3-state cohort state transition model in R

with simulation time and state-residence time dependencies

The DARTH workgroup

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- Alarid-Escudero F, Krijkamp EM, Enns EA, Yang A, Hunink MGM Pechlivanoglou P, Jalal H. A Tutorial on Time-Dependent Cohort State-Transition Models in R using a Cost-Effectiveness Analysis Example. Medical Decision Making, 2022 (Epub). https://doi.org/10.1177/0272989X221121747

- 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 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

```
# use this package to conveniently install other packages
if (!require('pacman')) install.packages('pacman'); library(pacman)
```

```
## Loading required package: pacman
```

```
# load (install if required) packages from CRAN
p_load("devtools","diagram","dampack","scales")

# 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

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

03 Model parameters

03.1 Define model input parameters

```
## General setup
n_time_horizon_yr <- 60                                # time horizon (in years)
cycle_length      <- 1                                 # cycle length in years (use 1/12 for monthly)
n_cycles          <- n_time_horizon_yr / cycle_length  # 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 rate
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
```

```r
## Within-cycle correction (WCC) using Simpson's 1/3 rule
v_wcc <- gen_wcc(n_cycles = n_cycles,  method = "Simpson1/3")

### Transition probabilities

## Constant transition probabilities
# Annual probability of becoming sick from Healthy, conditional on surviving cycle
p_HS_yr_SoC  <- 0.05  # under standard of care
p_HS_yr_trtA <- 0.04  # under treatment A
p_HS_yr_trtB <- 0.02  # under treatment B

## Simulation time-dependent transition probabilities
# Annual probability of dying when healthy (increases over time)
p_HD_yr_init <- 0.001    # Initial annual probability of death
p_HD_yr_inc  <- 0.0005   # Annual increase in baseline mortality
v_p_HD_yr    <- seq(from = p_HD_yr_init,
                      by = p_HD_yr_inc,
                    length.out = n_time_horizon_yr)

## State-residence time-dependent transition probabilities
# Annual probability of dying when Sick, increases the longer one is sick, up to 10 years
n_tunnel_size_yr <- 10
# Probability of dying follows a Weibull distribution on Sick state residence time
# Weibull parameters
p_SD_scale <- 0.08
p_SD_shape <- 1.1
# Weibull function
v_p_SD_tunnels_yr <- ((1:n_tunnel_size_yr)     * p_SD_scale) ^ p_SD_shape -
                     ((1:n_tunnel_size_yr - 1) * p_SD_scale) ^ p_SD_shape

### State rewards
#### Costs
c_H_yr     <- 400   # cost of one year in healthy state
c_S_yr     <- 1000  # cost of one year in sick state
c_D_yr     <- 0     # cost of one year in dead state
c_trtA_yr  <- 800   # cost of treatment A (per year) in healthy state
c_trtB_yr  <- 1500  # cost of treatment B (per year) in healthy state
#### Utilities
u_H       <- 1     # utility when healthy
u_S       <- 0.5   # utility when sick
u_D       <- 0     # utility when dead
```

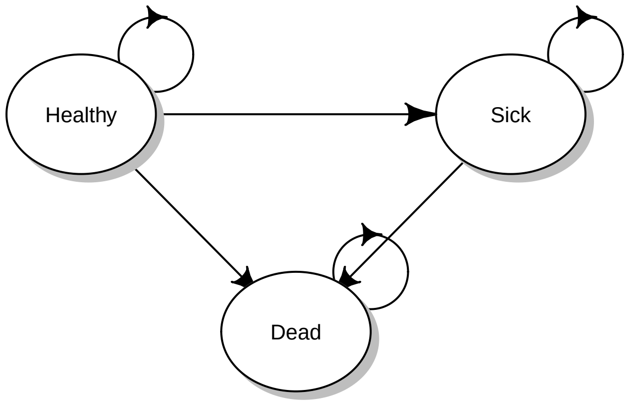
03.2 Calculate internal model parameters

```r
### 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))

### Calculate cycle-specific transition probabilities

## Constant transition probabilities
```

```
# probability of becoming sick from Healthy
p_HS_SoC  <- 1 - exp(-(-log(1 - p_HS_yr_SoC)  * cycle_length)) # Standard of Care
p_HS_trtA <- 1 - exp(-(-log(1 - p_HS_yr_trtA) * cycle_length)) # Treatment A
p_HS_trtB <- 1 - exp(-(-log(1 - p_HS_yr_trtB) * cycle_length)) # Treatment B

## Simulation time-dependent transition probabilities
# Probability of dying from Healthy state
# Expand the vector by number of cycles per year (1/cycle_length):
v_p_HD_yr_expanded <- rep(v_p_HD_yr, each = 1 / cycle_length)
# Convert to cycle-specific transition probabilities
v_p_HD <- 1 - exp(-(-log(1 - v_p_HD_yr_expanded) * cycle_length))

## State-residence time-dependent transition probabilities
# Set up cycle-specific tunnel to track time in Sick state
v_cycles_tunnel     <- 1:(n_tunnel_size_yr / cycle_length)          # tunnel state enumeration
v_names_Sick_tunnel <- paste0("Sick_", v_cycles_tunnel, "Cycle")     # names of tunnel states
n_tunnel_size       <- length(v_cycles_tunnel)                      # number of tunnel states
# Adjust model health states to account for tunnels
v_names_states_tunnels  <- c("Healthy", v_names_Sick_tunnel, "Dead") # state names with tunnels
n_states_tunnels  <- length(v_names_states_tunnels)                 # number of states with tunnels

# Probability of dying from Sick state
# Expand the vector by number of cycles per year (1/cycle_length):
v_p_SD_tunnels_yr_expanded <- rep(v_p_SD_tunnels_yr, each = 1 / cycle_length)
# Convert to cycle-specific transition probabilities
v_p_SD_tunnels <- 1 - exp(-(-log(1 - v_p_SD_tunnels_yr_expanded) * cycle_length))

### Calculate cycle-specific state rewards
#### Costs
v_c_SoC  <- c(c_H_yr, rep(c_S_yr,n_tunnel_size), c_D_yr) * cycle_length             # Standard of Care
v_c_trtA <- c(c_H_yr + c_trtA_yr, rep(c_S_yr,n_tunnel_size), c_D_yr) * cycle_length # Treatment A
v_c_trtB <- c(c_H_yr + c_trtB_yr, rep(c_S_yr,n_tunnel_size), c_D_yr) * cycle_length # Treatment B
#### QALYs
v_q_SoC  <- c(u_H, rep(u_S, n_tunnel_size), u_D) * cycle_length # Standard of Care
v_q_trtA <- v_q_trtB <- v_q_SoC             # Treatments A and B have same utilities as SoC
```

04 Construct state-transition models

```
m_P_diag <- matrix(0, nrow = n_states, ncol = n_states, dimnames = list(v_names_states, v_names_states)
m_P_diag["Healthy", "Sick" ]     = ""
m_P_diag["Healthy", "Dead" ]     = ""
m_P_diag["Healthy", "Healthy" ]  = ""
m_P_diag["Sick"   , "Dead" ]     = ""
m_P_diag["Sick"   , "Sick" ]     = ""
m_P_diag["Dead"   , "Dead" ]     = ""
layout.fig <- c(2, 1)
plotmat(t(m_P_diag), t(layout.fig), self.cex = 0.5, curve = 0, arr.pos = 0.8,
        latex = T, arr.type = "curved", relsize = 0.85, box.prop = 0.8,
        cex = 0.8, box.cex = 0.7, lwd = 1)
```



04.1 Initial state vector

```r
# All starting healthy
v_m_init_tunnels <- c(1, rep(0, n_tunnel_size), 0)
```

04.2 Initialize cohort traces with tunnels

```r
### Initialize cohort trace for state-residece dependent cSTM under SoC
m_M_tunnels_SoC <- matrix(0,
                          nrow     = (n_cycles + 1), ncol = n_states_tunnels,
                          dimnames = list(0:n_cycles, v_names_states_tunnels))
# Store the initial state vector in the first row of the cohort trace
m_M_tunnels_SoC[1, ] <- v_m_init_tunnels

### Initialize cohort trace for strategies A and B
# Structure and initial states are the same as for SoC
m_M_tunnels_trtA <- m_M_tunnels_SoC # Strategy A
m_M_tunnels_trtB <- m_M_tunnels_SoC # Strategy B
```

04.3 Create transition probability arrays

```r
## Create transition probability arrays for strategy SoC
### Initialize transition probability array for strategy SoC
# All transitions to a non-death state are assumed to be conditional on survival
a_P_tunnels_SoC <- array(0,  # Create 3-D array
                       dim = c(n_states_tunnels, n_states_tunnels, n_cycles),
                       dimnames = list(v_names_states_tunnels, v_names_states_tunnels,
                                       v_names_cycles[-length(v_names_cycles)])) # name the dimensions

### Fill in array
## from Healthy
a_P_tunnels_SoC["Healthy", "Healthy", ]     <- (1 - v_p_HD) * (1 - p_HS_SoC)
a_P_tunnels_SoC["Healthy", "Sick_1Cycle", ] <- (1 - v_p_HD) *      p_HS_SoC
a_P_tunnels_SoC["Healthy", "Dead", ]        <-      v_p_HD
```

```
## from Sick
for(i in 1:(n_tunnel_size - 1)){
  a_P_tunnels_SoC[v_names_Sick_tunnel[i],
                  v_names_Sick_tunnel[i + 1], ] <- 1 - v_p_SD_tunnels[i]

  a_P_tunnels_SoC[v_names_Sick_tunnel[i],
                  "Dead", ]                     <-     v_p_SD_tunnels[i]
}
# end of tunnel, stay in final Sick state
a_P_tunnels_SoC[v_names_Sick_tunnel[n_tunnel_size],
                v_names_Sick_tunnel[n_tunnel_size], ] <- 1 - v_p_SD_tunnels[n_tunnel_size]

a_P_tunnels_SoC[v_names_Sick_tunnel[n_tunnel_size],
                "Dead", ]                             <-     v_p_SD_tunnels[n_tunnel_size]

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

## Treatment A
a_P_tunnels_trtA <- a_P_tunnels_SoC
a_P_tunnels_trtA["Healthy", "Healthy", ]     <- (1 - v_p_HD) * (1 - p_HS_trtA)
a_P_tunnels_trtA["Healthy", "Sick_1Cycle", ] <- (1 - v_p_HD) *      p_HS_trtA

## Treatment B
a_P_tunnels_trtB <- a_P_tunnels_SoC
a_P_tunnels_trtB["Healthy", "Healthy", ]     <- (1 - v_p_HD) * (1 - p_HS_trtB)
a_P_tunnels_trtB["Healthy", "Sick_1Cycle", ] <- (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_tunnels_SoC,  verbose = TRUE)
```

```
## [1] "Valid transition probabilities"
```

```
check_transition_probability(a_P_tunnels_trtA, verbose = TRUE)
```

```
## [1] "Valid transition probabilities"
```

```
check_transition_probability(a_P_tunnels_trtB, verbose = TRUE)
```

```
## [1] "Valid transition probabilities"
```

```
# Check that all rows sum to 1
check_sum_of_transition_array(a_P_tunnels_SoC,  n_states = n_states_tunnels, n_cycles = n_cycles, verbo
```

```
## [1] "This is a valid transition array"
```

```
check_sum_of_transition_array(a_P_tunnels_trtA, n_states = n_states_tunnels, n_cycles = n_cycles, verbo
```

```
## [1] "This is a valid transition array"
```

```
check_sum_of_transition_array(a_P_tunnels_trtB, n_states = n_states_tunnels, n_cycles = n_cycles, verbo
```

```
## [1] "This is a valid transition array"
```

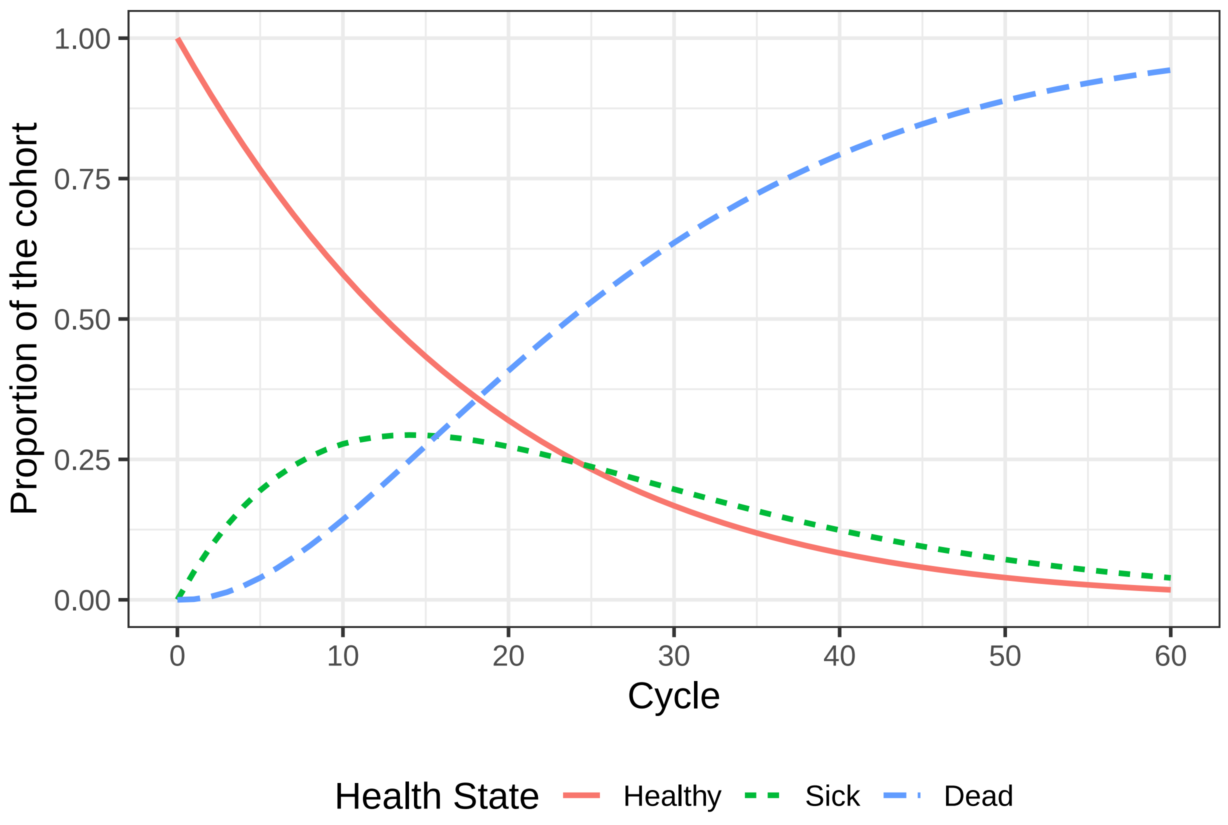
05 Run cSTM

```
## Loop over time
# Calculate cohort state based on previous state and appropriate time-slice of transition array
for (t in 1:n_cycles){
  ## Fill in cohort trace
  # For SoC
  m_M_tunnels_SoC [t + 1, ] <- m_M_tunnels_SoC [t, ] %*% a_P_tunnels_SoC [, , t]
  # For Strategy A
  m_M_tunnels_trtA[t + 1, ] <- m_M_tunnels_trtA[t, ] %*% a_P_tunnels_trtA[, , t]
  # For Strategy B
  m_M_tunnels_trtB[t + 1, ] <- m_M_tunnels_trtB[t, ] %*% a_P_tunnels_trtB[, , t]
}

# Create aggregated trace
m_M_tunnels_SoC_sum  <- cbind(Healthy = m_M_tunnels_SoC[, "Healthy"],
                              Sick    = rowSums(m_M_tunnels_SoC[, 2:(n_tunnel_size + 1)]),
                              Dead    = m_M_tunnels_SoC[, "Dead"])
m_M_tunnels_trtA_sum <- cbind(Healthy = m_M_tunnels_trtA[, "Healthy"],
                              Sick    = rowSums(m_M_tunnels_trtA[, 2:(n_tunnel_size + 1)]),
                              Dead    = m_M_tunnels_trtA[, "Dead"])
m_M_tunnels_trtB_sum <- cbind(Healthy = m_M_tunnels_trtB[, "Healthy"],
                              Sick    = rowSums(m_M_tunnels_trtB[, 2:(n_tunnel_size + 1)]),
                              Dead    = m_M_tunnels_trtB[, "Dead"])
```

06 Plot Outputs

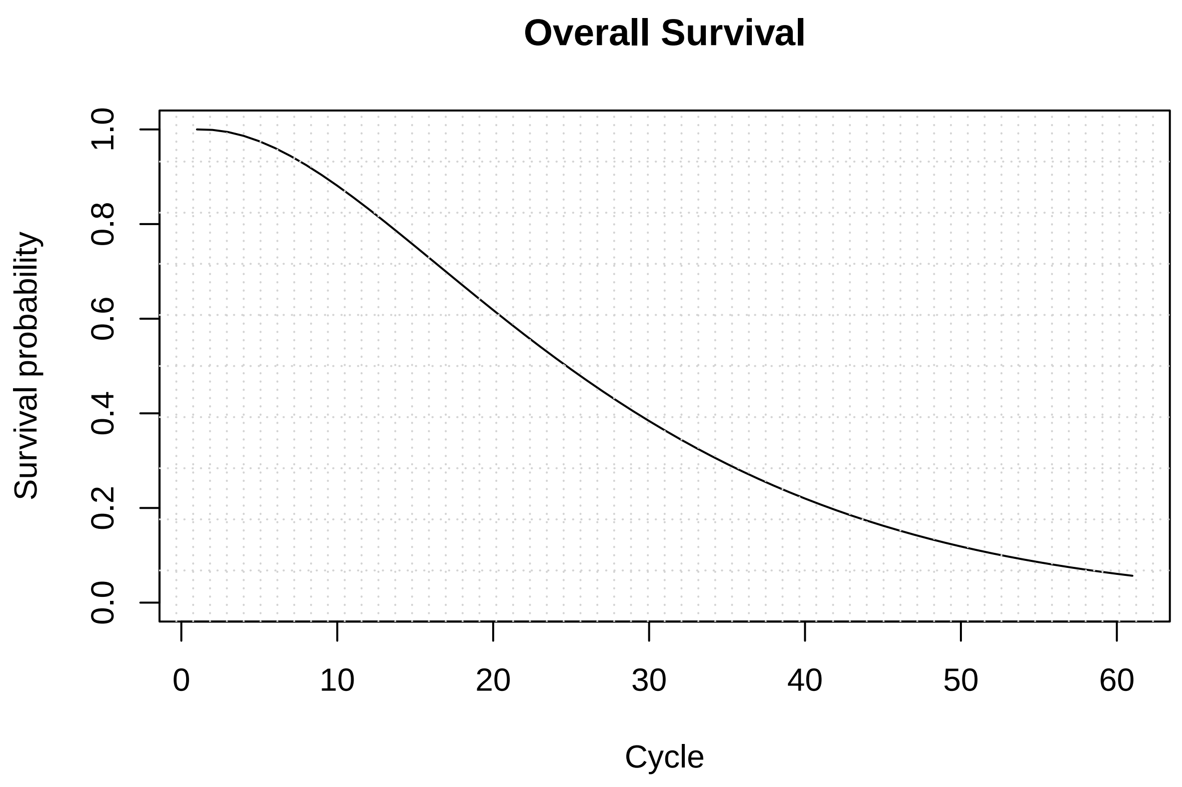
06.1 Plot the cohort trace for strategy SoC

```
## Plot the cohort trace for strategy SoC
plot_trace(m_M_tunnels_SoC_sum)
```



06.2 Overall Survival (OS)

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

# create a simple plot showing the OS
plot(v_os, type = 'l',
     ylim = c(0, 1),
     ylab = "Survival probability",
     xlab = "Cycle",
     main = "Overall Survival")
# add grid
grid(nx = n_cycles, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"), equilogs = TRUE)
```

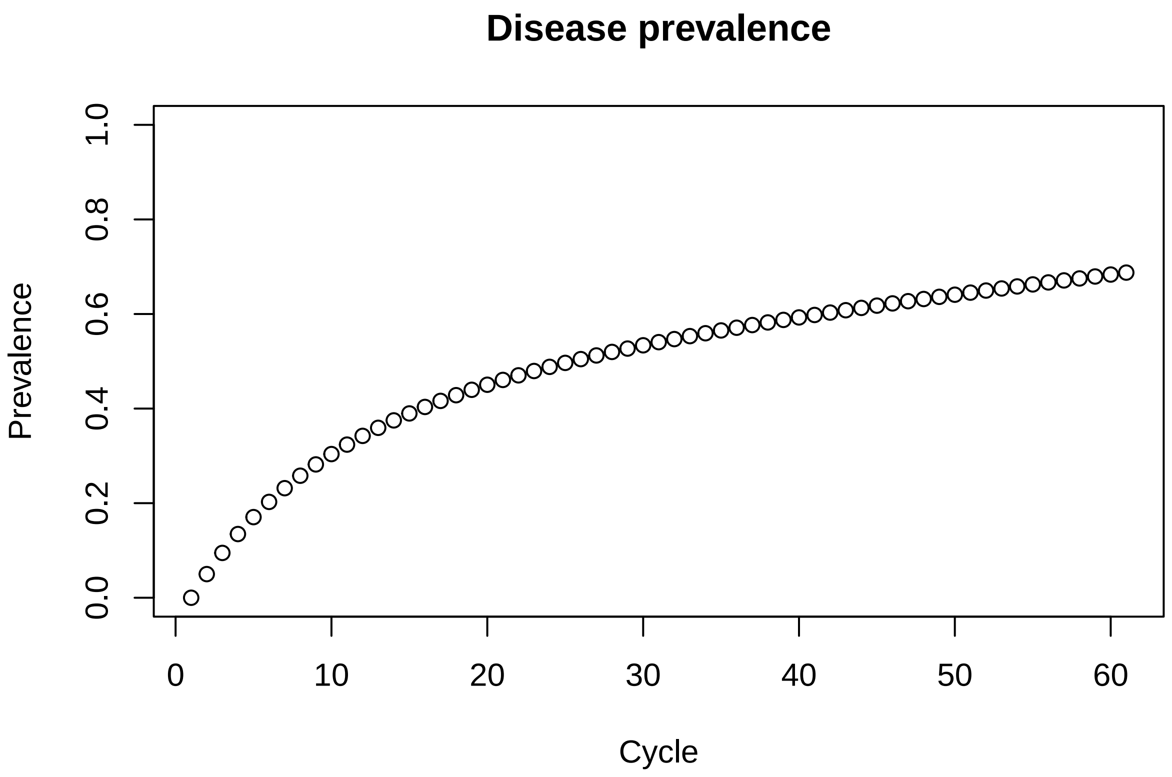


06.2.1 Life Expectancy (LE)

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

06.3 Disease prevalence

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



07 Compute expected outcomes

```
# Create empty vectors to store total costs and QALYs
v_tot_cost <- v_tot_qaly <- vector(mode = "numeric", length = n_str)
names(v_tot_qaly) <- names(v_tot_cost) <- v_names_str

### Expected discounted cost for each strategy
v_tot_cost["Standard of Care"] <- t(m_M_tunnels_SoC %*% v_c_SoC) %*% (v_dwe * v_wcc)
v_tot_cost["Treatment A"] <- t(m_M_tunnels_trtA %*% v_c_trtA) %*% (v_dwe * v_wcc)
v_tot_cost["Treatment B"] <- t(m_M_tunnels_trtB %*% v_c_trtB) %*% (v_dwe * v_wcc)

### Expected discounted QALYs for each strategy
v_tot_qaly["Standard of Care"] <- t(m_M_tunnels_SoC %*% v_q_SoC) %*% (v_dwe * v_wcc)
v_tot_qaly["Treatment A"] <- t(m_M_tunnels_trtA %*% v_q_trtA) %*% (v_dwe * v_wcc)
v_tot_qaly["Treatment B"] <- t(m_M_tunnels_trtB %*% v_q_trtB) %*% (v_dwe * v_wcc)
```

09 Cost-effectiveness analysis (CEA)

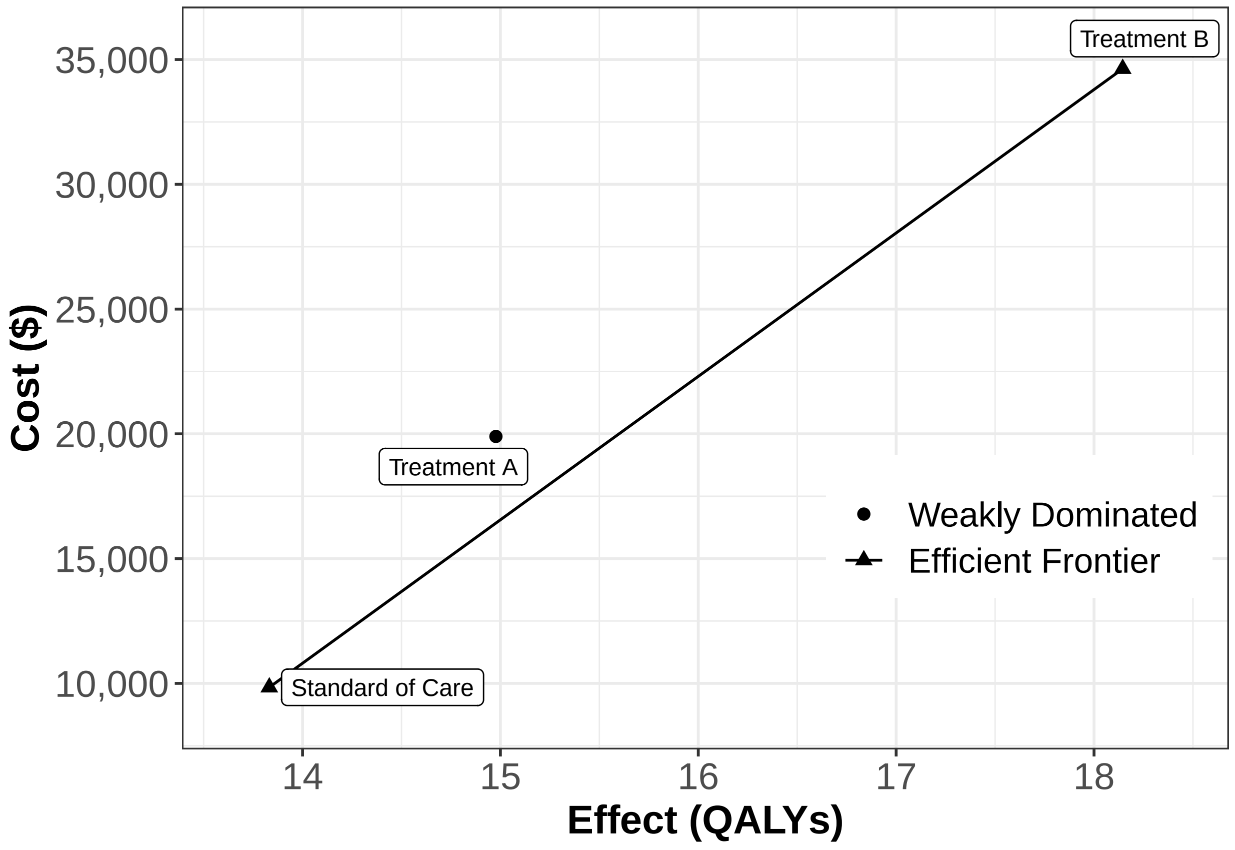
```
## Incremental cost-effectiveness ratios (ICERs)
df_cea <- calculate_icers(cost       = v_tot_cost,
                          effect     = v_tot_qaly,
                          strategies = v_names_str)
df_cea
```

```
##                                  Strategy      Cost    Effect Inc_Cost Inc_Effect
## Standard of Care Standard of Care   9841.86 13.83189       NA         NA
## Treatment B            Treatment B 34629.73 18.14492 24787.87   4.313034
## Treatment A            Treatment A 19895.47 14.97712       NA         NA
##                       ICER Status
## Standard of Care        NA     ND
## Treatment B       5747.201     ND
## Treatment A             NA     ED
```

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

```
##                                  Strategy Costs ($) QALYs Incremental Costs ($)
## Standard of Care Standard of Care     9,842 13.83                  <NA>
## Treatment B            Treatment B    34,630 18.14                24,788
## Treatment A            Treatment A    19,895 14.98                  <NA>
##                   Incremental QALYs ICER ($/QALY) Status
## Standard of Care                 NA          <NA>     ND
## Treatment B                    4.31         5,747     ND
## Treatment A                      NA          <NA>     ED
```

```
## CEA frontier
plot_icers(df_cea, label = "all", txtsize = 16) +
  expand_limits(x = max(table_cea$QALYs) + 0.1) +
  theme(legend.position = c(0.8, 0.3))
```


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