PSA: Three-strategy decision tree in R - HVE

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 MM, Jalal H. A Multidimensional Array Representation of State-Transition Model Dynamics. Med Decis Making. 2020 Online first. https://doi.org/10.1177/0272989X19893973
- Alarid-Escudero, F., Krijkamp, E. M., Enns, E. A., Hunink, M. G. M., Pechlivanoglou, P., & Jalal, H. (2020). Cohort state-transition models in R: From conceptualization to implementation. arXiv:2001.07824v1, 1–31. http://arxiv.org/abs/2001.07824
- Alarid-Escudero, F., Enns, E. A., Kuntz, K. M., Michaud, T. L., & Jalal, H. (2019). "Time Traveling Is Just Too Dangerous" But Some Methods Are Worth Revisiting: The Advantages of Expected Loss Curves Over Cost-Effectiveness Acceptability Curves and Frontier. Value in Health, 22(5), 611–618. https://doi.org/10.1016/j.jval.2019.02.008

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 install other packages
# load (install if required) packages from CRAN
p_load("here", "dplyr", "devtools", "scales", "ellipse", "ggplot2", "lazyeval",
       "igraph", "truncnorm", "ggraph", "reshape2", "knitr", "stringr", "reshape2")
# 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/dectree", force = TRUE) Uncomment if there is a newer version
# install_github("annaheath/EVSI", force = TRUE) #Uncomment if there is a newer version
p_load_gh("DARTH-git/dampack", "DARTH-git/dectree")
p_load_gh("annaheath/EVSI")
```

02 Load functions

```
source("Functions.R")
```

03 Define parameter input values

```
v_names_str <- c("No Tx", "Tx All", "Biopsy") # names of strategies
n_str       <- length(v_names_str)            # number of strategies
wtp         <- 100000                         # willingness to pay threshold

# Probabilities
p_HVE         <- 0.52 # prevalence of HVE
p_HVE_comp    <- 0.71 # complications with untreated HVE
p_OVE_comp    <- 0.01 # complications with untreated OVE
p_HVE_comp_tx <- 0.36 # complications with treated HVE
p_OVE_comp_tx <- 0.20 # complications with treated OVE
p_biopsy_comp <- 0.05 # probability of complications due to biopsy

# Costs
c_VE      <- 1200  # cost of viral encephalitis care without complications
c_VE_comp <- 9000  # cost of viral encephalitis care with complications
c_tx      <- 9500  # cost of treatment
c_biopsy  <- 25000 # cost of brain biopsy

# QALYs
```

```
q_VE          <- 20    # remaining QALYs for those without VE-related complications
q_VE_comp     <- 19    # remaining QALYs for those with VE-related complications
q_loss_biopsy <- -0.01 # one-time QALY loss due to brain biopsy

# store the parameters into a list
l_params_all <- list(p_HVE, p_HVE_comp, p_OVE_comp, p_HVE_comp_tx,
                     p_OVE_comp_tx, p_biopsy_comp,
                     c_VE, c_VE_comp, c_tx, c_biopsy,
                     q_VE, q_VE_comp, q_loss_biopsy)
# store the names of the parameters into a vector
v_names_params <- c('p_HVE', 'p_HVE_comp', 'p_OVE_comp', 'p_HVE_comp_tx',
                    'p_OVE_comp_tx', 'p_biopsy_comp',
                    'c_VE', 'c_VE_comp',  'c_tx', 'c_biopsy',
                    'q_VE', 'q_VE_comp', 'q_loss_biopsy')
names(l_params_all) <- v_names_params
```

04 Create and run decision tree model

```
decision_tree_HVE_output <- with(as.list(l_params_all), {

  # Create vector of weights for each strategy

  v_w_no_tx  <- c(  p_HVE  *    p_HVE_comp  ,  # HVE, complications
                    p_HVE  * (1-p_HVE_comp) ,  # HVE, no complications
                 (1-p_HVE) *    p_OVE_comp  ,  # OVE, complications
                 (1-p_HVE) * (1-p_OVE_comp))   # OVE, no complications

  v_w_tx     <- c(  1                          ,  # On treatment
                    p_HVE  *    p_HVE_comp_tx  ,  # HVE w/tx, complications
                    p_HVE  * (1-p_HVE_comp_tx) ,  # HVE w/tx, no complications
                 (1-p_HVE) *    p_OVE_comp_tx  ,  # OVE w/tx, complications
                 (1-p_HVE) * (1-p_OVE_comp_tx))   # OVE w/tx, no complications

  v_w_biopsy <- c(1                                    , # Undergo biopsy
                  p_biopsy_comp                        , # biopsy complications
                 # no biopsy comp., HVE w/tx,  complications
                 (1-p_biopsy_comp) *    p_HVE  *    p_HVE_comp_tx ,
                 # no biopsy comp., HVE w/tx, no complications
                 (1-p_biopsy_comp) *    p_HVE  * (1-p_HVE_comp_tx),
                 # no biopsy comp., OVE, complications
                 (1-p_biopsy_comp) * (1-p_HVE) *    p_OVE_comp    ,
                 # no biopsy comp., OVE, no complications
                 (1-p_biopsy_comp) * (1-p_HVE) * (1-p_OVE_comp))

  # Create vector of outcomes (QALYs) for each strategy

  v_qaly_no_tx  <- c(q_VE_comp, # HVE, complications
                     q_VE     , # HVE, no complications
                     q_VE_comp, # OVE, complications
                     q_VE)      # OVE, no complications
```

```r
v_qaly_tx     <- c(0          , # treatment does not directly add any QALYs
                   q_VE_comp , # HVE, complications
                   q_VE      , # HVE, no complications
                   q_VE_comp , # OVE, complications
                   q_VE)       # OVE, no complications


v_qaly_biopsy <- c(q_loss_biopsy, # loss due to biopsy
                   q_VE_comp    , # biopsy complications
                   q_VE_comp    , # no biopsy comp., HVE w/tx, complications
                   q_VE         , # no biopsy comp., HVE w/tx, no complications
                   q_VE_comp    , # no biopsy comp., OVE, complications
                   q_VE)          # no biopsy comp., OVE, no complications

# Create vector of costs for each strategy

v_cost_no_tx  <- c(c_VE_comp , # HVE, complications
                   c_VE      , # HVE, no complications
                   c_VE_comp , # OVE, complications
                   c_VE)       # OVE, no complications

v_cost_tx     <- c(c_tx       , # cost of treatment
                   c_VE_comp , # HVE, complications
                   c_VE      , # HVE, no complications
                   c_VE_comp , # OVE, complications
                   c_VE)       # OVE, no complications


v_cost_biopsy <- c(c_biopsy          , # cost of biopsy procedure
                   c_VE_comp         , # biopsy complications
                   c_VE_comp + c_tx , # no biopsy comp., HVE w/tx, complications
                   c_VE + c_tx       , # no biopsy comp., HVE w/tx, no complications
                   c_VE_comp         , # no biopsy comp., OVE, complications
                   c_VE)               # no biopsy comp., OVE, no complications

# Calculate total utilities for each strategy
total_qaly_no_tx  <- v_w_no_tx  %*% v_qaly_no_tx
total_qaly_tx     <- v_w_tx     %*% v_qaly_tx
total_qaly_biopsy <- v_w_biopsy %*% v_qaly_biopsy

# Calculate total costs for each strategy
total_cost_no_tx  <- v_w_no_tx  %*% v_cost_no_tx
total_cost_tx     <- v_w_tx     %*% v_cost_tx
total_cost_biopsy <- v_w_biopsy %*% v_cost_biopsy

# vector of total QALYs
v_total_qaly <- c(total_qaly_no_tx, total_qaly_tx, total_qaly_biopsy)
# vector of total costs
v_total_cost <- c(total_cost_no_tx, total_cost_tx, total_cost_biopsy)
# calculate vector of nmb
v_nmb        <- v_total_qaly * wtp - v_total_cost

# Name outcomes
```

```
  names(v_total_qaly) <- v_names_str  # names for the elements of the total QALYs vector
  names(v_total_cost) <- v_names_str  # names for the elements of the total cost vector
  names(v_nmb)        <- v_names_str  # names for the elements of the nmb vector

  df_output <- data.frame(Strategy = v_names_str,
                          Cost     = v_total_cost,
                          Effect   = v_total_qaly,
                          NMB      = v_nmb)
  return(df_output)
})

# model output
decision_tree_HVE_output
```

04.1 Plot the decision tree

```
# branches <- read.csv(here('data','decision_tree_HVE_branches.csv'),
#                      stringsAsFactors = F, header = T)
# tree     <- create_tree(branches)
# plot_tree(tree, font.size = 5)
```

05 Cost-Effectiveness Analysis

```
# create the transition probability matrix for NO treatment
decision_tree_HVE_cea  <- calculate_icers(cost       = decision_tree_HVE_output$Cost,
                                          effect     = decision_tree_HVE_output$Effect,
                                          strategies = decision_tree_HVE_output$Strategy)
decision_tree_HVE_cea
```

05.1 Plot frontier of Decision Tree

```
plot(decision_tree_HVE_cea, effect_units = "QALYs")
```

06 Deterministic Sensitivity Analysis

06.1 List of input parameters

```
l_params_all
```

06.2 Load decision tree model function

```
#### We wrapped the decision tree in a function which we called calculate_ce_out
# This function is stored in "Functions_decision_tree_HVE.R" and needes the list of parameters
source("Functions_decision_tree_HVE.R")
# Test function to see if it gives the CE results
calculate_ce_out(l_params_all)
```

06.3 One-way sensitivity analysis (OWSA)

```
options(scipen = 999) # disabling scientific notation in R
# dataframe containing all parameters, their basecase values, and the min and
# max values of the parameters of interest
df_params_owsa <- data.frame(pars = c("p_HVE", "p_biopsy_comp", "c_tx", "c_biopsy"),
                             min  = c(0.01, 0.01,  1000, 5000),  # min parameter values
                             max  = c(0.99, 0.50, 15000, 40000)  # max parameter values
                             )

owsa_nmb <- run_owsa_det(params_range = df_params_owsa,  # dataframe with parameters for owsa
                         params_basecase = l_params_all, # list with all parameters
                         nsamp      = 100,               # number of parameter values
                         FUN        = calculate_ce_out,  # function to compute outputs
                         outcomes   = c("NMB"),          # output to do the OWSA on
                         strategies = v_names_str,       # names of the strategies
                         n_wtp      = 450000)            # extra argument to pass to FUN
```

06.3.1 Plot OWSA

```
plot(owsa_nmb, txtsize = 16, n_x_ticks = 5, n_y_ticks = 3,
     facet_scales = "free") +
     theme(legend.position = "bottom",
           axis.text.x = element_text(angle = 45, vjust = 0.5))
```

06.3.2 Optimal strategy with OWSA

```
owsa_opt_strat(owsa = owsa_nmb)
```

06.3.3 Tornado plot

```
owsa_tornado(owsa = owsa_nmb) +
  theme(axis.text.x = element_text(angle = 45, vjust = 0.5))
```

06.4 Two-way sensitivity analysis (TWSA)

```r
# dataframe containing all parameters, their basecase values, and the min and
# max values of the parameters of interest
df_params_twsa <- data.frame(pars = c("p_HVE", "c_biopsy"),
                             min  = c(0.01, 2000), # min parameter values
                             max  = c(0.99, 40000) # max parameter values
                             )

twsa_nmb <- run_twsa_det(params_range = df_params_twsa, # dataframe with parameters for twsa
                         params_basecase = l_params_all,# list with all parameters
                         nsamp      = 40,               # number of parameter values
                         FUN        = calculate_ce_out, # function to compute outputs
                         outcomes   = c("NMB"),         # output to do the twsa on
                         strategies = v_names_str,      # names of the strategies
                         n_wtp      = 200000)           # extra argument to pass to FUN
```

06.4.1 Plot TWSA

```r
plot(twsa_nmb) +
  ggtitle(label = "Two-way sensitivity analysis",
          subtitle = "Net monetary benefit") +
          theme(legend.position = "bottom")
```

07 Probabilistic Sensitivity Analysis (PSA)

```r
# Function to generate PSA input dataset
generate_psa_params <- function(n_sim = 1000, seed = 071518){
  set.seed(seed)
  # Dataframe of input parameters
  df_psa_params   <- data.frame(

    # Transition probabilities (per cycle)
    p_HVE         = rbeta(n_sim, 52, 48), # prevalence of HVE
    p_HVE_comp    = rbeta(n_sim, 71, 29), # complications with untreated HVE
    p_OVE_comp    = rbeta(n_sim,  1, 99), # complications with untreated OVE
    p_HVE_comp_tx = rbeta(n_sim, 36, 64), # complications with treated HVE
    p_OVE_comp_tx = rbeta(n_sim, 20, 80), # complications with treated OVE
    p_biopsy_comp = rbeta(n_sim,  1, 19), # probability of complications due to biopsy

    # Costs
    c_VE      = rgamma(n_sim, shape = 36.0, scale = 33.33), # cost of remaining one cycle in state H
    c_VE_comp = rgamma(n_sim, shape = 81.0, scale = 111.1), # cost of remaining one cycle in state S1
    c_tx      = rgamma(n_sim, shape = 74.6, scale = 127.4), # cost of remaining one cycle in state S2
    c_biopsy  = rgamma(n_sim, shape = 25.0, scale = 1000) , # cost of treatment (per cycle)

    # Utilities
    q_VE          = rnorm(n_sim, mean = 20, sd = 1), # utility when healthy
    q_VE_comp     = rnorm(n_sim, mean = 19, sd = 2), # utility when sick
    q_loss_biopsy = -rbeta(n_sim, shape1 = 4, shape2 = 380)
```

```
  )
  return(df_psa_params)
}
# Try it
generate_psa_params(10)
```

```
# Generate PSA dataset for CEA
# Number of simulations
n_sim <- 1000

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

# Histogram of parameters
ggplot(reshape2::melt(df_psa_input, variable.name = "Parameter",
                      value.name = "Parameter value"),
                      aes(x = `Parameter value`)) +
                      facet_wrap(~Parameter, scales = "free") +
                      geom_histogram(aes(y = ..density..), alpha = 0.8) +
                      scale_x_continuous(breaks = number_ticks(3)) +
                      ylab("") +
                      theme_bw(base_size = 14) +
                      theme(axis.text.y = element_blank())

# 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
```

07.1 Conduct probabilistic sensitivity analysis

```
# Run decision tree on each parameter set of PSA input dataset
for(i in 1:n_sim){
  l_psa_input <- update_param_list(l_params_all, df_psa_input[i, ])
  df_out_psa  <- calculate_ce_out(l_psa_input)
  df_c[i, ] <- df_out_psa$Cost
  df_e[i, ] <- df_out_psa$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 = " "))
  }
}
```

07.2 Create PSA object for dampack

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

07.2.1 Save PSA objects

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

07.3 Create probabilistic analysis graphs

```
load(file = "decision_tree_HVE_PSA_dataset.RData")
```

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

```
v_wtp <- seq(0, 600000, by = 10000)
```

07.3.1 Cost-Effectiveness Scatter plot

```
plot(l_psa)
```

07.4 Conduct CEA with probabilistic output

```
# Compute expected costs and effects for each strategy from the PSA
df_out_ce_psa <- summary(l_psa)
df_out_ce_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 = "decision_tree_HVE_probabilistic_CEA_results.RData")
```

```r
# As .csv
write.csv(df_cea_psa,
          file = "decision_tree_HVE_probabilistic_CEA_results.csv")
```

07.4.1 Plot cost-effectiveness frontier

```r
plot(df_cea_psa)
```

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

```r
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)
```

07.4.3 Expected Loss Curves (ELCs)

```r
elc_obj <- calc_exp_loss(wtp = v_wtp, psa = l_psa)

# ELC plot
plot(elc_obj, log_y = FALSE)
```

07.4.4 Expected value of perfect information (EVPI)

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

07.4.5 Expected value of partial perfect information (EVPPI)

```r
evppi <- calc_evppi(psa = l_psa,
                    wtp = v_wtp,
                    params = c("q_VE_comp"),
                    outcome = c("nmb"),
                    type = c("gam", "poly"),
                    poly.order = 2,
                    k = -1,
                    pop = 1
)

dampack:::plot.evppi(evppi)
```