

# 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

```
## 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))
# probability to die in sick state by cycle of being sick
p_SD <- c(0.1, 0.2, 0.3, 0.4, 0.5, rep(0.7, n_cycles - 5))
```

```

### 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]

  # 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.

```

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.

```

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.

```
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] <- Effe(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] <- Effe(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%
```



[illegible]



```

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

```

```

outcomes_trtA <- MicroSim(n_i = n_i, df_X = df_X, seed = 1, Trt="A")

```

```

## [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"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"

```

[illegible]

[illegible]

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

```
outcomes_trtB <- MicroSim(n_i = n_i, df_X = df_X, seed = 1, Trt="B")
```

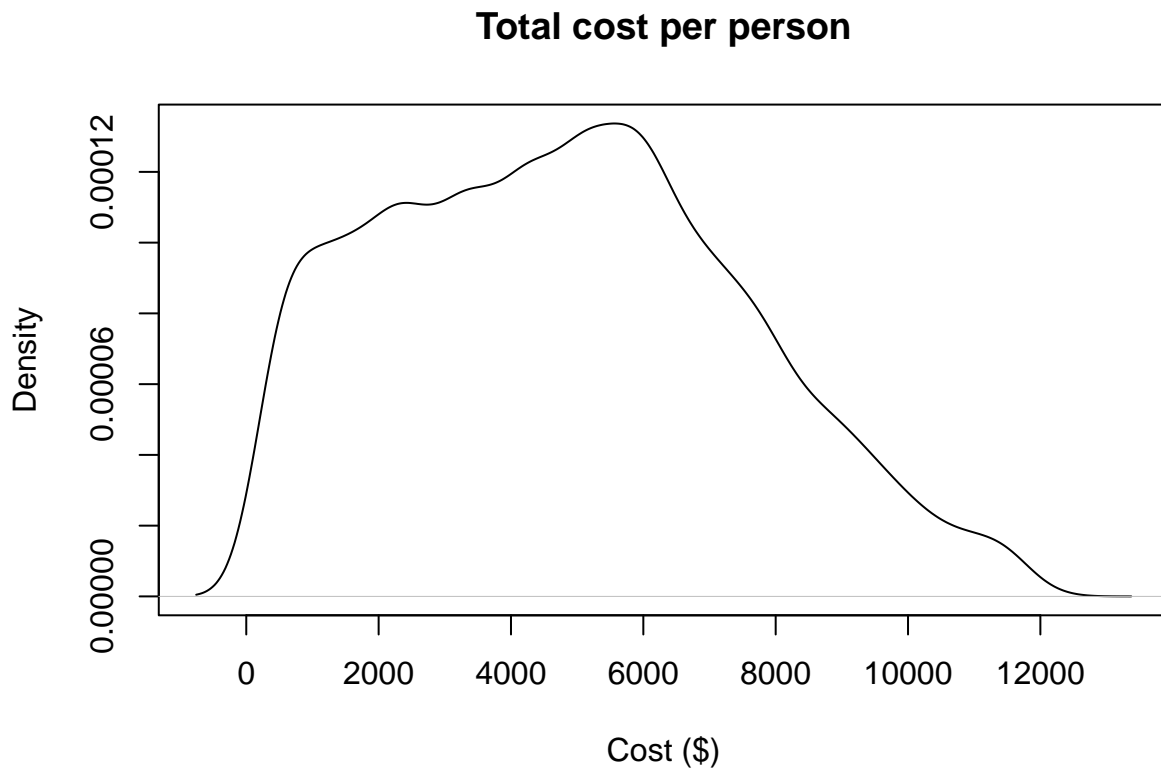
```
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This 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"
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## [1] "This is a valid transition matrix"
## 20 % done[1] "Valid transition probabilities"
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## [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"
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## [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"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
```

[illegible]

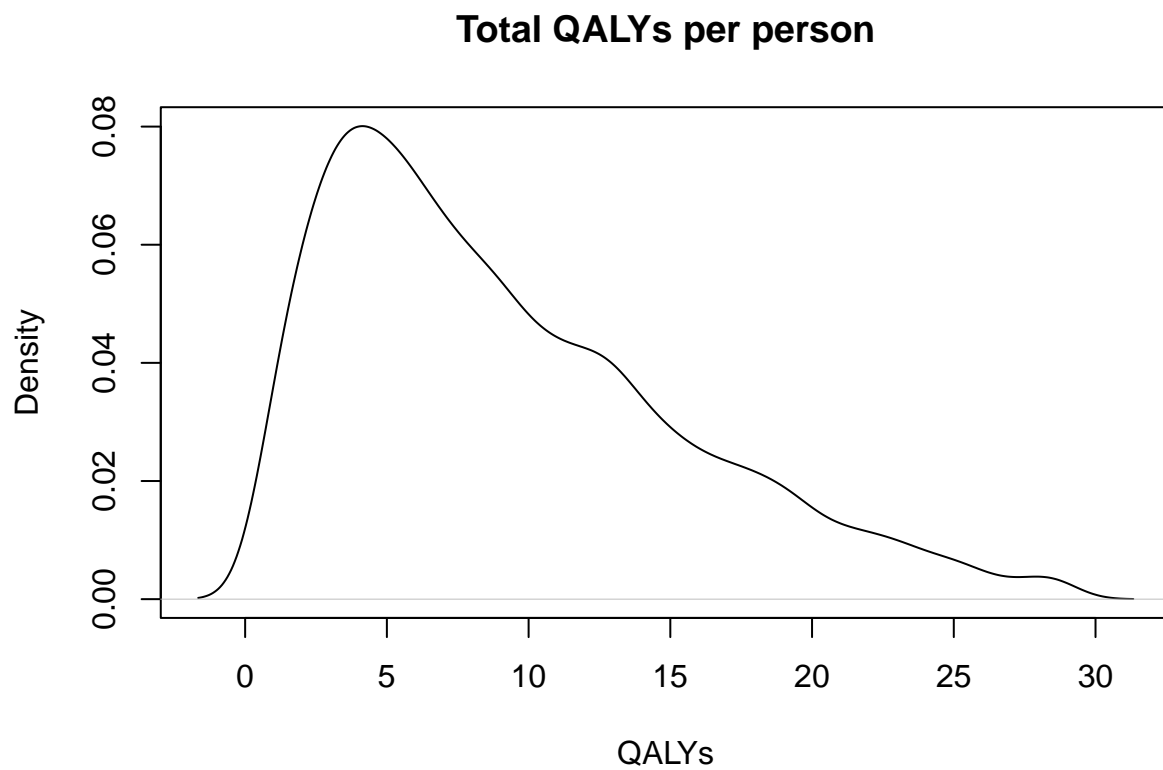
```
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## [1] "Valid transition probabilities"
## [1] "This is a valid transition matrix"
## 90 % done[1] "Valid transition probabilities"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

## 07 Visualize results

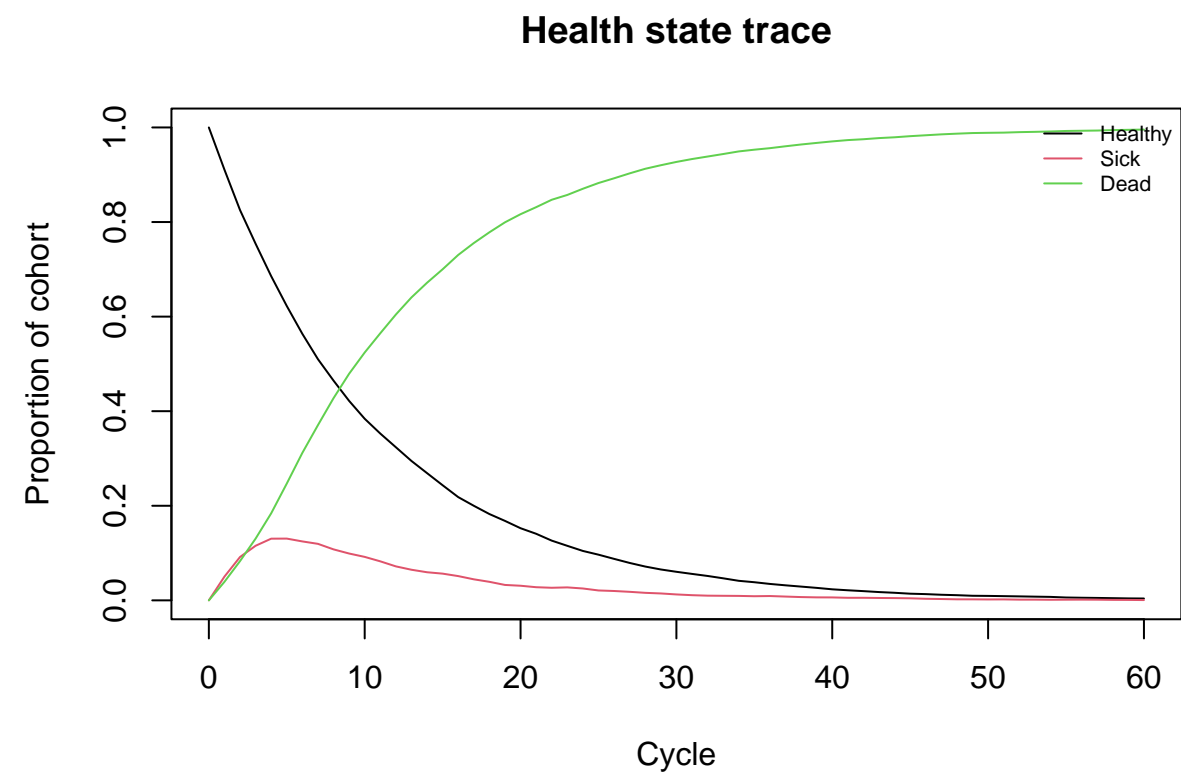
```
# Standard of Care
plot(density(outcomes_SoC$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
```



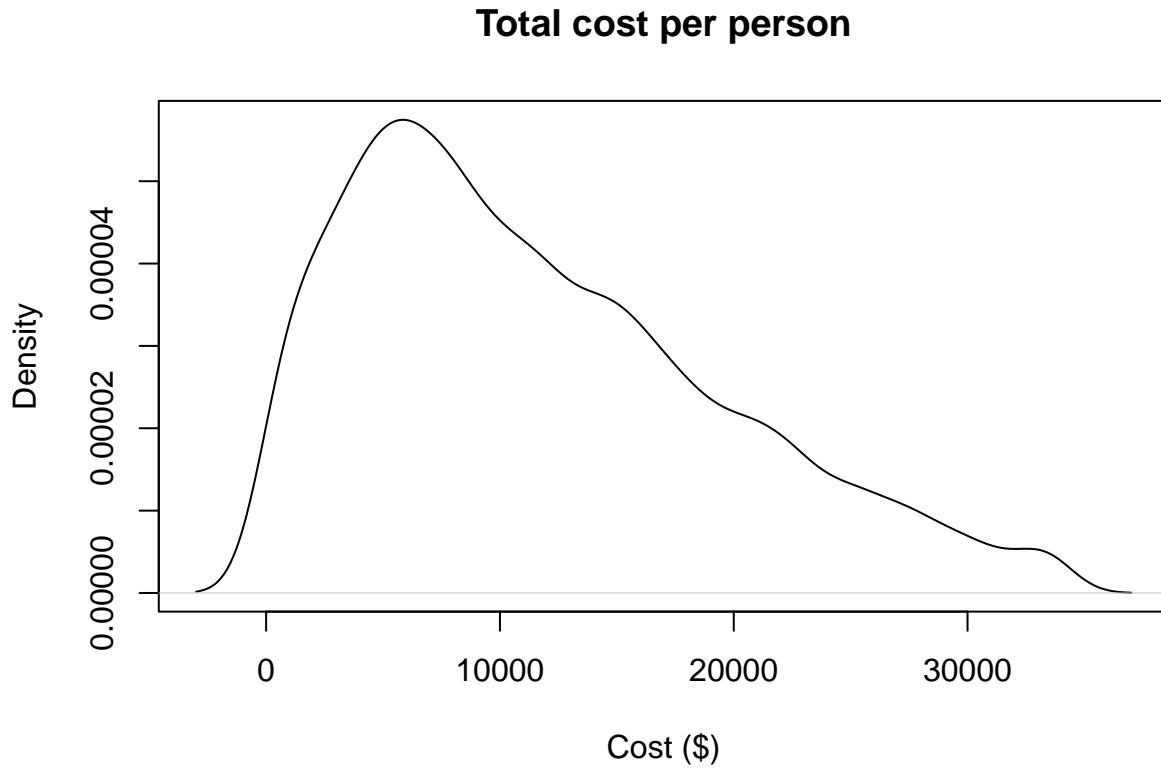
```
plot(density(outcomes_SoC$te), main = paste("Total QALYs per person"), xlab = "QALYs")
```



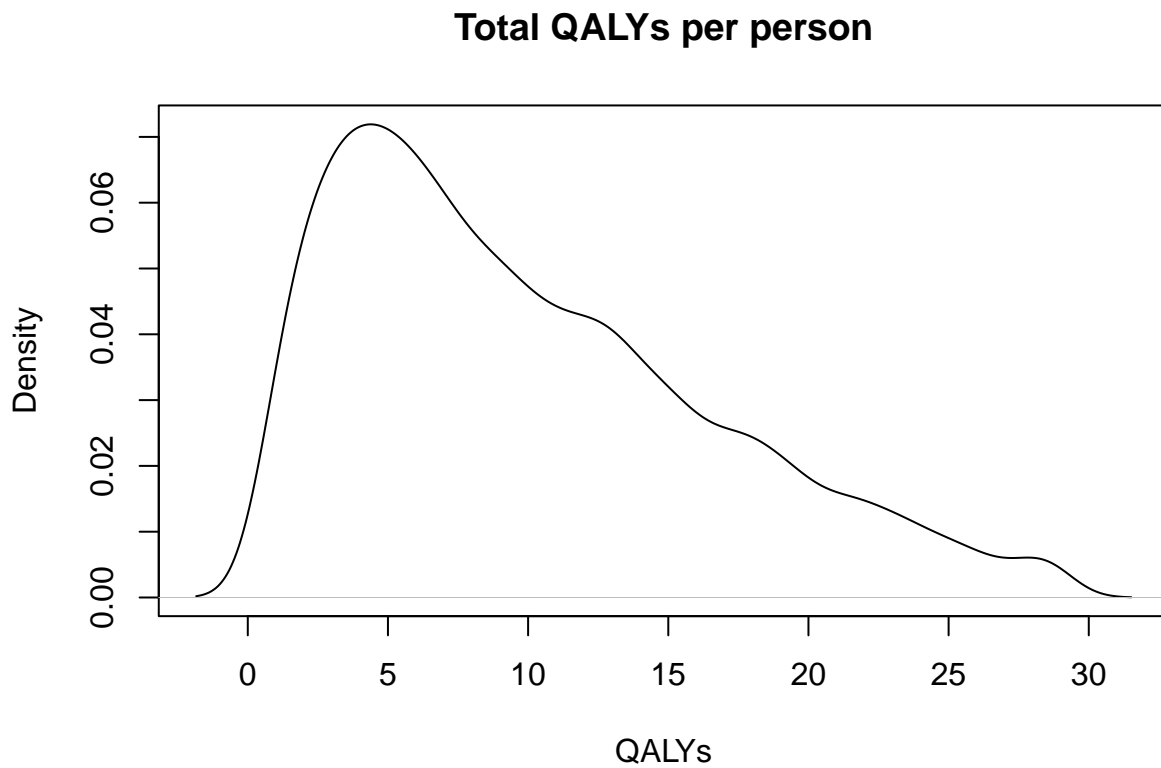
```
plot_trace_microsim(outcomes_SoC$m_M) # health state trace
```



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



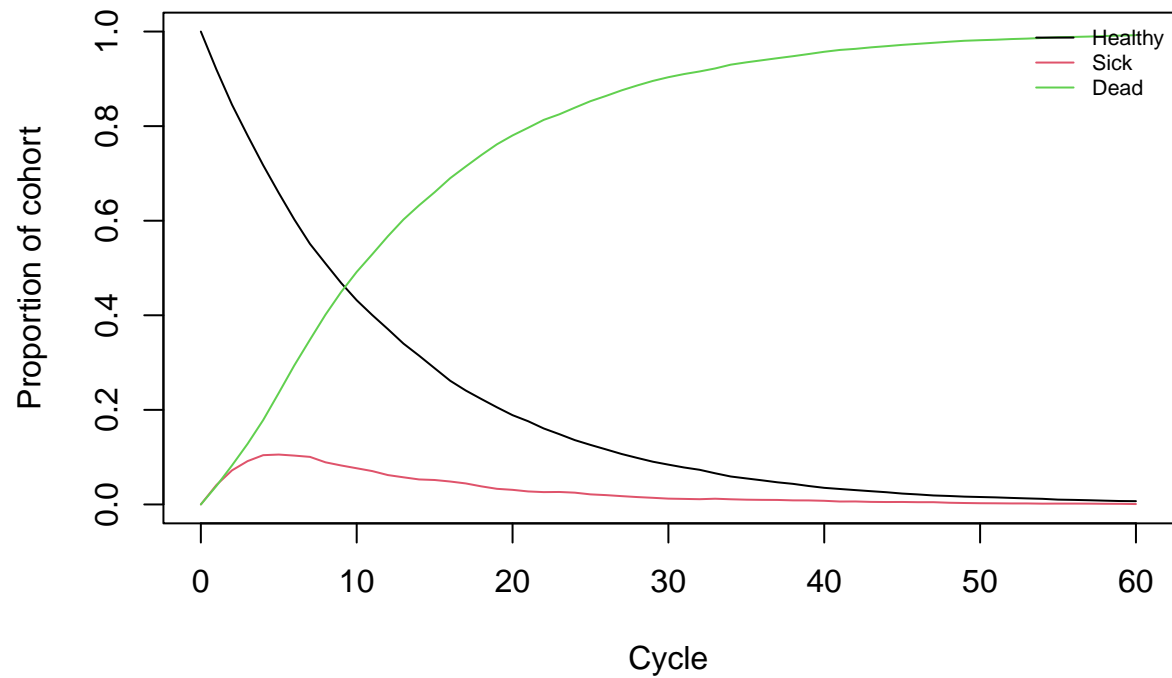
```
plot(density(outcomes_trtA$te), main = paste("Total QALYs per person"), xlab = "QALYs")
```





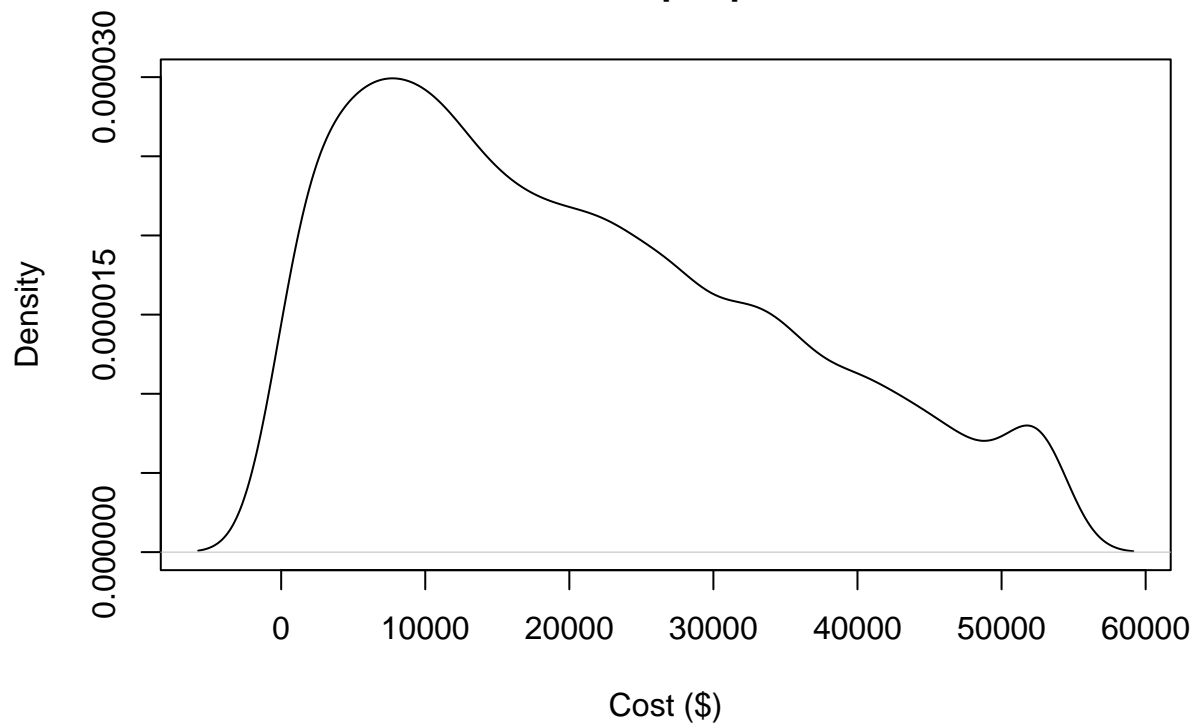
```
plot_trace_microsim(outcomes_trtA$m_M) # health state trace
```

### Health state trace

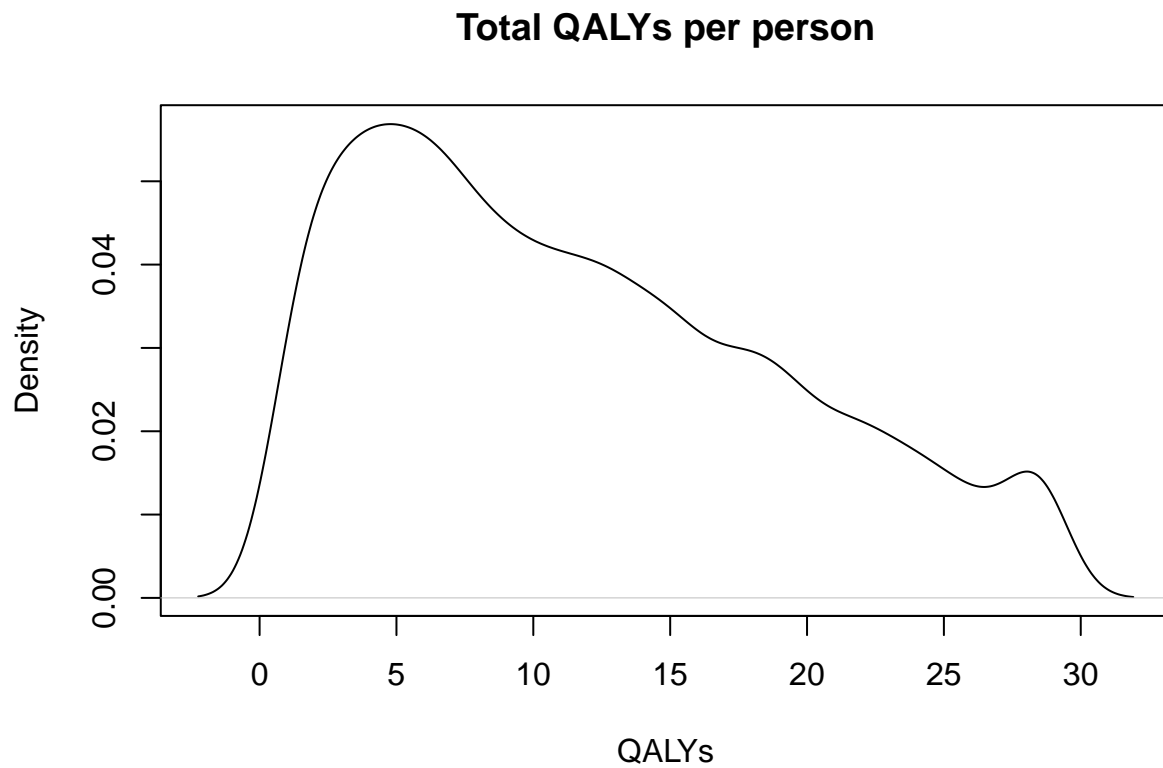


```
# Treatment B  
plot(density(outcomes_trtB$tc), main = paste("Total cost per person"), xlab = "Cost ($)")
```

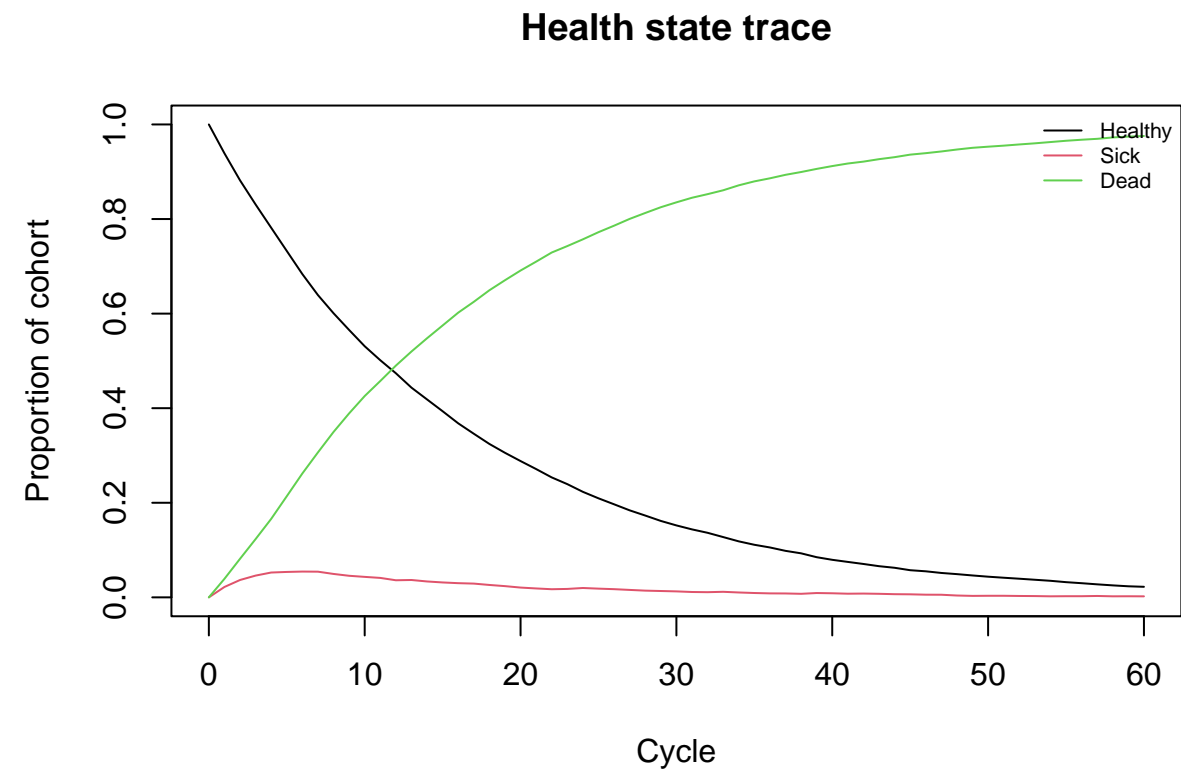
### Total cost per person



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



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



## 08 Cost-effectiveness analysis (CEA)

```
# 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)

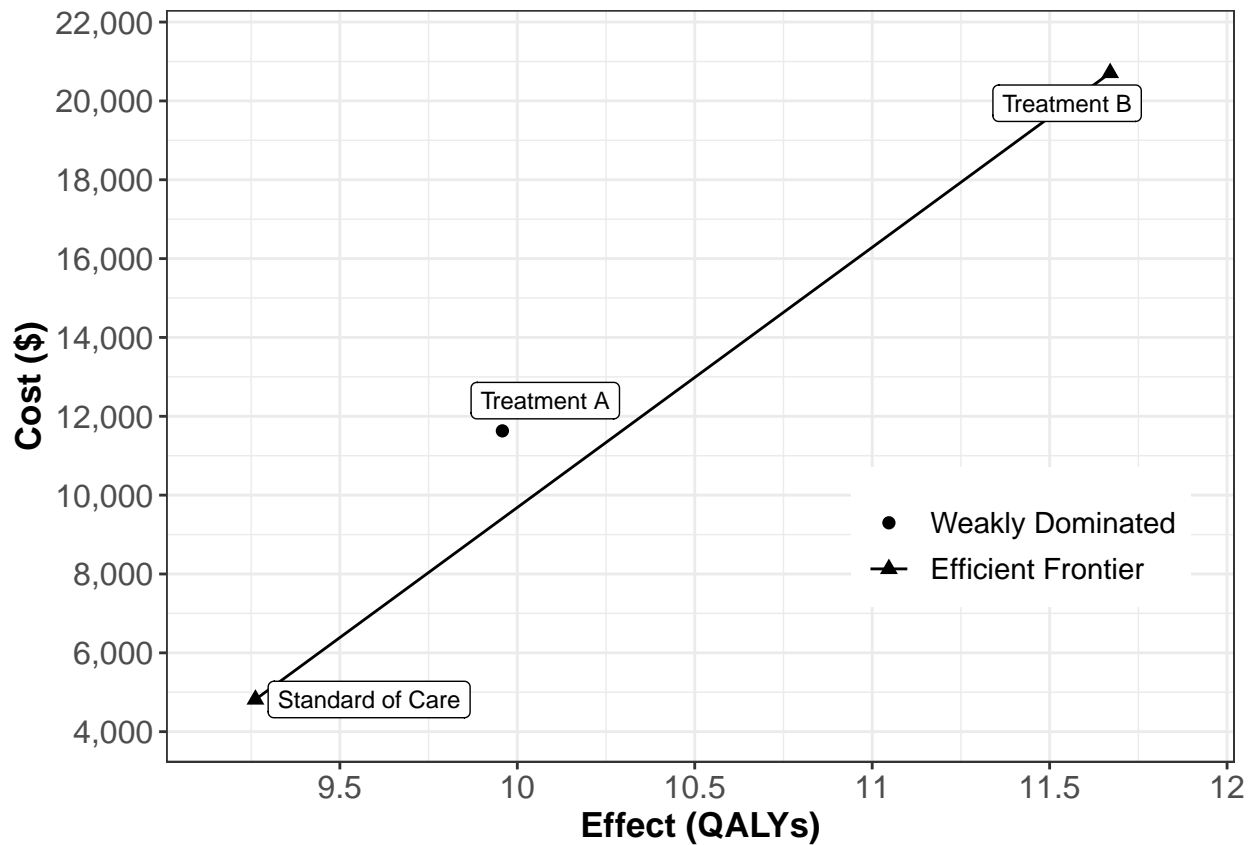
df_cea
```

```
##           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
```

```
## 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))
```



## 9 Sensitivity analysis

### 9.1 Make a list of the input parameters

```
## List of input parameters
l_params_all <- list(

  ### 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 sta
  p_HS_trtA    = 0.04, # probability of becoming sick when healthy, conditional on surviving, under tre
  p_HS_trtB    = 0.02, # probability of becoming sick when healthy, conditional on surviving, under tre
  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)),
  # probability to die in sick state by cycle of being sick
  p_SD         = c(0.1, 0.2, 0.3, 0.4, 0.5, rep(0.7, n_cycles - 5)) ,

  ## State rewards
  # Costs
  c_H          = 400,      # cost of one cycle in Healthy
  c_S          = 1000,     # cost of one cycle in Sick

```

```

c_D      = 0,          # cost of being dead (per cycle)
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

# Discount rates
d_c       = 0.03,       # annual discount rate for costs
d_e       = 0.03,       # annual discount rate for QALYs
# Cycle length
cycle_length = 1
)

```

## 09.1 Load function of microsimulation model

```
source("Function_Microsim_3-state_time.R")
```

## 09.2 Run the function with the list of parameters

```
df_ce <- calculate_ce_out(l_params_all)

## [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"
## [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"
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## [1] "This is a valid transition matrix"

```

[illegible]

[illegible]

[illegible]



[illegible]

[illegible]

[illegible]

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

```
# use dampack to calculate the ICER
calculate_icers(cost      = df_ce$Cost,
                effect    = df_ce$Effect,
                strategies = df_ce$Strategy)
```

##	Strategy	Cost	Effect	Inc_Cost	Inc_Effect	ICER	Status
## 1	Standard of Care	4813.562	9.262197	NA	NA	NA	ND
## 2	Treatment B	20631.983	11.629315	15818.42	2.367118	6682.565	ND
## 3	Treatment A	11623.138	9.953672	NA	NA	NA	ED