

Simple 3-state Markov model in R

With a probabilistic sensitivity analysis (PSA)

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>
- Alarid-Escudero F, Krijkamp EM, Enns EA, Yang A, Hunink MGM, Pechlivanoglou P, Jalal H. Cohort State-Transition Models in R: A Tutorial. *arXiv:200107824v2*. 2020:1-48. <http://arxiv.org/abs/2001.07824>
- 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*. Online First <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", "ggraph", "reshape2"
# load (install if required) packages from GitHub
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("Standard of Care", "Treatment")

# Number of strategies
n_str <- length(v_names_str)

# Markov model parameters
v_n  <- c("Healthy", "Sick", "Dead") # state names
n_states <- length(v_n)             # number of states
n_t  <- 60                          # number of cycles
v_init <- c(1, 0, 0)                 # initial cohort distribution (everyone allocated to the "healthy" state)

# Transition probabilities
p_HD <- 0.02                        # probability of dying when healthy
p_HS <- 0.05                        # probability of becoming sick when healthy, under standard of care
p_HS_trt <- 0.03                    # probability of becoming sick when healthy, under treatment
p_SD <- 0.1                         # probability of dying when sick

# Costs and utilities
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_trt <- 800                        # cost of treatment (per cycle)
u_H  <- 0.8                         # utility when healthy
u_S  <- 0.5                         # utility when sick
u_D  <- 0                           # utility when dead
d_e  <- d_c <- 0.03                 # discount rate per cycle equal discount of costs and QALYs by 3%
```

```

# calculate discount weights for costs for each cycle based on discount rate d_c
v_dwc <- 1 / (1 + d_e) ^ (0:n_t)
# calculate discount weights for effectiveness for each cycle based on discount rate d_e
v_dwe <- 1 / (1 + d_c) ^ (0:n_t)

```

Draw the state-transition cohort model

```

m_P_diag <- matrix(0, nrow = n_states, ncol = n_states, dimnames = list(v_n, v_n))
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 Define and initialize matrices and vectors

04.1 Cohort trace

```

# create the cohort trace
m_M <- m_M_trt <- matrix(NA,
                        nrow = n_t + 1 , # create Markov trace (n.t + 1 because R doesn't
                                           # understand Cycle 0)
                        ncol = n_states,
                        dimnames = list(0:n_t, v_n))

m_M[1, ] <- m_M_trt[1, ] <- v_init      # initialize first cycle of Markov trace

```

04.2 Transition probability matrix

```

# create the transition probability matrices
m_P <- m_P_trt <- matrix(0,
                        nrow = n_states, ncol = n_states,
                        dimnames = list(v_n, v_n)) # name the columns and rows of the transition
                                                    # probability matrices

m_P

```

Fill in the transition probability matrix:

```

# from Healthy
m_P["Healthy", "Healthy"] <- 1 - p_HS - p_HD
m_P["Healthy", "Sick"] <- p_HS
m_P["Healthy", "Dead"] <- p_HD

# from Sick
m_P["Sick", "Sick"] <- 1 - p_SD
m_P["Sick", "Dead"] <- p_SD

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

# Under treatment
m_P_trt <- m_P
m_P_trt["Healthy", "Healthy"] <- 1 - p_HS_trt - p_HD
m_P_trt["Healthy", "Sick"] <- p_HS_trt

```

05 Run Markov model

```

for (t in 1:n_t){
  m_M[t + 1, ] <- m_M[t, ] %*% m_P # loop through the number of cycles
  m_M_trt[t + 1, ] <- m_M_trt[t, ] %*% m_P_trt # estimate the state vector for the next cycle (t + 1)
  # for treatment
}

```

06 Compute and Plot Epidemiological Outcomes

06.1 Cohort trace

Standard of Care:

```

matplot(m_M, type = 'l',
  ylab = "Probability of state occupancy",
  xlab = "Cycle",
  main = "Cohort Trace - standard of care", lwd = 3) # create a plot of the data
legend("right", v_n, col = c("black", "red", "green"),
  lty = 1:3, bty = "n") # add a legend to the graph

abline(v = which.max(m_M[, "Sick"]), col = "gray") # plot a vertical line that helps identifying a

```

Treatment:

```

matplot(m_M_trt, type = 'l',
  ylab = "Probability of state occupancy",
  xlab = "Cycle",
  main = "Cohort Trace - treatment", lwd = 3) # create a plot of the data
legend("right", v_n, col = c("black", "red", "green"),
  lty = 1:3, bty = "n") # add a legend to the graph

abline(v = which.max(m_M[, "Sick"]), col = "gray") # plot a vertical line that helps identifying a

```

06.2 Overall Survival (OS)

Standard of Care:

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

plot(v_os, type = 'l',
     ylim = c(0, 1),
     ylab = "Survival probability",
     xlab = "Cycle",
     main = "Overall Survival")      # create a simple plot showing the OS

# add grid
grid(nx = n_t, ny = 10, col = "lightgray", lty = "dotted", lwd = par("lwd"),
     equilogs = TRUE)
```

Treatment:

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

plot(v_os_trt, type = 'l',
     ylim = c(0, 1),
     ylab = "Survival probability",
     xlab = "Cycle",
     main = "Overall Survival")      # create a simple plot showing the OS

# 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)               # summing probability of OS over time (i.e. life expectancy)
v_le_trt  <- sum(v_os_trt)           # summing probability of OS over time (i.e. life expectancy), treatment
```

06.3 Disease prevalence

Standard of Care:

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

Treatment:

```
v_prev_trt <- m_M_trt[, "Sick"]/v_os_trt
plot(v_prev_trt,
     ylim = c(0, 1),
     ylab = "Prevalence",
     xlab = "Cycle",
     main = "Disease prevalence")
```

07 Compute Cost-Effectiveness Outcomes

07.1 Mean Costs and QALYs

```
# per cycle
# calculate expected costs by multiplying m_M with the cost vector for the different
# health states
v_tc      <- m_M      %*% c(c_H, c_S, c_D)      # Standard of Care
v_tc_trt  <- m_M_trt  %*% c(c_H, c_S + c_trt, c_D) # Treatment
# calculate expected QALYs by multiplying m_M with the utilities for the different
# health states
v_tu      <- m_M      %*% c(u_H, u_S, u_D)      # Standard of Care
v_tu_trt  <- m_M_trt  %*% c(u_H, u_S, u_D)      # Treatment
```

07.2 Discounted Mean Costs and QALYs

```
# Discount costs by multiplying the cost vector with discount weights
tc_d      <- t(v_tc)      %*% v_dwc      # Standard of Care
tc_d_trt  <- t(v_tc_trt) %*% v_dwc      # Treatment
# Discount QALYS by multiplying the QALYs vector with discount weights
tu_d      <- t(v_tu)      %*% v_dwc      # Standard of Care
tu_d_trt  <- t(v_tu_trt) %*% v_dwc      # Treatment

# store them into a vector
v_tc_d    <- c(tc_d, tc_d_trt)
v_tu_d    <- c(tu_d, 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
```

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
```

07.4 Plot frontier of the Markov model

```
plot(df_cea, effect_units = "QALYs", xlim = c(10, 12))
```

08 Probabilistic Sensitivity Analysis

08.1 List of input parameters

Create list `l_params_all` with all input probabilities, cost and utilities.

```
l_params_all <- as.list(data.frame(
  p_HD = 0.02, # probability of dying when healthy
  p_HS = 0.05, # probability of becoming sick when healthy, conditioned on not dying
  p_HS_trt = 0.03, # probability of becoming sick when healthy, conditioned on not dying
  p_SD = 0.1, # probability of dying when sick
  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_trt = 800, # cost of treatment (per cycle)
  u_H = 0.8, # utility when healthy
  u_S = 0.5, # utility when sick
  u_D = 0, # utility when dead
  d_e = 0.03, # discount factor for effectiveness
  d_c = 0.03 # discount factor for costs
))

# store the parameter names into a vector
v_names_params <- names(l_params_all)
```

08.2 Load Sick-Sicker Markov model function

```
source("Functions_markov_3state.R")
# Test function
calculate_ce_out(l_params_all)
```

08.3 Generate PSA datasets

```
# Function to generate PSA input dataset
gen_psa <- function(n_sim = 1000, seed = 071818){
  set.seed(seed) # set a seed to be able to reproduce the same results
  df_psa <- data.frame(
    # Transition probabilities (per cycle)
```



```

# probability to become sick when healthy
p_HS      = rbeta(n_sim, shape1 = 24, shape2 = 450),
p_HS_trt  = rbeta(n_sim, shape1 = 9,  shape2 = 281),  # under treatment
# probability of dying when healthy
p_HD      = rbeta(n_sim, shape1 = 16, shape2 = 767),
# probability of dying when sick
p_SD      = rbeta(n_sim, shape1 = 22.4, shape2 = 201.6),

# Cost vectors with length n_sim
# cost of remaining one cycle in state H
c_H        = rgamma(n_sim, shape = 16, scale = 25),
# cost of remaining one cycle in state S1
c_S        = rgamma(n_sim, shape = 100, scale = 10),
# cost of being in the death state
c_D        = 0,
# cost of treatment (per cycle)
c_trt      = rgamma(n_sim, shape = 64, scale = 12.5),

# Utility vectors with length n_sim
# utility when healthy
u_H        = rbeta(n_sim, shape1 = 50.4, shape2 = 12.6),
# utility when sick
u_S        = rbeta(n_sim, shape1 = 49.5, shape2 = 49.5),
# utility when dead
u_D        = 0
)
return(df_psa)
}
# Try it
gen_psa(10)

# Number of simulations
n_sim <- 1000

# Generate PSA input dataset
df_psa_input <- gen_psa(n_sim = n_sim)
# First six observations
head(df_psa_input)

# Histogram of parameters
ggplot(melt(df_psa_input, variable.name = "Parameter"), aes(x = value)) +
  facet_wrap(~Parameter, scales = "free") +
  geom_histogram(aes(y = ..density..)) +
  theme_bw(base_size = 16) +
  theme(axis.text = element_text(size=8))

# Initialize dataframes with PSA output
# Dataframe of costs
df_c <- as.data.frame(matrix(0,
                             nrow = n_sim,
                             ncol = n_str))
colnames(df_c) <- v_names_str
# Dataframe of effectiveness

```

```
df_e <- as.data.frame(matrix(0,
                             nrow = n_sim,
                             ncol = n_str))
colnames(df_e) <- v_names_str
```

08.4 Conduct probabilistic sensitivity analysis

```
# Run Markov model on each parameter set of PSA input dataset
for(i in 1:n_sim){
  l_out_temp <- calculate_ce_out(df_psa_input[i, ])
  df_c[i, ] <- l_out_temp$Cost
  df_e[i, ] <- l_out_temp$Effect
  # Display simulation progress
  if(i/(n_sim/10) == round(i/(n_sim/10), 0)) { # display progress every 10%
    cat('\r', paste(i/n_sim * 100, "% done", sep = " "))
  }
}
```

08.5 Analyze and visualize PSA results using R package: dampack

Create PSA object for dampack

```
l_psa <- make_psa_obj(cost      = df_c,
                     effectiveness = df_e,
                     parameters  = df_psa_input,
                     strategies  = v_names_str)
```

08.5.1 Save PSA objects

```
save(df_psa_input, df_c, df_e, v_names_str, n_str, l_psa,
     file = "markov_3state_PSA_dataset.RData")
```

Vector with willingness-to-pay (WTP) thresholds.

```
v_wtp <- seq(0, 5000, by = 1000)
```

08.5.2 Cost-Effectiveness Scatter plot

```
plot(l_psa)
```

08.5.3 Conduct CEA with probabilistic output

```

# Compute expected costs and effects for each strategy from the PSA
df_out_ce_psa <- summary(l_psa)

# Calculate incremental cost-effectiveness ratios (ICERs)
df_cea_psa <- calculate_icers(cost      = df_out_ce_psa$meanCost,
                             effect    = df_out_ce_psa$meanEffect,
                             strategies = df_out_ce_psa$Strategy)

df_cea_psa

# Save CEA table with ICERs
# As .RData
save(df_cea_psa,
     file = "markov_3state_probabilistic_CEA_results.RData")
# As .csv
write.csv(df_cea_psa,
          file = "markov_3state_probabilistic_CEA_results.csv")

```

08.5.4 Plot cost-effectiveness frontier

```
plot(df_cea_psa)
```

08.5.6 Cost-effectiveness acceptability curves (CEACs) and frontier (CEAF)

```

ceac_obj <- ceac(wtp = v_wtp, psa = l_psa)
# Regions of highest probability of cost-effectiveness for each strategy
summary(ceac_obj)
# CEAC & CEAF plot
plot(ceac_obj)

```

08.5.7 Expected Loss Curves (ELCs)

The expected loss is the the quantification of the foregone benefits when choosing a suboptimal strategy given current evidence.

```

elc_obj <- calc_exp_loss(wtp = v_wtp, psa = l_psa)
elc_obj
# ELC plot
plot(elc_obj, log_y = FALSE)

```

08.5.8 Expected value of perfect information (EVPI)

```

evpi <- calc_evpi(wtp = v_wtp, psa = l_psa)
# EVPI plot
plot(evpi, effect_units = "QALY")

```