

Markov Sick-Sicker model in R

The DARTH workgroup

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Please cite our publications when using this code:

- 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*. Feb;40(2):242-248. <https://doi.org/10.1177/0272989X19893973>

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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("dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval", "igraph", "truncnorm", "ggraph")
# load (install if required) packages from GitHub
# install_github("DARTH-git/dampack", force = TRUE) Uncomment if there is a newer version
# install_github("DARTH-git/darthtools", force = TRUE) Uncomment if there is a newer version
p_load_gh("DARTH-git/dampack", "DARTH-git/darthtools")
```

02 Load functions

```
# all functions are in the darthtools package
```

03 Input model parameters

```
# Strategy names
v_names_str <- c("No Treatment", "Treatment")

# 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)

v_init <- c("H" = 1,    # initial cohort distribution (everyone
            "S1" = 0,    # allocated to the "healthy" state)
            "S2" = 0,
            "D" = 0)

# 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
d_e      <- d_c <- 0.03              # discount rate per cycle equal discount of costs and QALYs by 3%

n_str     <- length(v_names_str)      # Number of strategies
n_states  <- length(v_n)              # number of states

# Discount weights for costs and effects
v_dwc <- 1 / (1 + d_c) ^ (0:n_t)
v_dwe <- 1 / (1 + d_e) ^ (0:n_t)

```

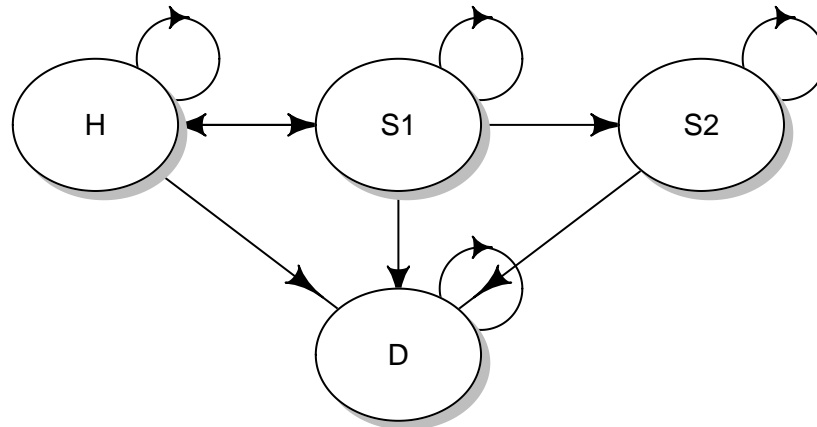
Create a state-transition diagram of the cohort model

```

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 Define and initialize matrices and vectors

04.1 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

```

```

##           H S1 S2  D
## cycle 0 NA NA NA NA
## cycle 1 NA NA NA NA
## cycle 2 NA NA NA NA
## cycle 3 NA NA NA NA
## cycle 4 NA NA NA NA
## cycle 5 NA NA NA NA

```

```

# The cohort starts as healthy
m_M_notrt[1, ] <- m_M_trt[1, ] <- v_init # initiate first cycle of cohort trace

```

04.2 Transition probability matrix

```
# create the transition probability matrix for NO treatment
m_P_notrt <- m_P_trt <- matrix(0,
                                nrow = n_states,
                                ncol = n_states,
                                dimnames = list(v_n, v_n)) # name the columns and rows of the matrix
m_P_notrt
```

```
##      H S1 S2 D
## H    0  0  0  0
## S1   0  0  0  0
## S2   0  0  0  0
## D    0  0  0  0
```

```
m_P_trt
```

```
##      H S1 S2 D
## H    0  0  0  0
## S1   0  0  0  0
## S2   0  0  0  0
## D    0  0  0  0
```

Fill in the transition probability matrix:

```
# from Healthy
m_P_notrt["H", "H" ] <- (1 - p_HD) * (1 - p_HS1)
m_P_notrt["H", "S1" ] <- (1 - p_HD) * p_HS1
m_P_notrt["H", "D"  ] <- p_HD
# from Sick
m_P_notrt["S1", "H" ] <- (1 - p_S1D) * p_S1H
m_P_notrt["S1", "S1" ] <- (1 - p_S1D) * (1 - (p_S1H + p_S1S2))
m_P_notrt["S1", "S2" ] <- (1 - p_S1D) * p_S1S2
m_P_notrt["S1", "D"  ] <- p_S1D
# from Sicker
m_P_notrt["S2", "S2" ] <- 1 - p_S2D
m_P_notrt["S2", "D"  ] <- p_S2D
# from Dead
m_P_notrt["D", "D"  ] <- 1

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

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

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

```

```

##           H           S1           S2           D
## cycle 0 1.0000000 0.0000000 0.0000000 0.0000000
## cycle 1 0.8457500 0.1492500 0.0000000 0.00500000
## cycle 2 0.7888043 0.1843020 0.01543735 0.01145632
## cycle 3 0.7579069 0.1894418 0.03374551 0.01890581
## cycle 4 0.7343069 0.1868303 0.05169021 0.02717260
## cycle 5 0.7130610 0.1822918 0.06848747 0.03615973

```

06 Compute and Plot Epidemiological Outcomes

06.1 Cohort trace

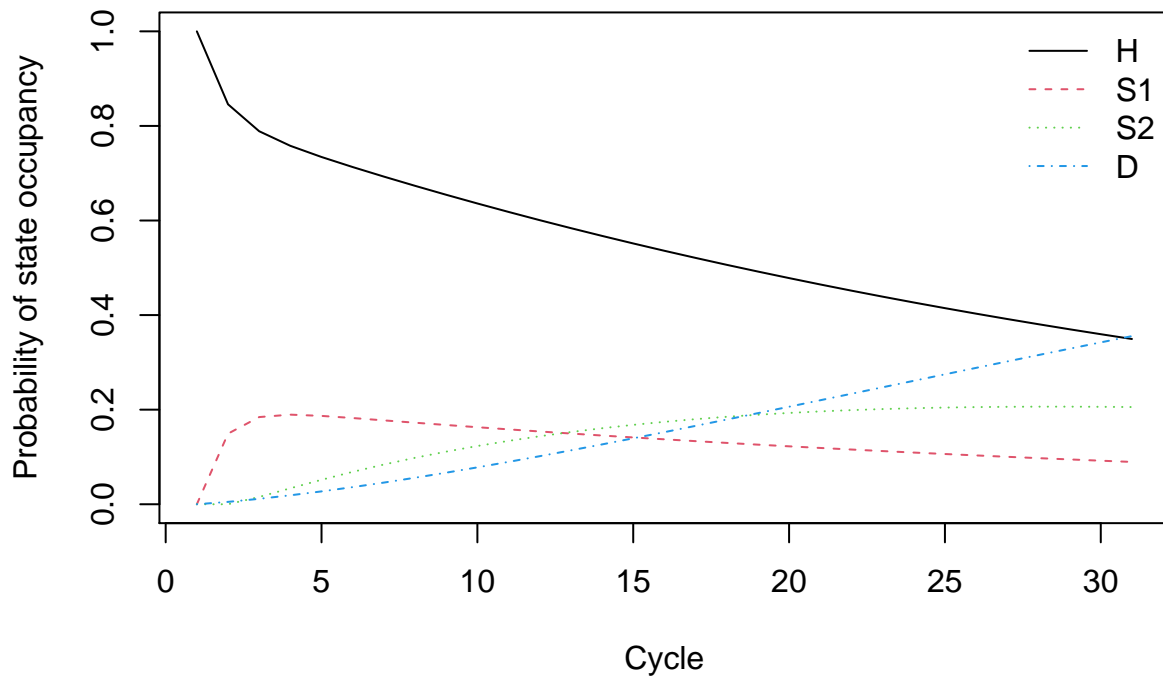
The transition probabilities are similar in both strategies. Therefore, the cohort trace figure applies to both strategies.

```

# 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")

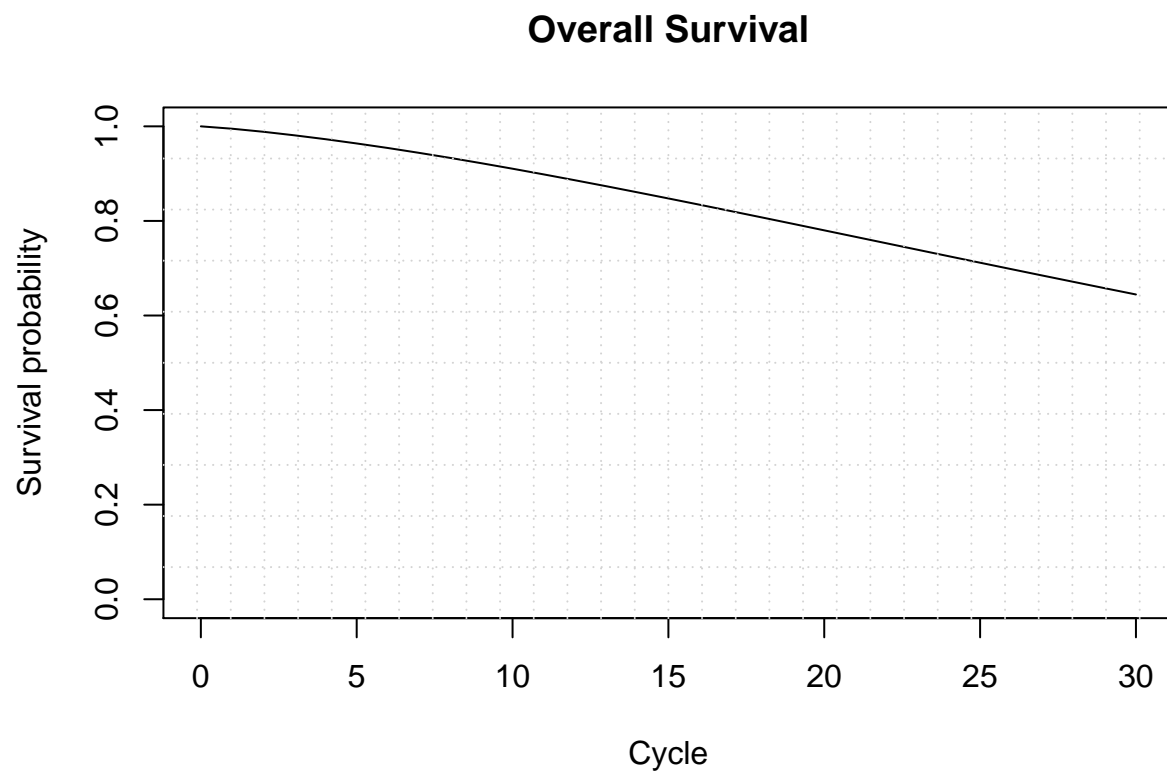
```

Cohort Trace



06.2 Overall Survival (OS)

```
# 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)
```

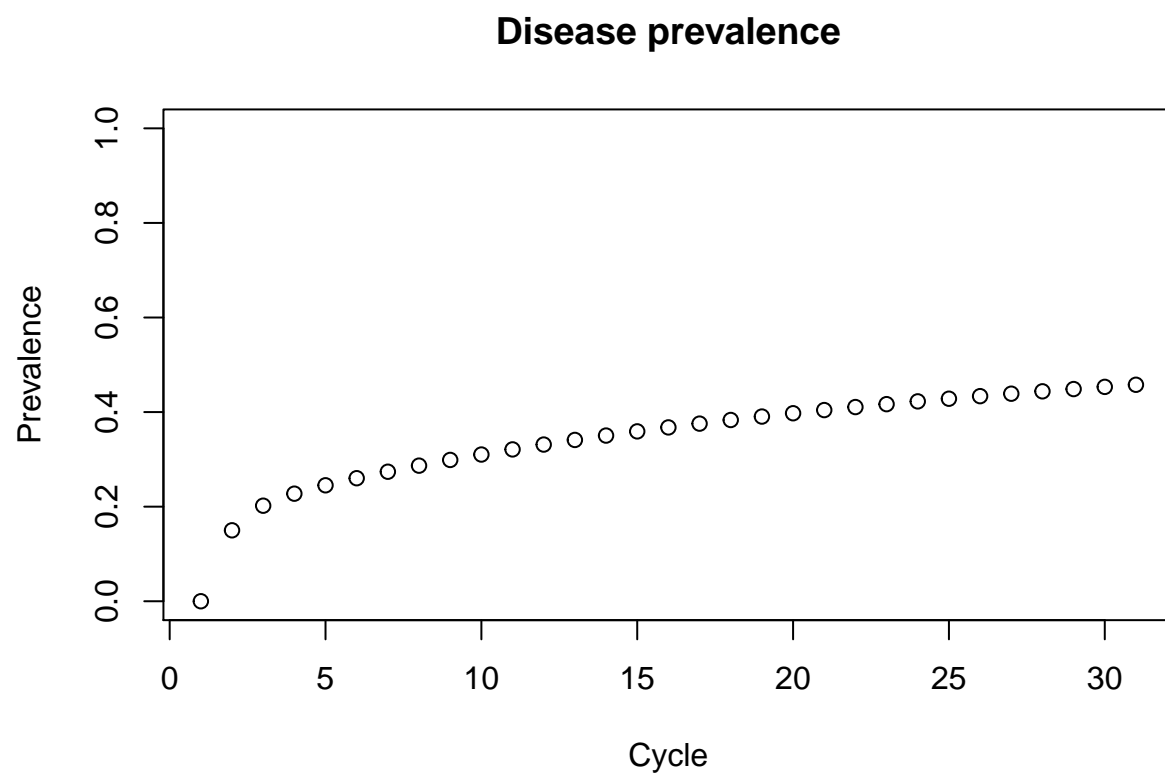


06.2.1 Life Expectancy (LE)

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

06.3 Disease prevalence

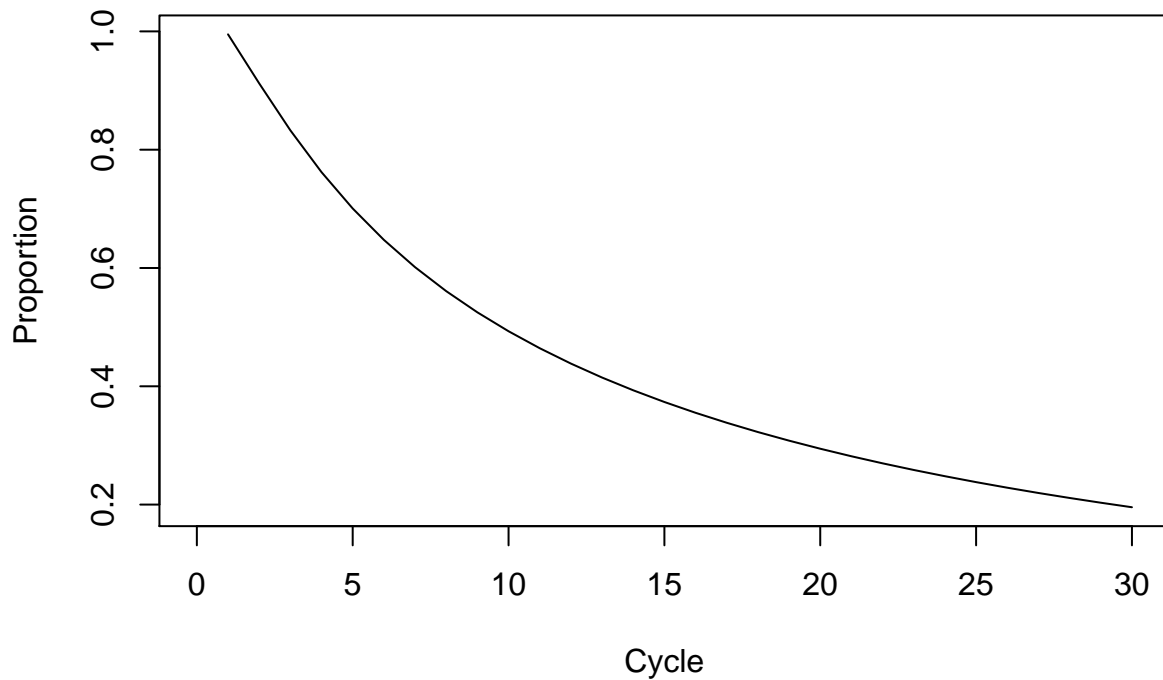
```
v_prev <- rowSums(m_M_notrt[, c("S1", "S2")]) / v_os_notrt
plot(v_prev,
     ylim = c(0, 1),
     ylab = "Prevalence",
     xlab = "Cycle",
     main = "Disease prevalence")
```

06.4 Proportion of sick in S1 state

```
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")
```

Proportion of sick in S1 state



07 Compute Cost-Effectiveness Outcomes

```
# 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
```

```
##      Strategy      Cost      Effect
## 1 No Treatment  75795.04  15.84802
## 2   Treatment 141511.41  16.41446
```

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
```

```
##      Strategy      Cost      Effect Inc_Cost Inc_Effect      ICER Status
## 1 No Treatment  75795.04  15.84802      NA      NA      NA      ND
## 2   Treatment 141511.41  16.41446  65716.37  0.5664367 116017.2      ND
```

07.4 Plot frontier of the Markov model

```
plot(df_cea, effect_units = "QALYs", xlim = c(15.6, 16.6))
```

