Simple 3-state microsimulation model

Includes sex specific probability of dying when healthy and state occupation: probability of dying when sick depends on the time of being sick

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 MGM, 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.

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

03.1 Define model input parameters

```
## General setup
set.seed(1)                                    # set the seed
cycle_length    <- 1                           # cycle length equal to one year (use 1/12 for monthly
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
n_i             <- 10000                       # number of individuals

### 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
                     "Treatment A",
                     "Treatment B")
n_str           <- length(v_names_str)         # number of strategies

### Transition probabilities
# (all non-dead probabilities are conditional on survival)
p_HS_SoC    <- 0.05  # probability of becoming sick when healthy, conditional on surviving, under stand
p_HS_trtA   <- 0.04  # probability of becoming sick when healthy, conditional on surviving, under treat
p_HS_trtB   <- 0.02  # probability of becoming sick when healthy, conditional on surviving, under treat
p_HD_female <- 0.0382  # probability healthy -> dead when female
p_HD_male   <- 0.0463  # probability healthy -> dead when male
```

```
df_p_HD     <- data.frame(Sex = c("Female", "Male"), p_HD = c(p_HD_female, p_HD_male)) #dataframe for s
p_SD        <- c(0.1, 0.2, 0.3, 0.4, 0.5, rep(0.7, n_cycles - 5)) # probability to die in sick state by

### State rewards
#### Costs
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
#### Utilities
u_H        <- 1     # utility when healthy
u_S        <- 0.5   # utility when sick
u_D        <- 0     # utility when dead
```

03.2 Calculate internal model parameters

```
### Cycle-specific 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

```
# randomly sample the sex of an individual (50% female)
v_sex <- sample(x = c("Female", "Male"), prob = c(0.5, 0.5), size = n_i, replace = TRUE)
```

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("Healthy", 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

```
# create a data frame with each individual's
# ID number, treatment effect modifier, age and initial time in sick state
df_X  <- data.frame(ID = 1:n_i, Sex = v_sex, n_cycles_s = v_Ts_init, M_init = v_M_init)
# NOTE: we use n_cycles_s for the number of times being sick, we start the data frame with the initial
head(df_X) # print the first rows of the dataframe
```

```
##   ID    Sex n_cycles_s  M_init
## 1  1   Male          0 Healthy
## 2  2   Male          0 Healthy
## 3  3 Female          0 Healthy
## 4  4 Female          0 Healthy
## 5  5   Male          0 Healthy
## 6  6 Female          0 Healthy
```

05 Define Simulation Functions

05.1 Probability function

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

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

  # Treatment specific transition probabilities
  if (Trt == "SoC") {
    p_HS <- p_HS_SoC
  } else if (Trt == "A") {
    p_HS <- p_HS_trtA
  } else if (Trt == "B") {
    p_HS <- p_HS_trtB
  }

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

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

  # update m_p_t with the appropriate probabilities
  # (all non-death probabilities are conditional on survival)
  # transition probabilities when Healthy
  m_p_t["Healthy", M_t == "Healthy"] <- (1 - p_HD) * (1 - p_HS)
  m_p_t["Sick",    M_t == "Healthy"] <- (1 - p_HD) *      p_HS
  m_p_t["Dead",    M_t == "Healthy"] <-      p_HD

  # transition probabilities when Sick
  m_p_t["Healthy", M_t == "Sick"]    <-  0
  m_p_t["Sick",    M_t == "Sick"]    <-  1 - p_SD[df_X$n_cycles_s]
  m_p_t["Dead",    M_t == "Sick"]    <-      p_SD[df_X$n_cycles_s]
```

```r
  # transition probabilities when Dead
  m_p_t["Healthy", M_t == "Dead"]    <- 0
  m_p_t["Sick",    M_t == "Dead"]    <- 0
  m_p_t["Dead",    M_t == "Dead"]    <- 1

  return(t(m_p_t))
}
```

05.2 Cost function

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

```r
Costs <- function (M_t, Trt = "SoC") {
  # Arguments:
    # M_t: health state occupied at cycle t (character variable)
  # Returns:
    # costs accrued in this cycle
    # Trt:  treatment

  # Treatment specific transition costs
  if (Trt == "SoC") {
    c_trt <- 0
  } else if (Trt == "A") {
    c_trt <- c_trtA
  } else if (Trt == "B") {
    c_trt <- c_trtB
  }

  c_t <- c()
  c_t[M_t == "Healthy"] <- c_H + c_trt  # costs accrued by being healthy this cycle
  c_t[M_t == "Sick"]    <- c_S          # costs accrued by being sick this cycle
  c_t[M_t == "Dead"]    <- c_D          # costs at dead state

  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, cl = 1) {
  # Arguments:
    # M_t: health state occupied at cycle t (character variable)
     # cl:   cycle length (default is 1)
  # Returns:
    # QALYs accrued this cycle

  q_t <- c()
  q_t[M_t == "Healthy"] <- u_H  # utility for being healthy this cycle
  q_t[M_t == "Sick"]    <- u_S  # utility for being sick this cycle
  q_t[M_t == "Dead"]    <- u_D  # utility for dead state
  QALYs <- q_t * cl  # calculate the QALYs during cycle t
  return(QALYs)      # return the QALYs accrued this cycle
}
```

05.4 Microsimulation function

Below we develop the microsimulation function that allows the model to be run.

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

  set.seed(seed) # set a seed to be able to reproduce the same results

  # 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 = " ")))

  m_M[, 1] <- as.character(df_X$M_init) # initial health state
  m_C[, 1] <- Costs(m_M[, 1])  # costs accrued during cycle 0
  m_E[, 1] <- Effs(m_M[, 1], cl = 1)   # QALYs accrued during cycle 0

  # 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, Trt = Trt)
    # check if transition probabilities are between 0 and 1
    check_transition_probability(m_P, verbose = TRUE)
    # check if each of the rows of the transition probabilities matrix sum to one
    check_sum_of_transition_array(m_P, n_rows = n_i, n_cycles = n_cycles, verbose = TRUE)

    # sample the next 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 = Trt)
    # calculate QALYs per individual during cycle t + 1
    m_E[, t + 1]  <- Effs (m_M[, t + 1], cl = 1)

    # update time since illness onset for t + 1
    # NOTE: this code has a "reset of history" for time being sick
    # once someone is not "Sick" anymore, we reset n_cycles_s (set back to zero)
    # when you don't want a "reset" replace the last zero with teh current value
    df_X$n_cycles_s <- if_else(m_M[, t + 1] == "Sick", df_X$n_cycles_s + 1, 0)

    # 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
```

06 Run Microsimulation

```r
# 06 Run Microsimulation
# By specifying all the arguments in the `MicroSim()` the simulation can be started
# Run the simulation model
outcomes_SoC  <- MicroSim(n_i = n_i, df_X = df_X, seed = 1, Trt = "SoC")
```

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```r
outcomes_trtA <- MicroSim(n_i = n_i, df_X = df_X, seed = 1, Trt = "A")
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```
outcomes_trtB <- MicroSim(n_i = n_i, df_X = df_X, seed = 1, Trt = "B")
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##  50 % done[1] "Valid transition probabilities"
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##  60 % done[1] "Valid transition probabilities"
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##  70 % done[1] "Valid transition probabilities"
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##  80 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
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## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  90 % done[1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
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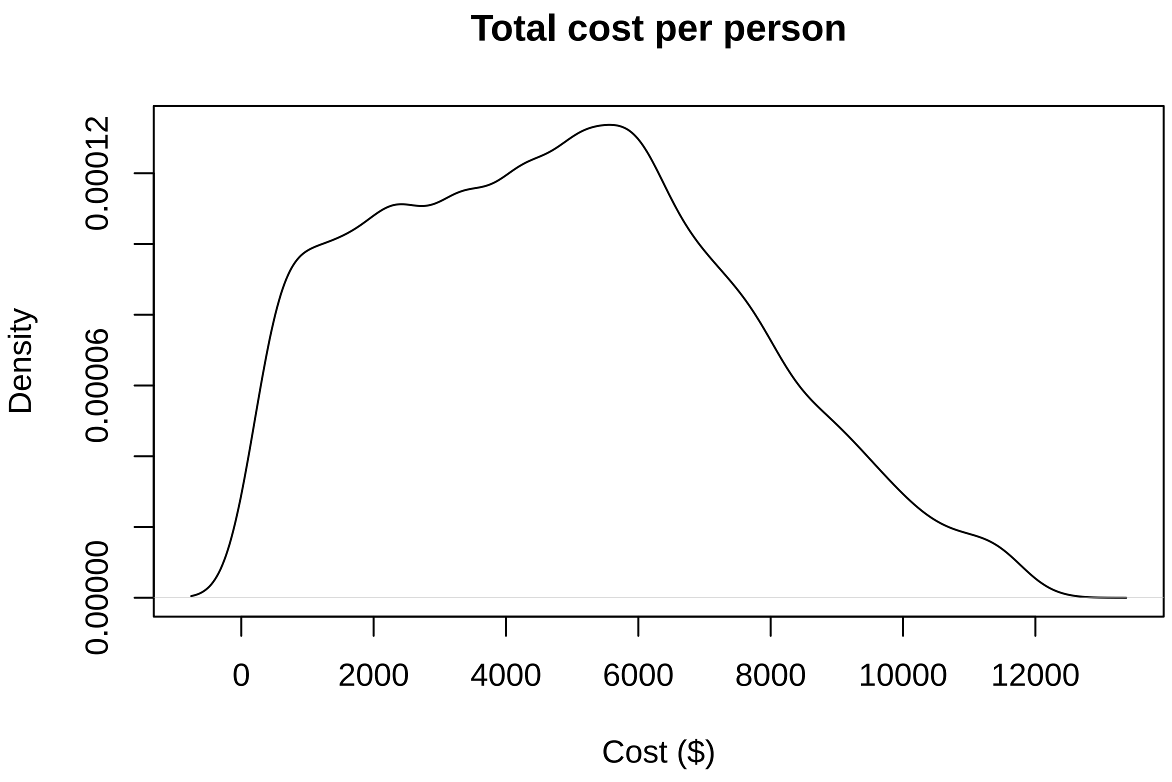
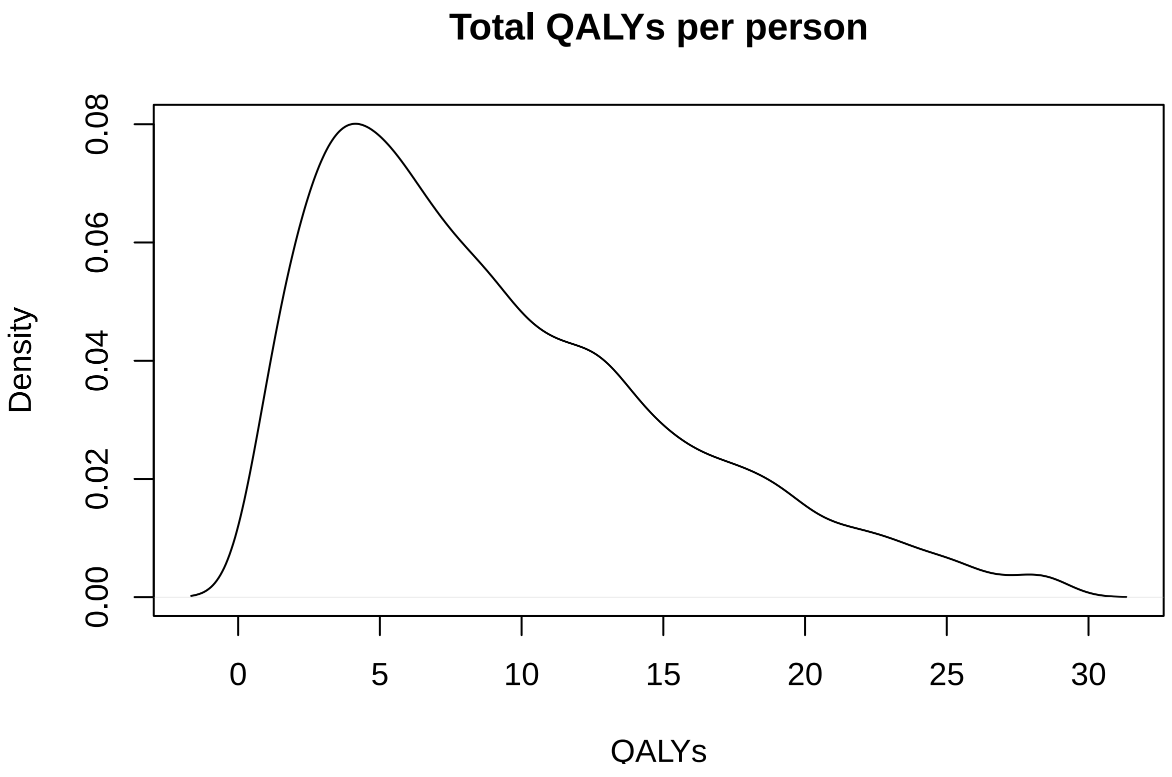
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
##  100 % done
```

07 Visualize results

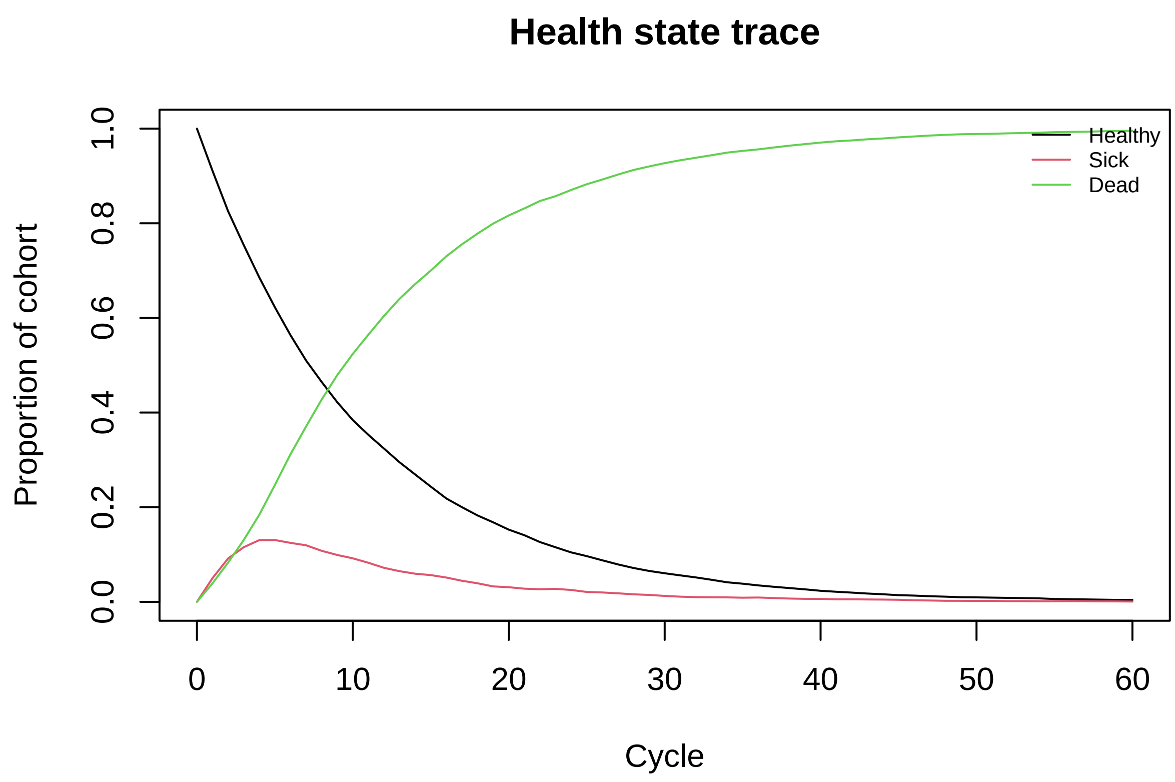
```r
# Standard of Care
plot(density(outcomes_SoC$tc), main = paste("Total cost per person"),  xlab = "Cost ($)")
```



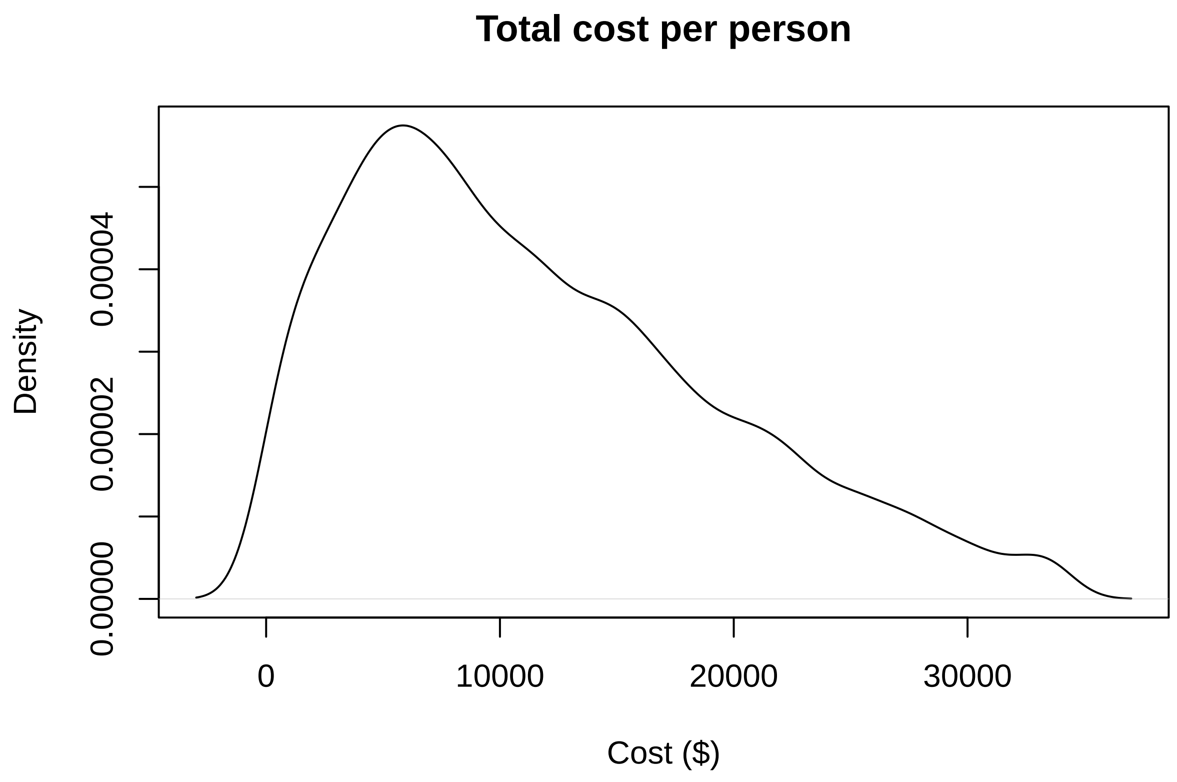
```
plot(density(outcomes_SoC$te), main = paste("Total QALYs per person"), xlab = "QALYs")
```



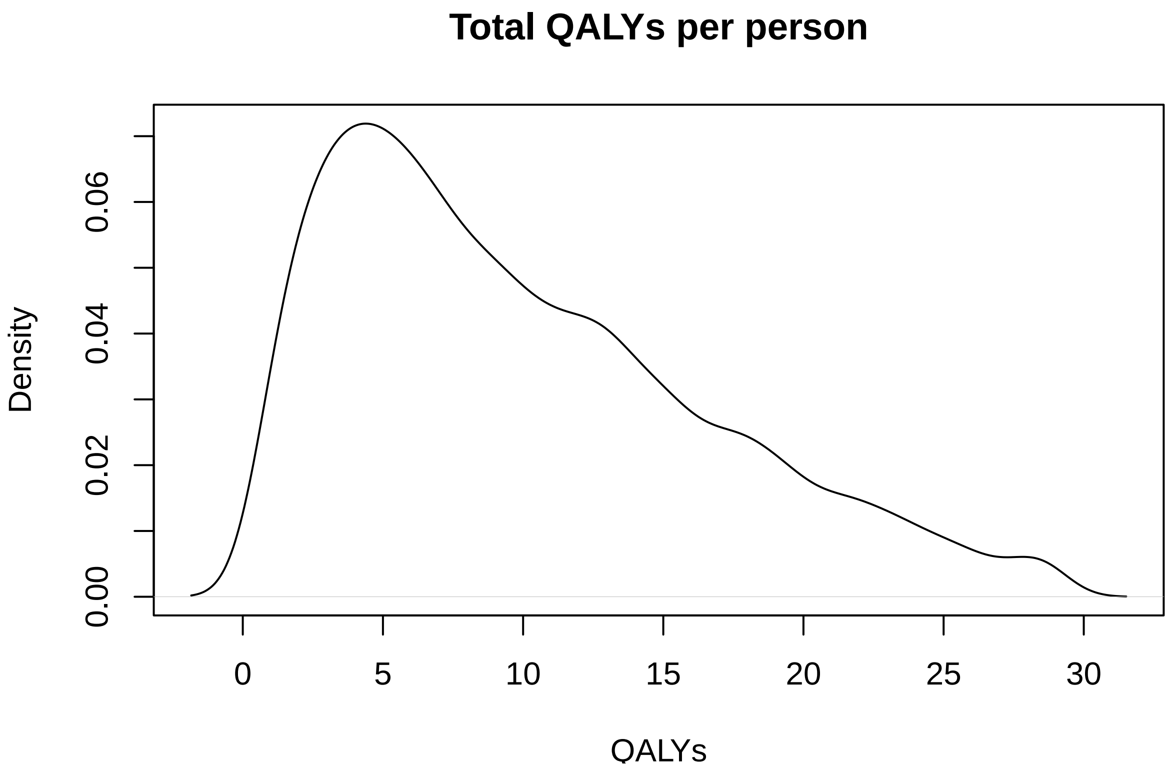
```r
plot_trace_microsim(outcomes_SoC$m_M)       # health state trace
```



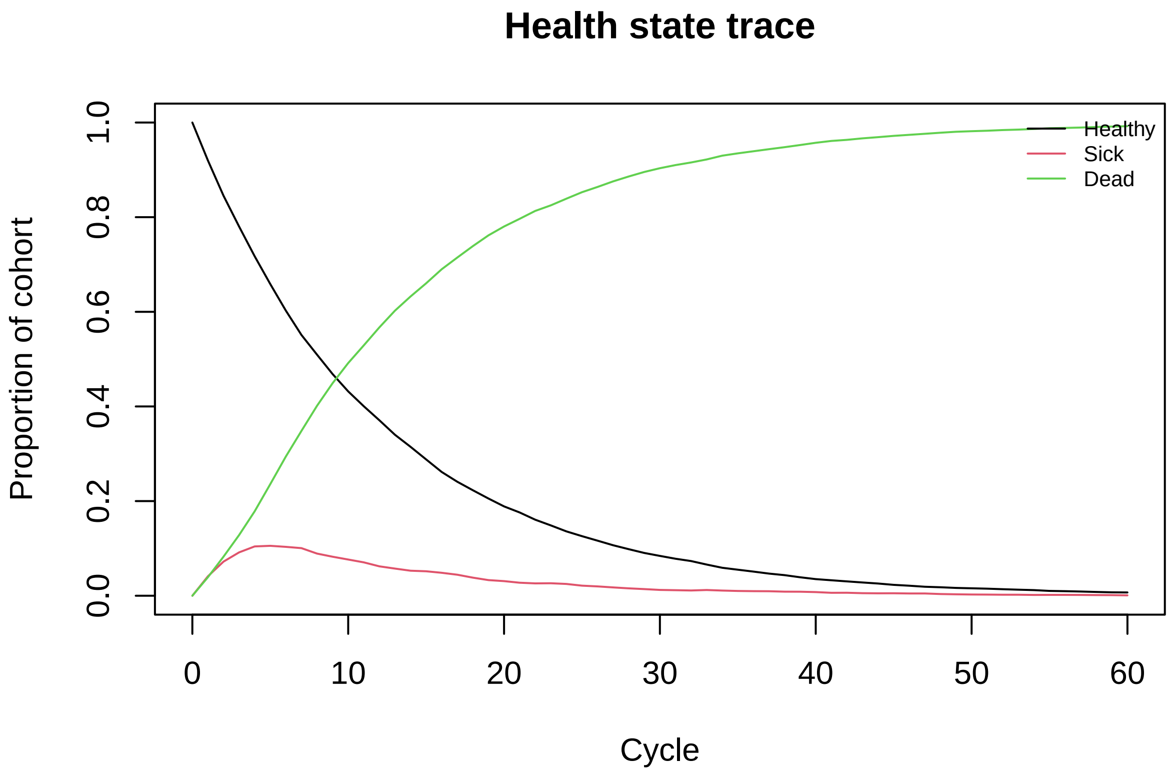
```r
# Treatment A
plot(density(outcomes_trtA$tc), main = paste("Total cost per person"),  xlab = "Cost ($)")
```



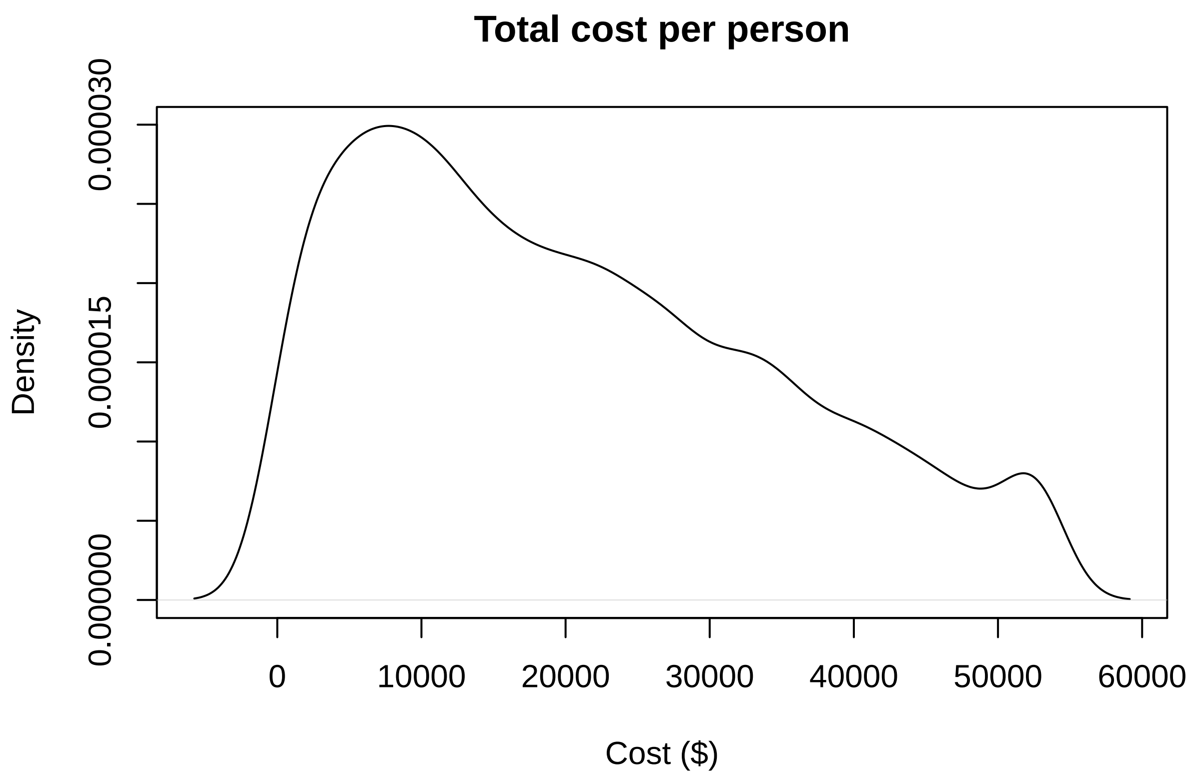
```
plot(density(outcomes_trtA$te), main = paste("Total QALYs per person"), xlab = "QALYs")
```



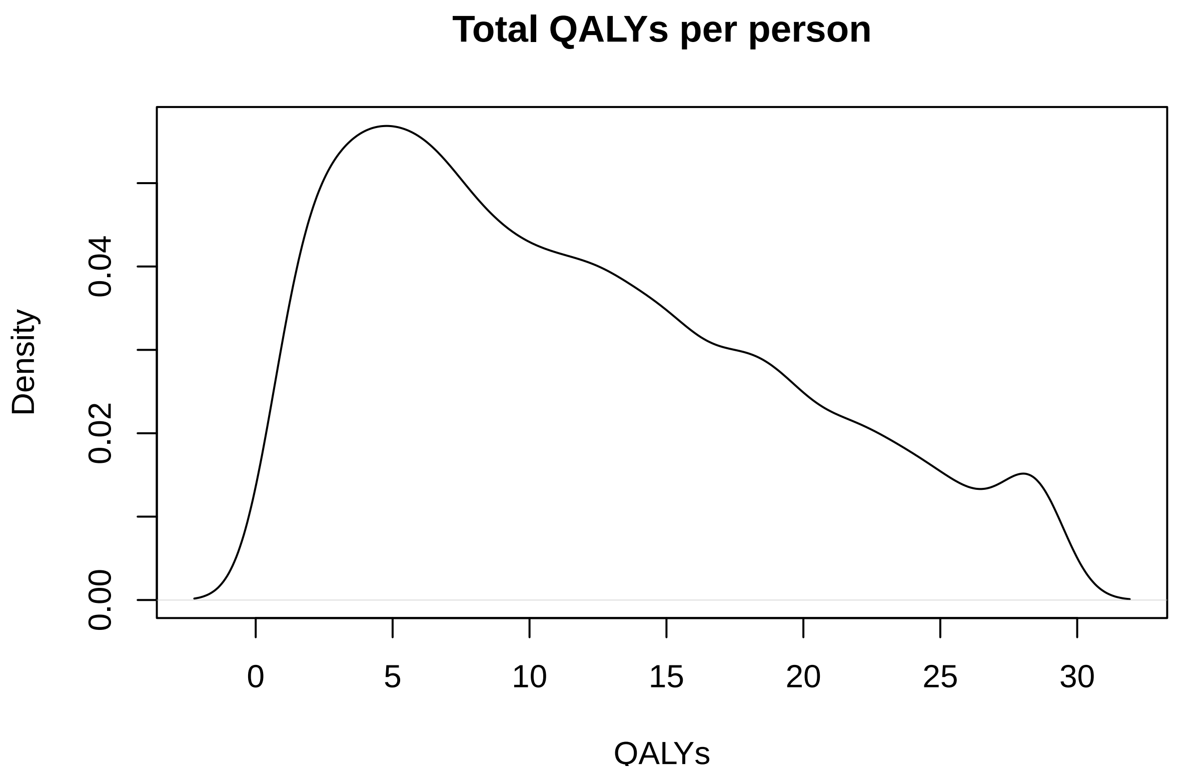
```
plot_trace_microsim(outcomes_trtA$m_M)        # health state trace
```



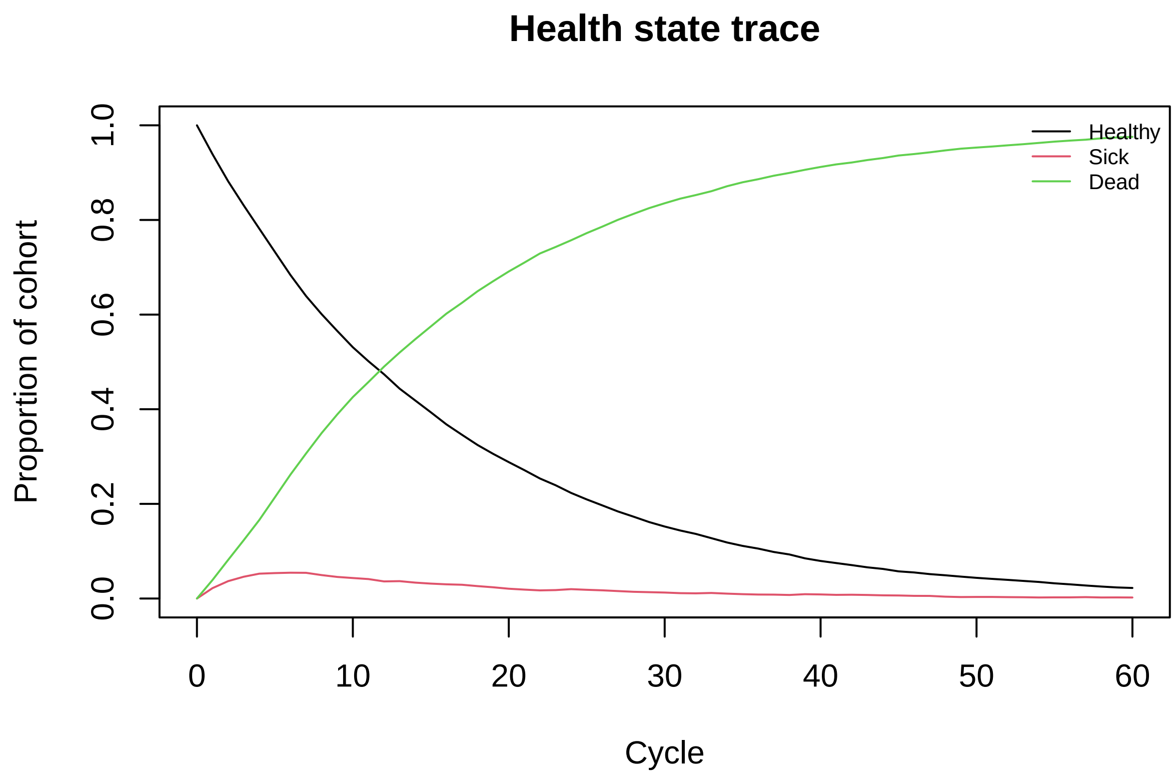
```r
# Treatment B
plot(density(outcomes_trtB$tc), main = paste("Total cost per person"),  xlab = "Cost ($)")
```



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



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



08 Cost-effectiveness analysis (CEA)

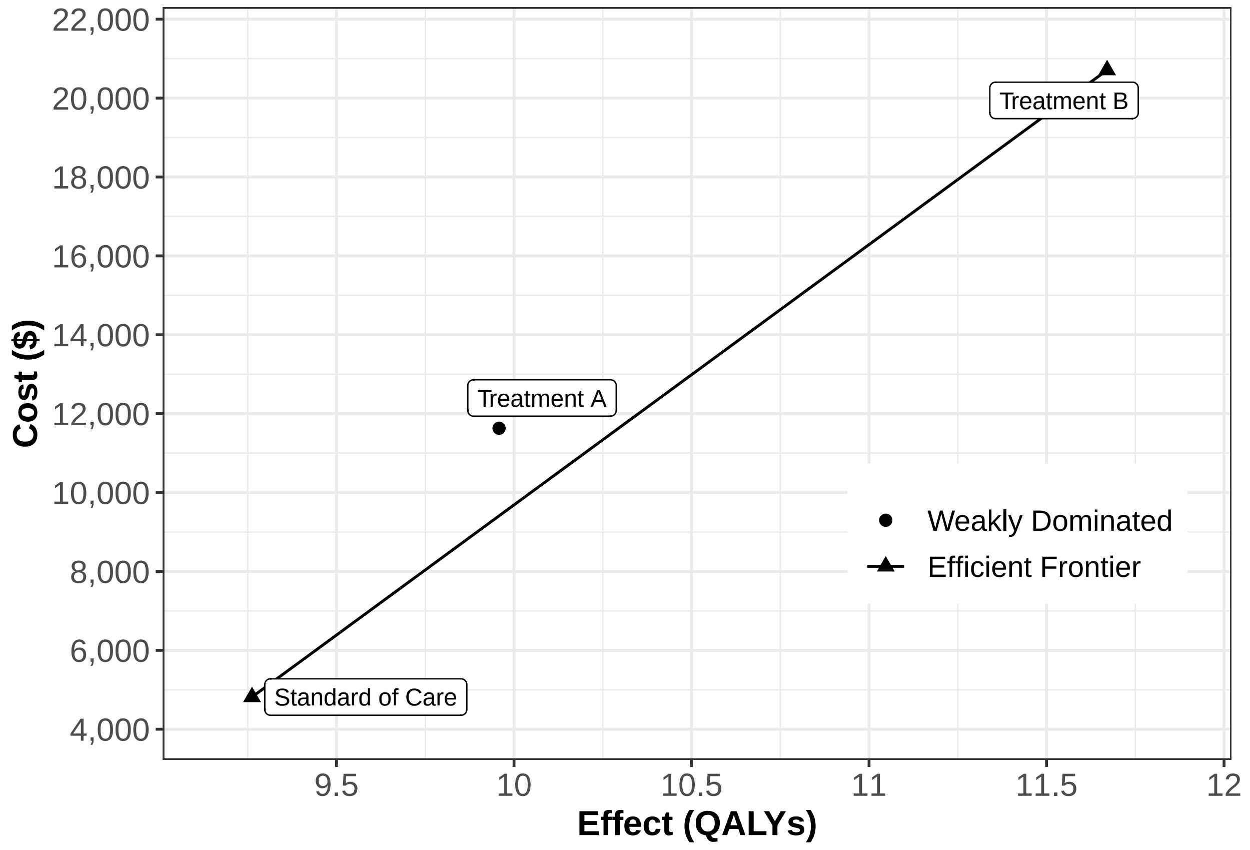
```r
# store the mean costs of each strategy in a new variable C (vector of costs)
v_C <- c(outcomes_SoC$tc_hat, outcomes_trtA$tc_hat, outcomes_trtB$tc_hat)
# store the mean QALYs of each strategy in a new variable E (vector of effects)
v_E <- c(outcomes_SoC$te_hat, outcomes_trtA$te_hat, outcomes_trtB$te_hat)

# 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  4817.465  9.262123       NA         NA       NA     ND
## 2      Treatment B 20709.997 11.670548 15892.53   2.408425 6598.724     ND
## 3      Treatment A 11630.222  9.957949       NA         NA       NA     ED
```

```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     4,817  9.26                  <NA>                NA
## 2       Treatment B    20,710 11.67                15,893              2.41
## 3       Treatment A    11,630  9.96                  <NA>                NA
##   ICER ($/QALY) Status
## 1          <NA>     ND
## 2         6,599     ND
## 3          <NA>     ED
```

```
## CEA frontier
plot(df_cea, label = "all", txtsize = 14) +
  expand_limits(x = max(table_cea$QALYs) + 0.1) +
  theme(legend.position = c(0.8, 0.3))
```


Cost ($)
Effect (QALYs)
Treatment B
Treatment A
Standard of Care
● Weakly Dominated
▲ Efficient Frontier