Calibrating a 3-state cancer model

Directed search using Nelder-mead

The DARTH workgroup

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Please cite our publications when using this code:

- Alarid-Escudero F, Maclehose RF, Peralta Y, Kuntz KM, Enns EA. Non-identifiability in model calibration and implications for medical decision making. Med Decis Making. 2018; 38(7):810-821. https://pubmed.ncbi.nlm.nih.gov/30248276/
- 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

A walkthrough of the code could be found in the following link: - https://darth-git.github.io/calibSMDM2018-materials/

Change `eval` to `TRUE` if you want to knit this document.

```
rm(list = ls())      # clear memory (removes all the variables from the workspace)
```

00 Calibration Specifications

Model: 3-State Cancer Relative Survival (CRS) Markov Model

Inputs to be calibrated: p_Mets, p_DieMets

Targets: Surv

Calibration method: Directed search using Nelder-mead

Goodness-of-fit measure: Sum of Log-Likelihood

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("lhs", "plotrix", "psych")
```

02 Load target data

```
load("CRS_CalibTargets.RData")
lst_targets <- CRS_targets

# Plot the targets

# TARGET 1: Survival ("Surv")
plotrix::plotCI(x = lst_targets$Surv$time, y = lst_targets$Surv$value,
                ui = lst_targets$Surv$ub,
                li = lst_targets$Surv$lb,
                ylim = c(0, 1),
                xlab = "Time", ylab = "Pr Survive")

# TARGET 2: (if you had more...)
# plotrix::plotCI(x = lst_targets$Target2$time, y = lst_targets$Target2$value,
#                 ui = lst_targets$Target2$ub,
#                 li = lst_targets$Target2$lb,
#                 ylim = c(0, 1),
#                 xlab = "Time", ylab = "Target 2")
```

03 Load model as a function

```r
# - inputs are parameters to be estimated through calibration
# - outputs correspond to the target data

source("CRS_MarkovModel_Function.R") # creates the function run_crs_markov()

# Check that it works
v_params_test <- c(p_Mets = 0.10, p_DieMets = 0.05)
run_crs_markov(v_params_test) # It works!
```

04 Specify calibration parameters

```r
# Specify seed (for reproducible sequence of random numbers)
set.seed(072218)

# number of initial starting points
n_init <- 100

# names and number of input parameters to be calibrated
v_param_names <- c("p_Mets","p_DieMets")
n_param <- length(v_param_names)

# range on input search space
lb <- c(p_Mets = 0.04, p_DieMets = 0.04) # lower bound
ub <- c(p_Mets = 0.16, p_DieMets = 0.16) # upper bound

# number of calibration targets
v_target_names <- c("Surv")
n_target <- length(v_target_names)
```

05 Calibration functions

```r
# Write goodness-of-fit function to pass to Nelder-Mead algorithm
f_gof <- function(v_params){

  # Run model for parametr set "v_params"
  model_res <- run_crs_markov(v_params)

  # Calculate goodness-of-fit of model outputs to targets
  v_GOF <- numeric(n_target)
  # TARGET 1: Survival ("Surv")
  # log likelihood
  v_GOF[1] <- sum(dnorm(x = lst_targets$Surv$value,
                        mean = model_res$Surv,
                        sd = lst_targets$Surv$se,
                        log = T))

  # TARGET 2: (if you had more...)
```

```
  # log likelihood
  # v_GOF[2] <- sum(dnorm(x = lst_targets$Target2$value,
  #                       mean = model_res$Target2,
  #                       sd = lst_targets$Target2$se,
  #                       log = T))

  # OVERALL
  # can give different targets different weights
  v_weights <- rep(1,n_target)
  # weighted sum
  GOF_overall <- sum(v_GOF[1:n_target] * v_weights)

  # return GOF
  return(GOF_overall)
}
```

06 Calibrate!

```
# record start time of calibration
t_init <- Sys.time()

###  Sample multiple random starting values for Nelder-Mead  ###
v_params_init <- matrix(nrow=n_init, ncol=n_param)
for (i in 1:n_param){
  v_params_init[,i] <- runif(n_init,min=lb[i],max=ub[i])
}
colnames(v_params_init) <- v_param_names

###  Run Nelder-Mead for each starting point  ###
m_calib_res <- matrix(nrow = n_init, ncol = n_param+1)
colnames(m_calib_res) <- c(v_param_names, "Overall_fit")
for (j in 1:n_init){

  ### use optim() as Nelder-Mead ###
  fit_nm <- optim(v_params_init[j,], f_gof,
                  control = list(fnscale = -1, # switches from minimization to maximization
                                 maxit = 1000), hessian = T)
  m_calib_res[j,] <- c(fit_nm$par,fit_nm$value)

  ### to use a simulated annealing instead ###
  # fit_sa <- optim(v_params_init[j,], f_gof,
  #                 method = c("SANN"),  # switches to using simulated annealing
  #                 control = list(temp = 10, tmax = 10, # algorithm tuning parameters
  #                                fnscale = -1, maxit = 1000),
  #                 hessian = T)
  # m_calib_res[j,] = c(fit_sa$par,fit_sa$value)

  ### to use a genetic algorithm instead ###
  # library(DEoptim)
  # f_fitness <- function(params){
  #   names(params) = v_param_names
```

```
  #   return(-f_gof(params))}
  # fit_ga = DEoptim(f_fitness, lower=lb, upper=ub)
  # m_calib_res[j,] = c(fit_ga$optim$bestmem,-1*fit_ga$optim$bestval)

  }

# Calculate computation time
comp_time <- Sys.time() - t_init
```

07 Exploring best-fitting input sets

```
# Arrange parameter sets in order of fit
m_calib_res <- m_calib_res[order(-m_calib_res[,"Overall_fit"]),]

# Examine the top 10 best-fitting sets
m_calib_res[1:10, ]

# Plot the top 10 (top 10%)
plot(m_calib_res[1:10,1],m_calib_res[1:10,2],
     xlim=c(lb[1],ub[1]),ylim=c(lb[2],ub[2]),
     xlab = colnames(m_calib_res)[1],ylab = colnames(m_calib_res)[2])

# Pairwise comparison of top 10 sets
pairs.panels(m_calib_res[1:10,v_param_names])


### Plot model-predicted output at mean vs targets ###
v_out_best <- run_crs_markov(m_calib_res[1,])

# TARGET 1: Survival ("Surv")
plotrix::plotCI(x = lst_targets$Surv$time, y = lst_targets$Surv$value,
                ui = lst_targets$Surv$ub,
                li = lst_targets$Surv$lb,
                ylim = c(0, 1),
                xlab = "Time", ylab = "Pr Survive")
points(x = lst_targets$Surv$time,
       y = v_out_best$Surv,
       pch = 8, col = "red")
legend("topright",
       legend = c("Target", "Model-predicted output"),
       col = c("black", "red"), pch = c(1, 8))

# TARGET 2: (if you had more...)
# plotrix::plotCI(x = lst_targets$Target2$time, y = lst_targets$Target2$value,
#                 ui = lst_targets$Target2$ub,
#                 li = lst_targets$Target2$lb,
#                 ylim = c(0, 1),
#                 xlab = "Time", ylab = "Target 2")
# points(x = lst_targets$Target2$time,
#        y = v_out_best$Target2,
#        pch = 8, col = "red")
```

```
# legend("topright",
#        legend = c("Target", "Model-predicted output"),
#        col = c("black", "red"), pch = c(1, 8))
```