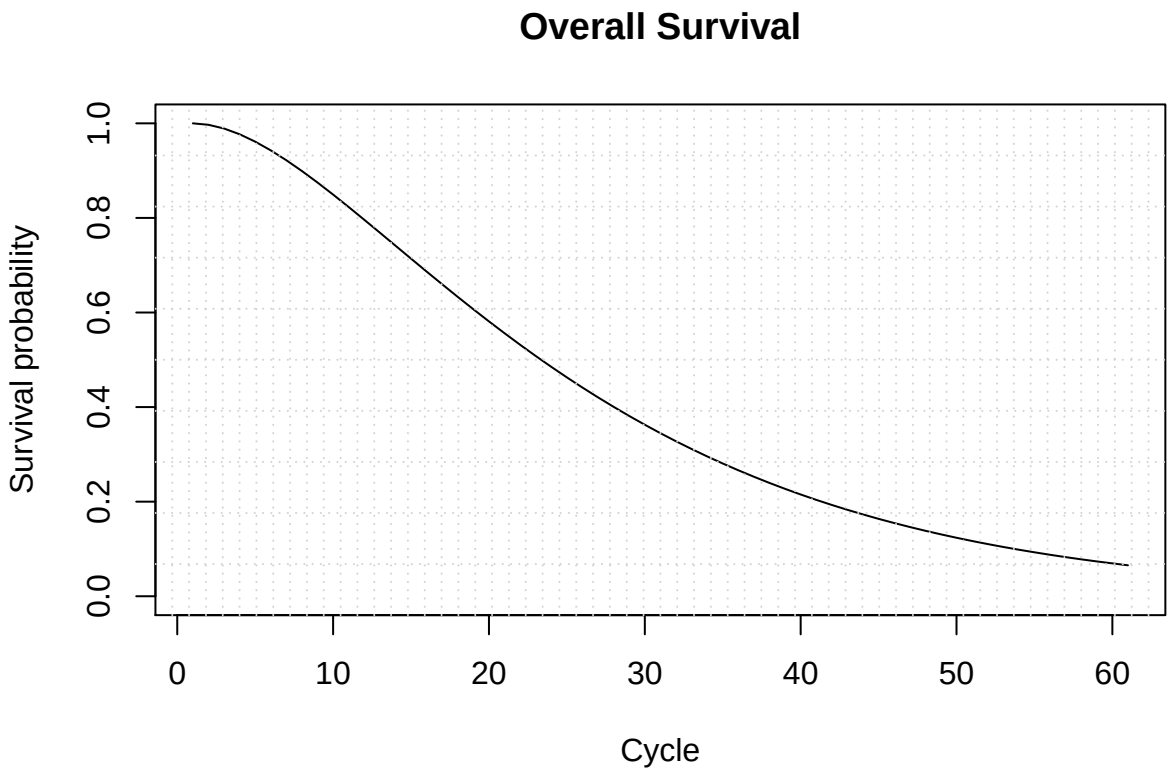


06.2 Overall Survival (OS)

```
v_os <- 1 - m_M_SoC[, "Dead"]     # calculate the overall survival (OS) probability
v_os <- rowSums(m_M_SoC[, 1:2])  # alternative way of calculating the OS probability

plot(v_os, type = 'l',
     ylim = c(0, 1),
     ylab = "Survival probability",
     xlab = "Cycle",
     main = "Overall Survival")  # create a simple plot showing the OS
```

```r
# add grid
grid(nx = n_cycles, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"),
     equilogs = TRUE)
```

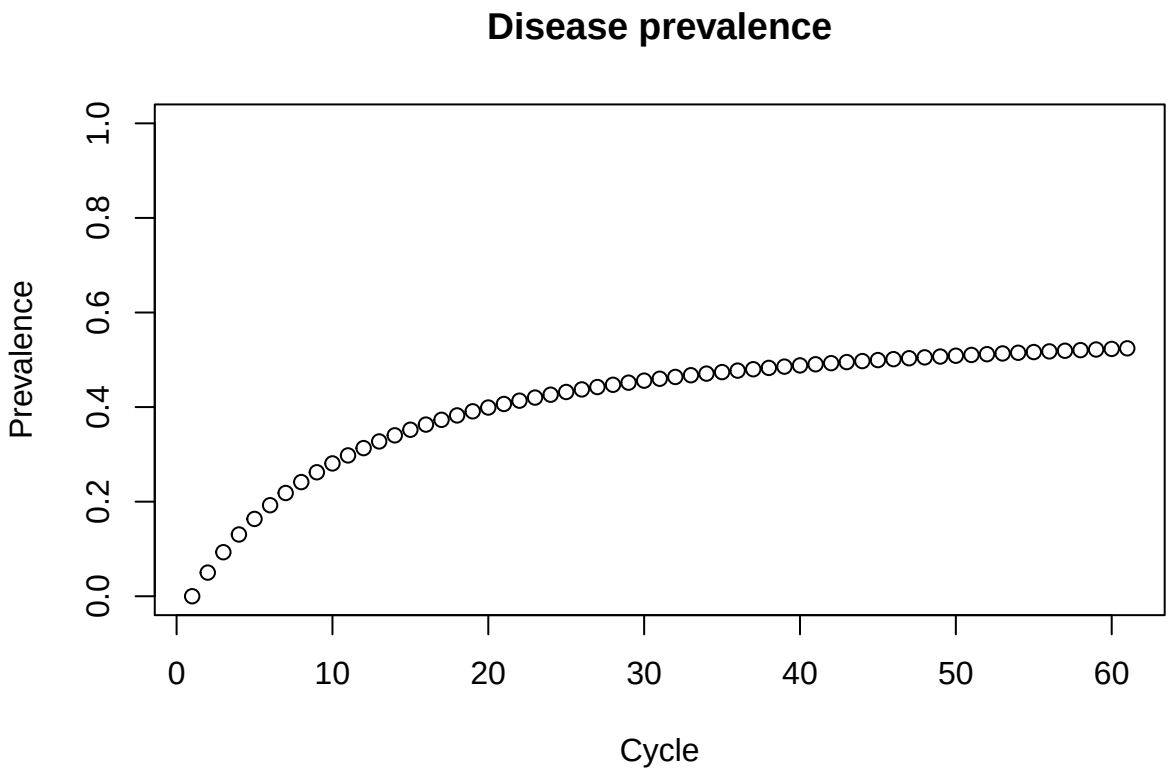


06.2.1 Life Expectancy (LE)

```r
v_le <- sum(v_os)  # summing probability of OS over time  (i.e. life expectancy)
```

06.3 Disease prevalence

```r
v_prev <- m_M_SoC[, "Sick"]/v_os
plot(v_prev,
     ylim = c(0, 1),
     ylab = "Prevalence",
     xlab = "Cycle",
     main = "Disease prevalence")
```



07 Compute Cost-Effectiveness Outcomes

07.1 Mean Costs and QALYs

```
# per cycle
# calculate expected costs by multiplying cohort trace with the cost vector for the different health st
v_tc_SoC  <- m_M_SoC  %*% c(c_H, c_S, c_D)
v_tc_trtA <- m_M_trtA %*% c(c_H + c_trtA, c_S, c_D)
v_tc_trtB <- m_M_trtB %*% c(c_H + c_trtB, c_S, c_D)

# calculate expected QALYs by multiplying cohort trace with the utilities for the different health stat
v_tu_SoC  <- m_M_SoC  %*% c(u_H, u_S, u_D)
v_tu_trtA <- m_M_trtA %*% c(u_H, u_S, u_D)
v_tu_trtB <- m_M_trtB %*% c(u_H, u_S, u_D)
```

07.2 Discounted Mean Costs and QALYs

```
# Discount costs by multiplying the cost vector with discount weights (v_dw)
tc_d_SoC  <-  t(v_tc_SoC)  %*% v_dwc
tc_d_trtA <-  t(v_tc_trtA) %*% v_dwc
tc_d_trtB <-  t(v_tc_trtB) %*% v_dwc

# Discount QALYS by multiplying the QALYs vector with discount weights (v_dw)
tu_d_SoC  <-  t(v_tu_SoC)  %*% v_dwe
```

```r
tu_d_trtA <-  t(v_tu_trtA) %*% v_dwe
tu_d_trtB <-  t(v_tu_trtB) %*% v_dwe

# Store them into a vector
v_tc_d <- c(tc_d_SoC, tc_d_trtA, tc_d_trtB)
v_tu_d <- c(tu_d_SoC, tu_d_trtA, tu_d_trtB)

# 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 Standard of Care  9504.301 14.50646
## 2      Treatment A 20648.861 15.82191
## 3      Treatment B 37325.926 19.57368
```

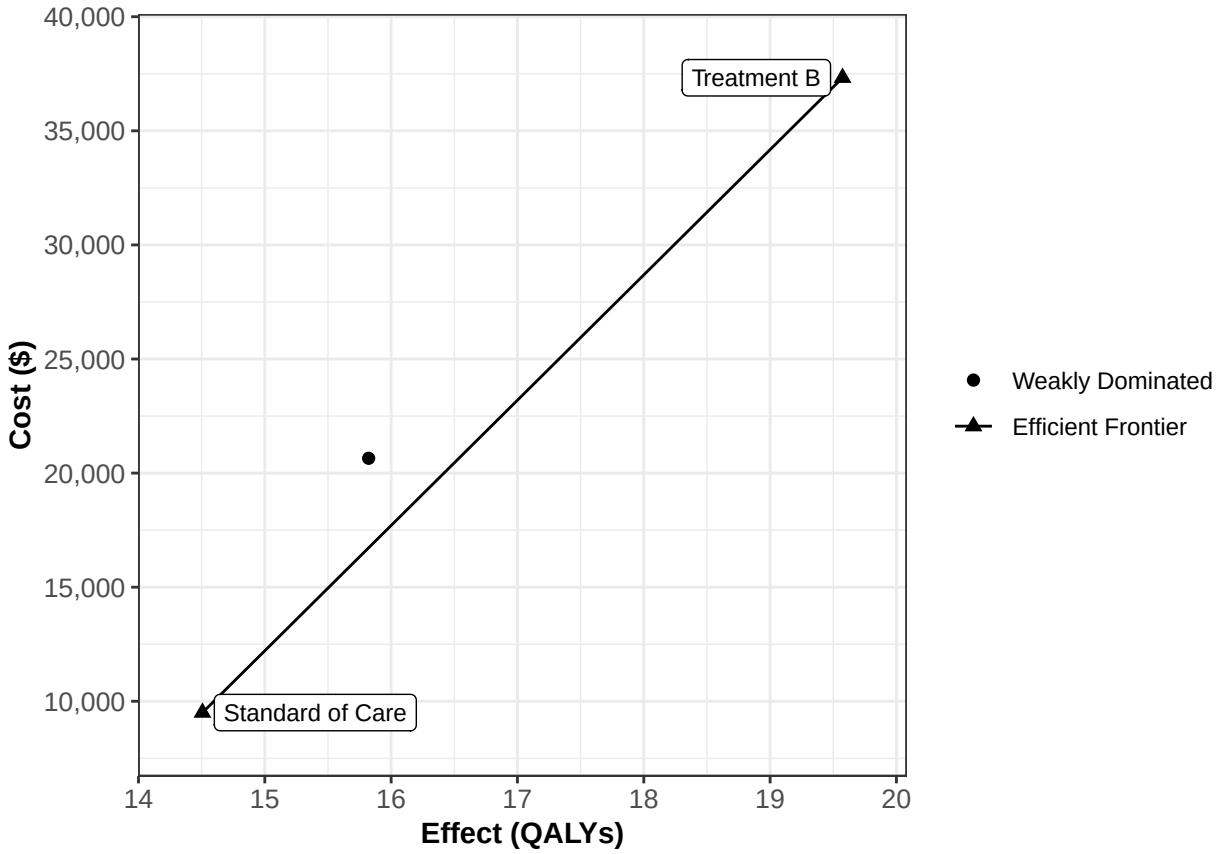
07.3 Compute ICERs of the Markov model

```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 Standard of Care  9504.301 14.50646       NA         NA       NA     ND
## 2      Treatment B 37325.926 19.57368 27821.63   5.067224 5490.507     ND
## 3      Treatment A 20648.861 15.82191       NA         NA       NA     ED
```

07.4 Plot frontier of the Markov model

```r
plot(df_cea, effect_units = "QALYs")
```


40,000
35,000
30,000
25,000
20,000
15,000
10,000
Cost ($)
14
15
16
17
18
19
20
Effect (QALYs)
Treatment B
Standard of Care
Weakly Dominated
Efficient Frontier