Microsimulation Sick-Sicker model with time dependency

Includes individual characteristics: age, age dependent mortality, individual treatment effect modifer, state-residency for the sick (S1) state, increasing change of death in the first 6 year of sickness

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 EA, et al. A Multidimensional Array Representation of State-Transition Model Dynamics. Med Decis Mak. https://doi.org/10.1177/0272989X19893973

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

01 Load packages

```
if (!require('pacman')) install.packages('pacman'); library(pacman)
# load (install if required) packages from CRAN
p_load("devtools", "dplyr", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "truncnorm", "ggraph"
# 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")
```

02 Load functions

```
# No functions needed
```

03 Model input

```
## General setup
set.seed(1)                # set the seed
cycle_length   <- 1        # cycle length equal to one year (use 1/12 for monthly)
n_cycles       <- 30       # time horizon, number of cycles
n_i            <- 100000   # number of individuals

# the 4 health states of the model:
v_names_states <- c("H",  # Healthy (H)
                    "S1", # Sick (S1)
                    "S2", # Sicker (S2)
                    "D")  # Dead (D)
n_states       <- length(v_names_states) # number of health states

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

### Strategies
v_names_str   <- c("Standard of care",   # store the strategy names
                   "Strategy AB")
n_str         <- length(v_names_str)     # number of strategies

# (all non-probabilities are conditional on survival)
p_HS1         <- 0.15     # probability of becoming sick when healthy
p_S1H         <- 0.5      # probability of recovering to healthy when sick
p_S1S2_SoC    <- 0.105    # probability of becoming sicker when sick under standard of care
p_S1S2_trtAB  <- 0.05     # probability of becoming sicker when sick under treatment AB

# Annual probabilities of death
```

```r
# load age dependent probability
p_mort   <- read.csv("mortProb_age.csv")
# load age distribution
dist_Age <- read.csv("MyPopulation-AgeDistribution.csv")

# probability to die in S1 by cycle (is increasing)
p_S1D    <- c(0.0149, 0.018, 0.021, 0.026, 0.031, rep(0.037, n_cycles - 5))
p_S2D    <- 0.048   # probability to die in S2

### State rewards
#### Costs
c_H     <- 2000  # annual cost of being Healthy
c_S1    <- 4000  # annual cost of being Sick
c_S2    <- 15000 # annual cost of being Sicker
c_D     <- 0     # annual cost of being dead
c_trtAB <- 25000 # annual cost of receiving treatment AB when in Sick
#### Utilities
u_H     <- 1     # annual utility of being Healthy
u_S1    <- 0.75  # annual utility of being Sick
u_S2    <- 0.5   # annual utility of being Sicker
u_D     <- 0     # annual utility of being dead
u_trtAB <- 0.95  # annual utility when receiving treatment AB when in Sick

### Discount weight for costs and effects
v_dwc   <- 1 / ((1 + (d_e * cycle_length)) ^ (0:n_cycles))
v_dwe   <- 1 / ((1 + (d_c * cycle_length)) ^ (0:n_cycles))
```

04 Sample individual level characteristics

04.1 Static characteristics

```r
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)
```

04.2 Dynamic characteristics

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

04.3 Create a dataframe with the individual characteristics

```r
# create a data frame with each individual's
# ID number, treatment effect modifier, age and initial time in sick state
```

```r
df_X <- data.frame(ID = 1:n_i, x = v_x, Age = v_age0, n_cycles_s = v_Ts_init, M_init = v_M_init)
head(df_X)  # print the first rows of the dataframe
```

```
##   ID         x Age n_cycles_s M_init
## 1  1 0.9765509  43          0      H
## 2  2 0.9872124  43          0      H
## 3  3 1.0072853  32          0      H
## 4  4 1.0408208  41          0      H
## 5  5 0.9701682  46          0      H
## 6  6 1.0398390  27          0      H
```

05 Define Simulation Functions

05.1 Probability function

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

```r
Probs <- function(M_t, df_X, t, Trt = "Standard of care") {
  # Arguments:
    # M_t:  health state occupied by individual i at cycle t (character variable)
    # df_X: data frame with individual characteristics data
    # t:    current cycle
    # Trt:  treatment
  # Returns:
    # transition probabilities for that cycle

  # Treatment specific transition probabilities
  if (Trt == "Standard of care") {
    p_S1S2 <- p_S1S2_SoC
  } else if (Trt == "Strategy AB") {
    p_S1S2 <- p_S1S2_trtAB
  }

  # create matrix of state transition probabilities
  m_p_t           <- matrix(0, nrow = n_states, ncol = n_i)
  rownames(m_p_t) <-  v_names_states  # 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 m_p with the appropriate probabilities
  # (all non-death probabilities are conditional on survival)
  # transition probabilities when Healthy
  m_p_t["H",  M_t == "H"]  <- (1 - p_HD)  * (1 - p_HS1)
  m_p_t["S1", M_t == "H"]  <- (1 - p_HD)  *      p_HS1
  m_p_t["S2", M_t == "H"]  <-                    0
  m_p_t["D",  M_t == "H"]  <-      p_HD

  # transition probabilities when Sick
  m_p_t["H",  M_t == "S1"] <- (1 - p_S1D[df_X$n_cycles_s]) *      p_S1H
```

```
  m_p_t["S1", M_t == "S1"] <- (1 - p_S1D[df_X$n_cycles_s]) * (1 - p_S1H - p_S1S2)
  m_p_t["S2", M_t == "S1"] <- (1 - p_S1D[df_X$n_cycles_s]) *              p_S1S2
  m_p_t["D",  M_t == "S1"] <-      p_S1D[df_X$n_cycles_s]

  # transition probabilities when Sicker
  m_p_t["H",  M_t == "S2"] <-  0
  m_p_t["S1", M_t == "S2"] <-  0
  m_p_t["S2", M_t == "S2"] <-  1 - p_S2D
  m_p_t["D",  M_t == "S2"] <-      p_S2D

  # transition probabilities when Dead
  m_p_t["H",  M_t == "D"]  <- 0
  m_p_t["S1", M_t == "D"]  <- 0
  m_p_t["S2", M_t == "D"]  <- 0
  m_p_t["D",  M_t == "D"]  <- 1

  return(t(m_p_t))
}
```

05.2 Cost function

The `Costs` function estimates the costs at every cycle.

```
Costs <- function (M_t, Trt = "Standard of care") {
  # Arguments:
    # M_t: health state occupied by individual i at cycle t (character variable)
    # Trt: Treatment
  # Returns:
    # costs accrued in this cycle

  # Treatment specific costs
  if (Trt == "Standard of care") {
    c_Trt <- 0
  } else if (Trt == "Strategy AB") {
    c_Trt <- c_trtAB
  }

  c_t <- 0                          # by default the cost for everyone is zero
  c_t[M_t == "H"]  <- c_H           # update the cost if healthy
  c_t[M_t == "S1"] <- c_S1 + c_Trt  # update the cost if sick conditional on treatment
  c_t[M_t == "S2"] <- c_S2 + c_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 costs accrued this cycle
}
```

05.3 Health outcome function

The `Effs` function to update the utilities at every cycle.

```r
Effs <- function (M_t, df_X, Trt = "Standard of care", cl = 1) {
  # Arguments:
    # M_t: health state occupied by individual i at cycle t (character variable)
    # df_X: data frame with individual characteristics data
    # Trt:  Treatment
    # cl:   cycle length (default is 1)
  # Returns:
    # QALYs accrued this cycle

  u_t <- 0                          # by default the utility for everyone is zero
  u_t[M_t == "H"]    <- u_H         # update the utility if healthy

  if (Trt == "Standard of care") {  # update the utility if sick under standard of care
    u_t[M_t == "S1"] <- u_S1
  } else if (Trt == "Strategy AB") {
  # update the utility if sick but on treatment AB (adjust for individual effect modifier)
    u_t[M_t == "S1"] <- u_trtAB * 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 accrued this cycle
}
```

05.4 The Microsimulation function

```r
MicroSim <- function(n_i, df_X, Trt = "Standard of care", seed = 1) {
  # Arguments:
    # n_i : number of individuals
    # df_X: data frame with individual characteristics data
    # Trt : treatment
    # seed: seed for the random number generator, default is 1
  # Returns:
    # results: data frame with total cost and QALYs

  set.seed(seed) # set the seed

  n_states <- length(v_names_states) # 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_cycles
  # (the initial state and all the n_cycles 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 <-  matrix(nrow = n_i, ncol = n_cycles + 1,
                               dimnames = list(paste("ind"  , 1:n_i, sep = " "),
                                               paste("cycle", 0:n_cycles, sep = " ")))
```

```r
    m_M [, 1] <- as.character(df_X$M_init) # initial health state at cycle 0 for individual i

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

    # open a loop for time running cycles 1 to n_cycles
    for (t in 1:n_cycles) {
      # calculate the transition probabilities for the cycle based on  health state t
      m_P <- Probs(m_M[, t], df_X, t, Trt = Trt)
      # check if transition probabilities are between 0 and 1
      check_transition_probability(m_P, verbose = TRUE)
      # check if checks if each of the rows of the transition probabilities matrix sum to one
      ## NOTE: to make this function work n_states = n_i in a Microsimulation
      check_sum_of_transition_array(m_P, n_rows = n_i, n_cycles = n_cycles, verbose = TRUE) ##
      # 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)

      # update time since illness onset for t + 1
      df_X$n_cycles_s <- if_else(m_M[, t + 1] == "S1", df_X$n_cycles_s + 1, 0)
      # update the age of individuals that are alive
      df_X$Age[m_M[, t + 1] != "D"]  <- df_X$Age[m_M[, t + 1] != "D"] + 1

      # Display simulation progress
      if(t/(n_cycles/10) == round(t/(n_cycles/10), 0)) { # display progress every 10%
        cat('\r', paste(t/n_cycles * 100, "% done", sep = " "))
      }

    } # close the loop for the time points

  # calculate
  tc <- m_C %*% v_dwc  # total (discounted) cost per individual
  te <- m_E %*% v_dwe  # total (discounted) QALYs per individual
  tc_hat <- mean(tc)   # average (discounted) cost
  te_hat <- mean(te)   # average (discounted) QALY
  # 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_SoC` and `ou
```

06 Run Microsimulation

```
# Run the simulation for both no treatment and treatment options
outcomes_SoC   <- MicroSim(n_i = n_i, df_X = df_X, Trt = "Standard of care", seed = 1)
```

```
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  10 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  20 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  30 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  40 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  50 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  60 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  70 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
```

```
## [1] "This is a valid transition matrix"
##  80 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  90 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  100 % done
```

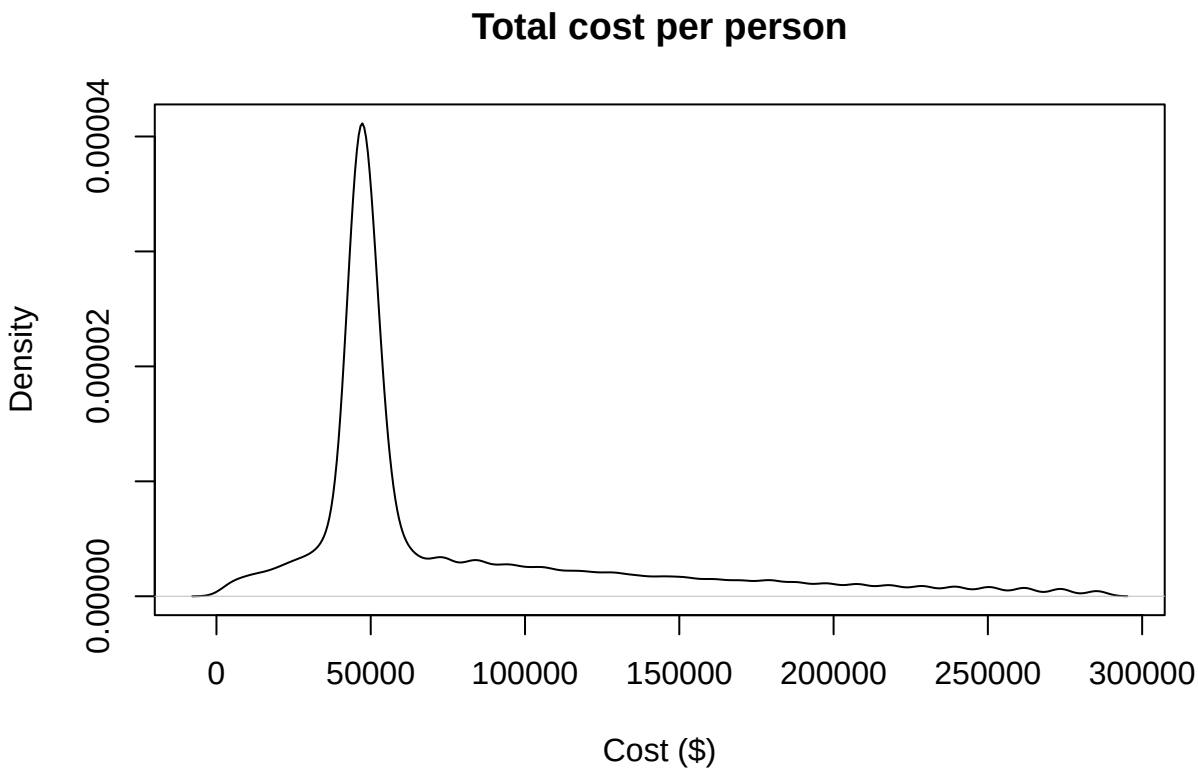
```
outcomes_trtAB <- MicroSim(n_i = n_i, df_X = df_X, Trt = "Strategy AB",  seed = 1)
```

```
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  10 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  20 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  30 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  40 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  50 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  60 % done[1] "Valid transition probabilities"
```

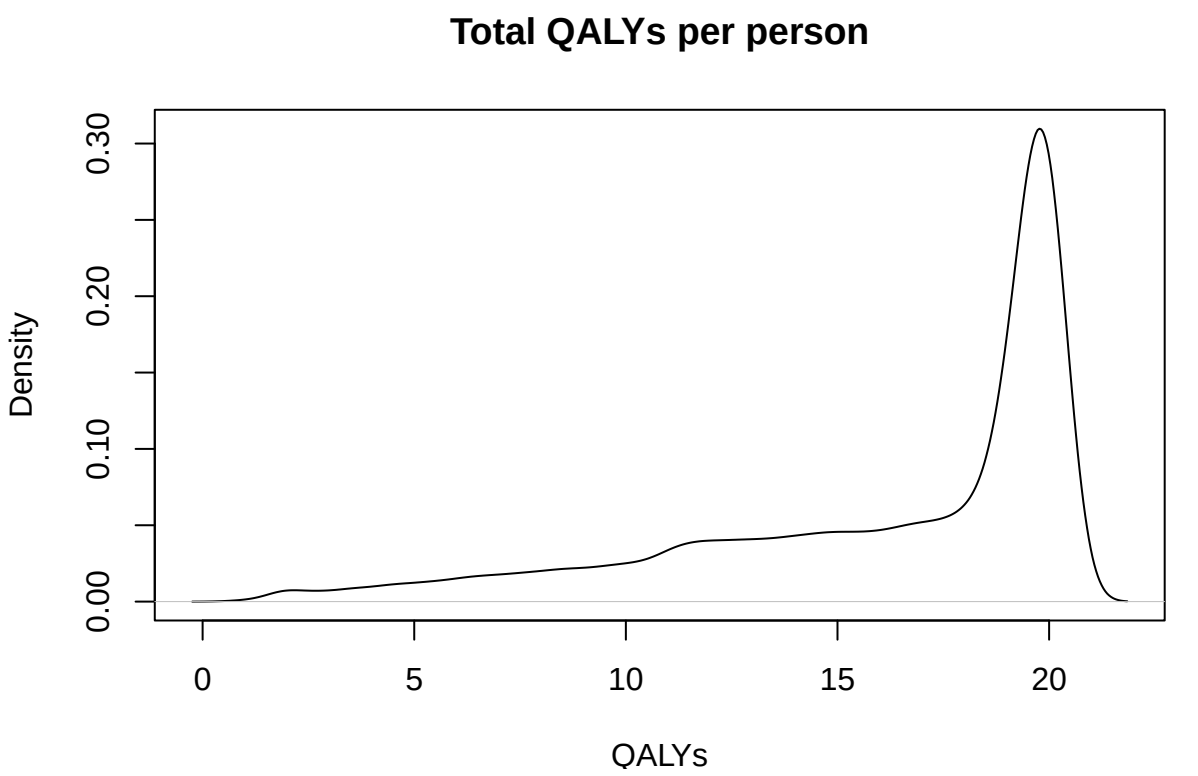
```
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  70 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  80 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  90 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  100 % done
```

07 Visualize results

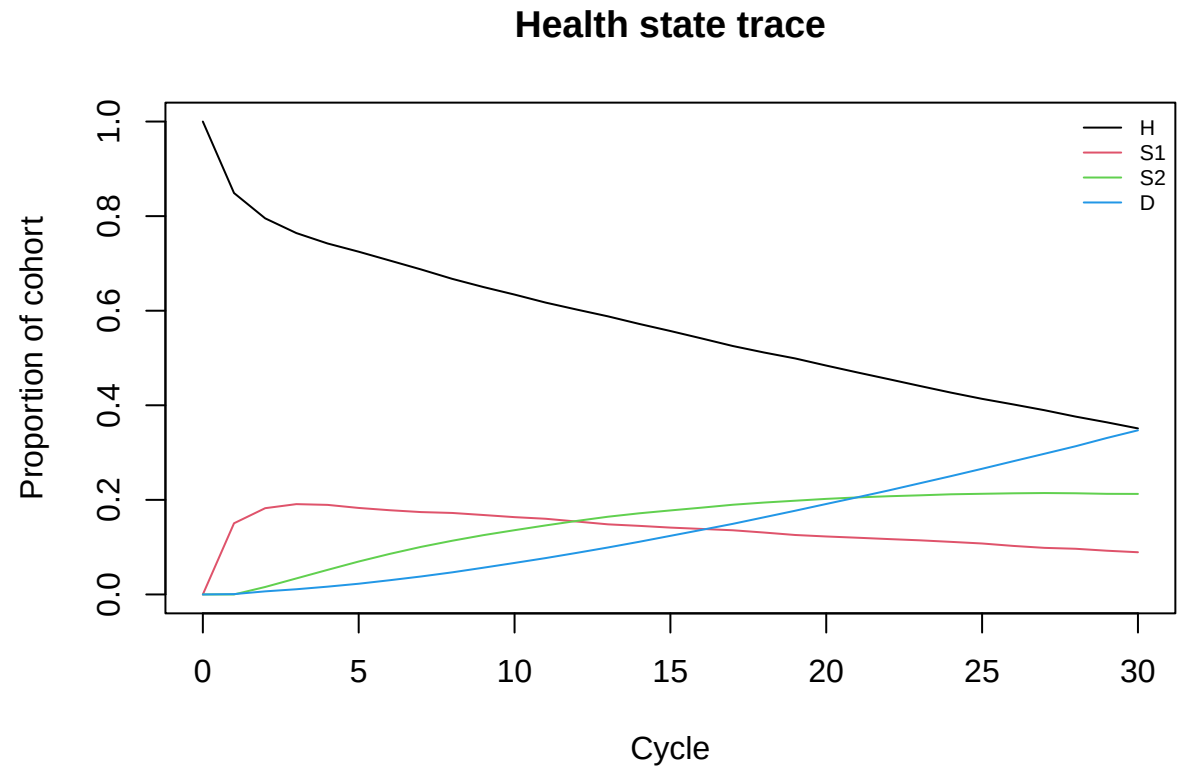
```r
# Standard of care
plot(density(outcomes_SoC$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
```



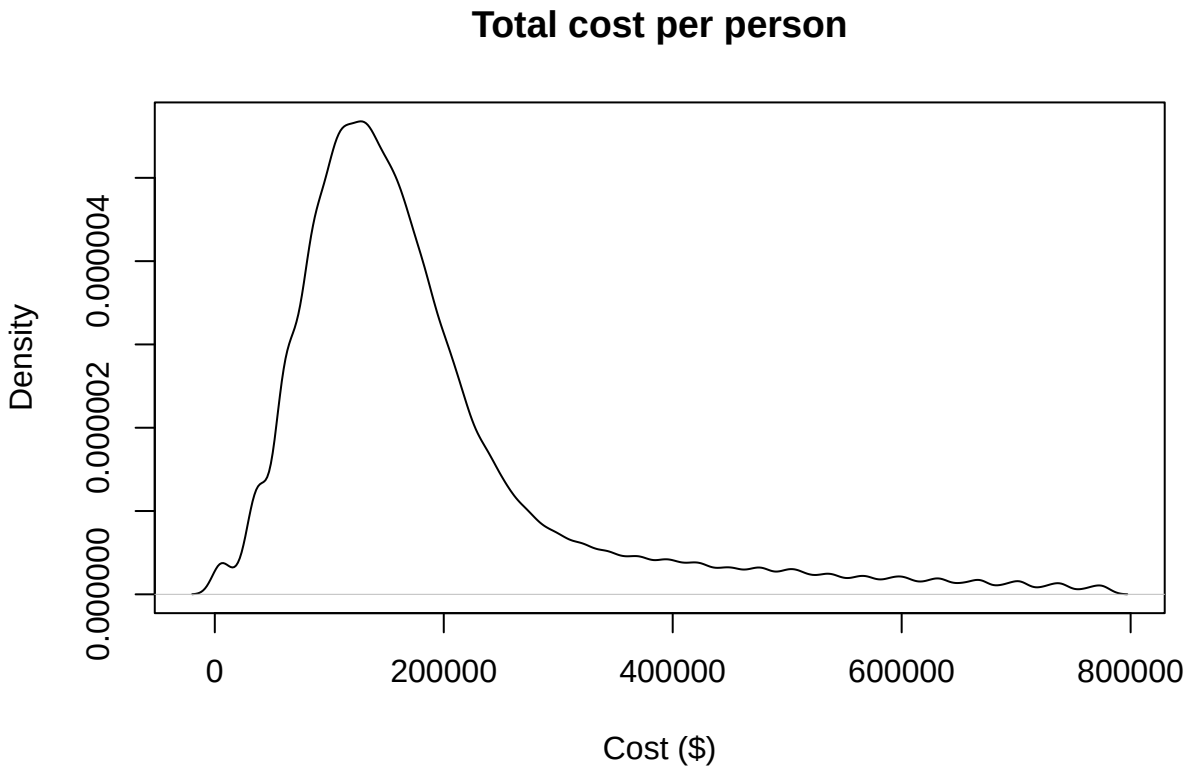

```
plot(density(outcomes_SoC$te), main = paste("Total QALYs per person"), xlab = "QALYs")
```



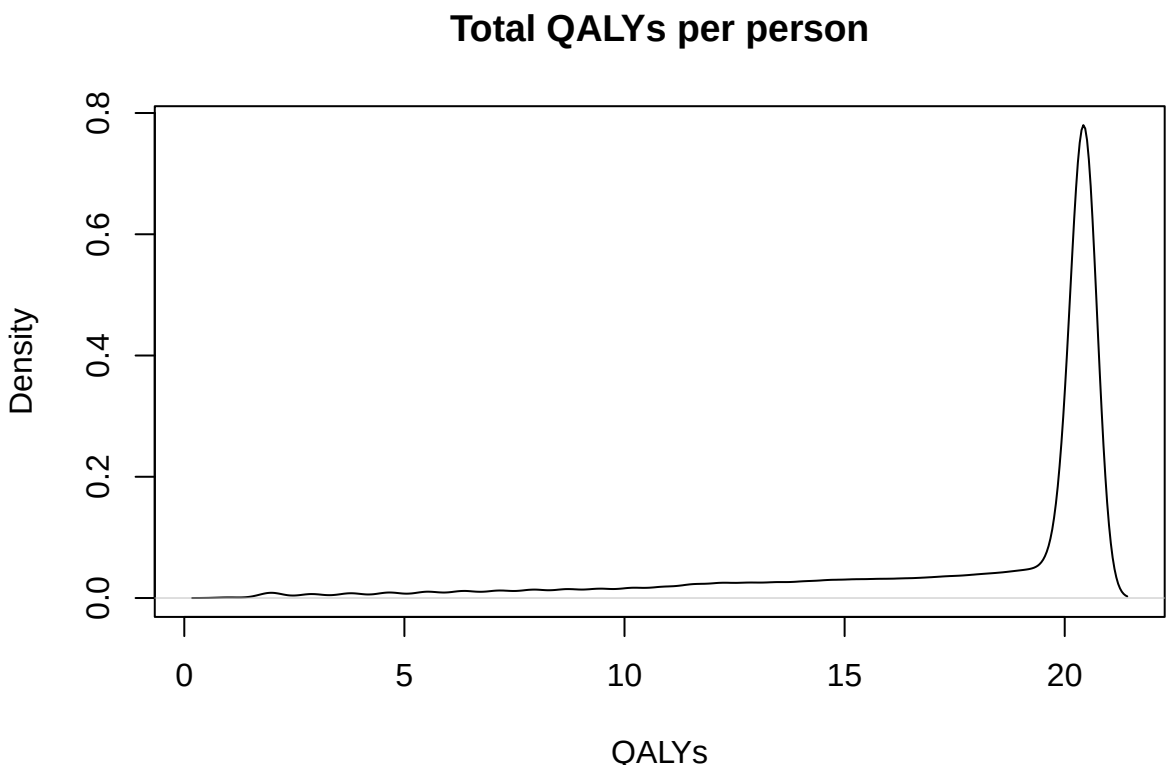
```r
plot_trace_microsim(outcomes_SoC$m_M)  # health state trace
```



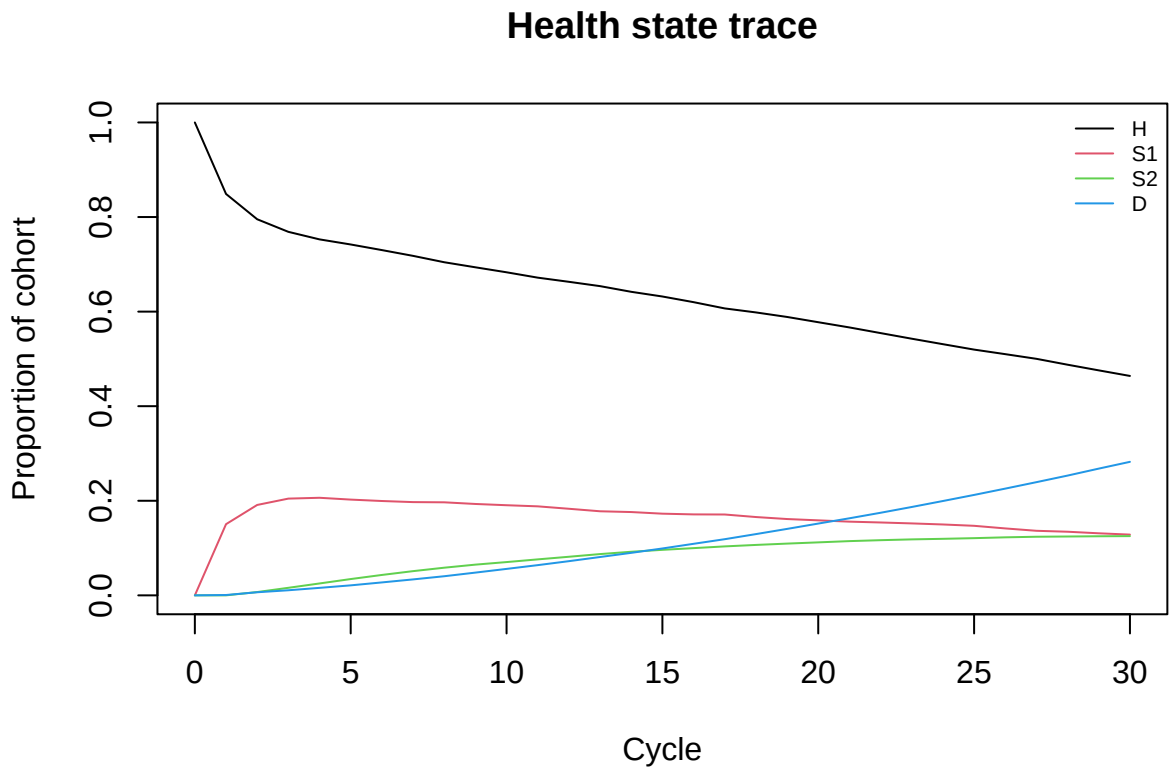

```r
# Strategy AB
plot(density(outcomes_trtAB$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
```



```r
plot(density(outcomes_trtAB$te), main = paste("Total QALYs per person"), xlab = "QALYs")
```




```r
plot_trace_microsim(outcomes_trtAB$m_M)     # health state trace
```



08 Cost-effectiveness analysis (CEA)

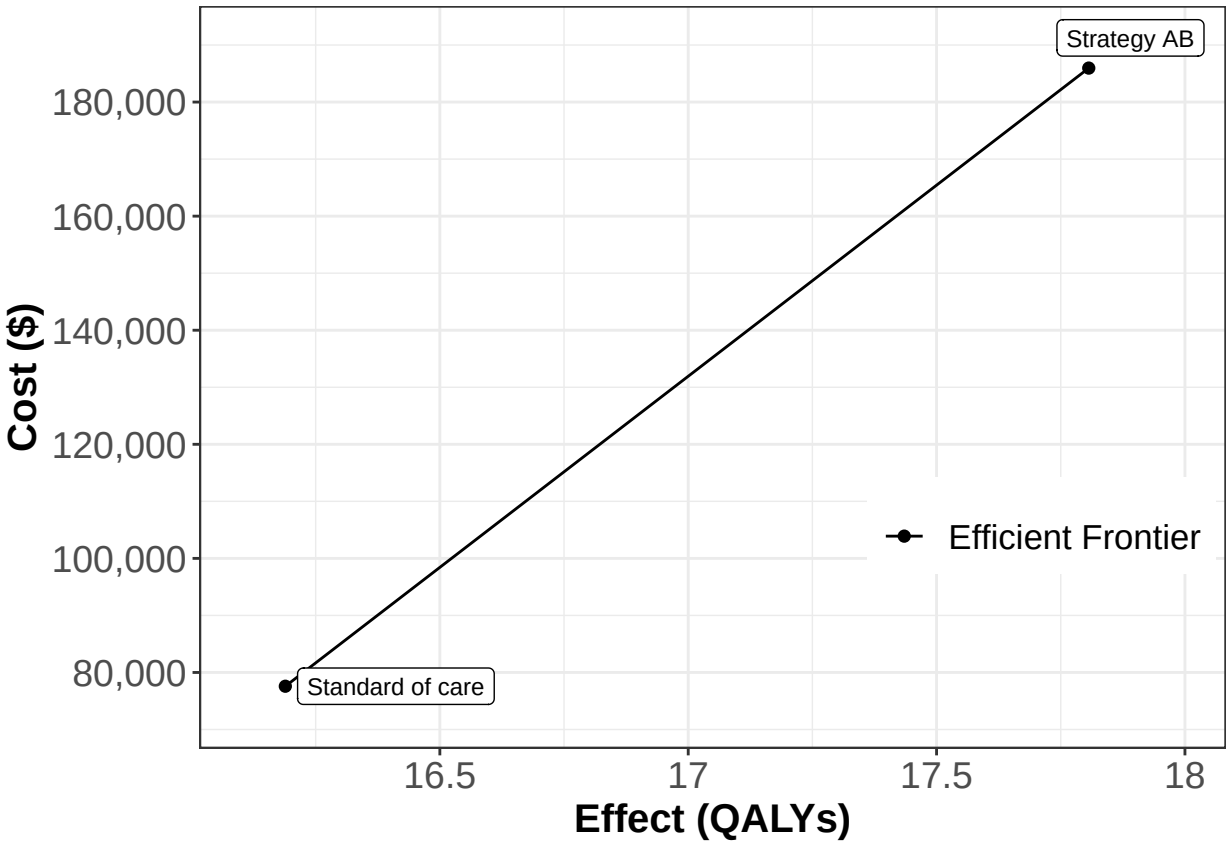
```r
# store the mean costs of each strategy in a new variable C (vector of costs)
v_C <- c(outcomes_SoC$tc_hat, outcomes_trtAB$tc_hat)
# store the mean QALYs of each strategy in a new variable E (vector of effects)
v_E <- c(outcomes_SoC$te_hat, outcomes_trtAB$te_hat)

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

```
##           Strategy     Cost   Effect Inc_Cost Inc_Effect     ICER Status
## 1 Standard of care  77583.0 16.18890       NA         NA       NA     ND
## 2      Strategy AB 185953.8 17.80638 108370.8   1.617478 66999.86     ND
```

```r
## CEA table in proper format
table_cea <- format_table_cea(df_cea)
table_cea
```

```
##           Strategy Costs ($) QALYs Incremental Costs ($) Incremental QALYs
## 1 Standard of care    77,583 16.19                   <NA>                NA
## 2      Strategy AB   185,954 17.81                108,371              1.62
##   ICER ($/QALY) Status
## 1          <NA>     ND
## 2        67,000     ND
```

```r
## CEA frontier
plot(df_cea, label = "all", txtsize = 16) +
  expand_limits(x = max(table_cea$QALYs) + 0.1) +
  theme(legend.position = c(0.82, 0.3))
```


Strategy AB
Standard of care
Efficient Frontier
Cost ($)
Effect (QALYs)
180,000
160,000
140,000
120,000
100,000
80,000
16.5
17
17.5
18