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/

```r
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

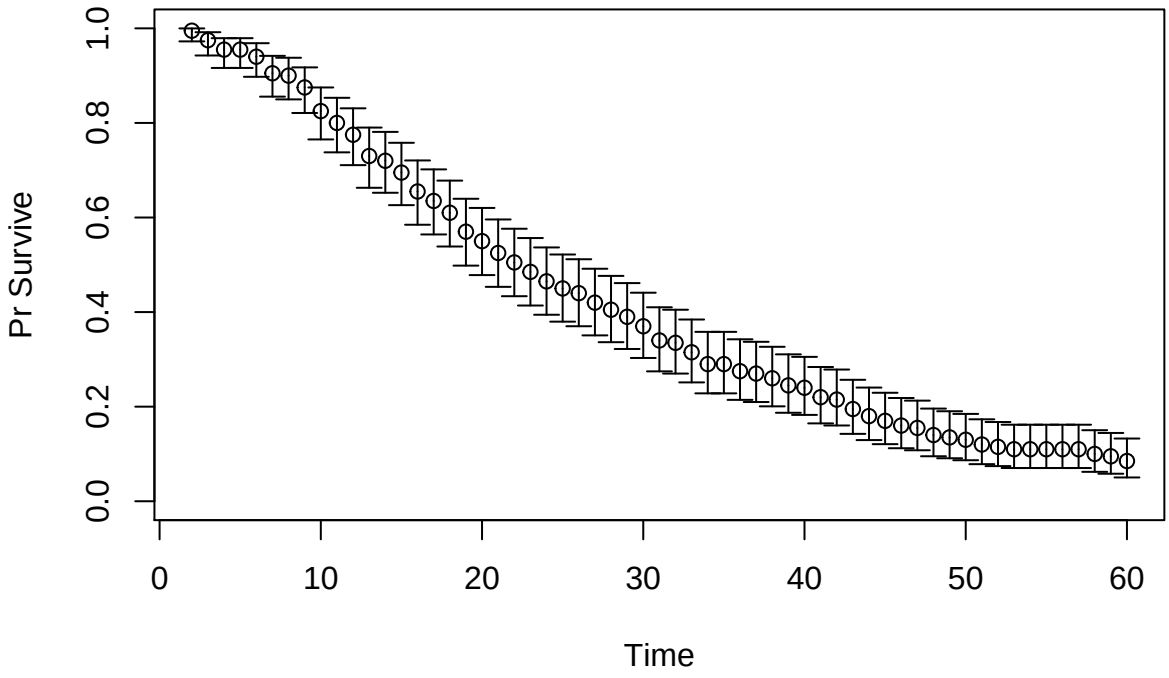
Goodness-of-fit measure: Sum of Log-Likelihood

01 Load packages

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

02 Load target data

```r
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

```
# - 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!
```

```
## $Surv
##          2          3          4          5          6          7          8
## 0.99500000 0.98575000 0.97291250 0.95707188 0.93874278 0.91837769 0.89637365
##          9         10         11         12         13         14         15
## 0.87307833 0.84879544 0.82378959 0.79829064 0.77249758 0.74658203 0.72069133
##         16         17         18         19         20         21         22
## 0.69495132 0.66946885 0.64433400 0.61962203 0.59539519 0.57170426 0.54859000
```

```
##         23         24         25         26         27         28         29
## 0.52608435 0.50421161 0.48298935 0.46242937 0.44253844 0.42331901 0.40476980
##         30         31         32         33         34         35         36
## 0.38688637 0.36966161 0.35308613 0.33714867 0.32183639 0.30713521 0.29303003
##         37         38         39         40         41         42         43
## 0.27950495 0.26654348 0.25412871 0.24224343 0.23087030 0.21999193 0.20959096
##         44         45         46         47         48         49         50
## 0.19965017 0.19015255 0.18108132 0.17242001 0.16415250 0.15626300 0.14873618
##         51         52         53         54         55         56         57
## 0.14155706 0.13471112 0.12818429 0.12196293 0.11603386 0.11038433 0.10500206
##         58         59         60
## 0.09987521 0.09499237 0.09034259
```

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)
```

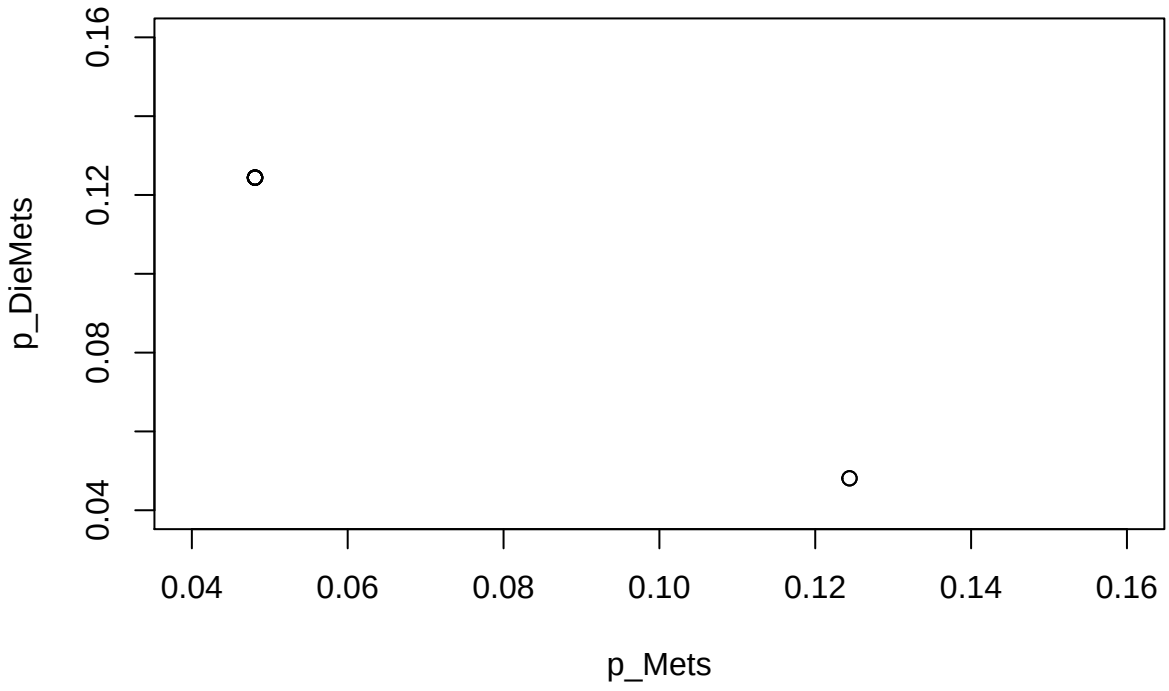
```
  # m_calib_res[j,] = c(fit_ga$optim$bestmem,-1*fit_ga$optim$bestval)

  }

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

07 Exploring best-fitting input sets

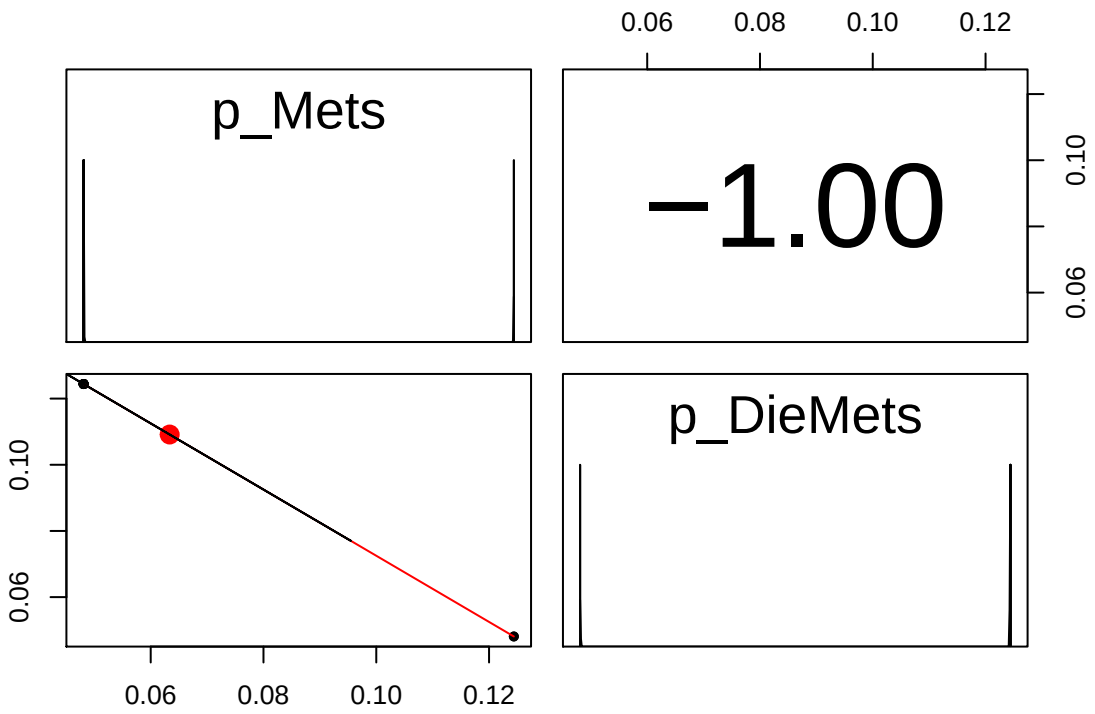
```
# Arrange parameter sets in order of fit
m_calib_res <- m_calib_res[order(-m_calib_res[,"Overall_fit"]),]

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

```
##           p_Mets  p_DieMets Overall_fit
##  [1,] 0.04810740 0.12439706    156.0328
##  [2,] 0.04810703 0.12439834    156.0328
##  [3,] 0.12439619 0.04810733    156.0328
##  [4,] 0.04810708 0.12439961    156.0328
##  [5,] 0.04810765 0.12439450    156.0328
##  [6,] 0.04810695 0.12439797    156.0328
##  [7,] 0.04810655 0.12440104    156.0328
##  [8,] 0.04810789 0.12439263    156.0328
##  [9,] 0.12439411 0.04810754    156.0328
## [10,] 0.04810769 0.12439731    156.0328
```

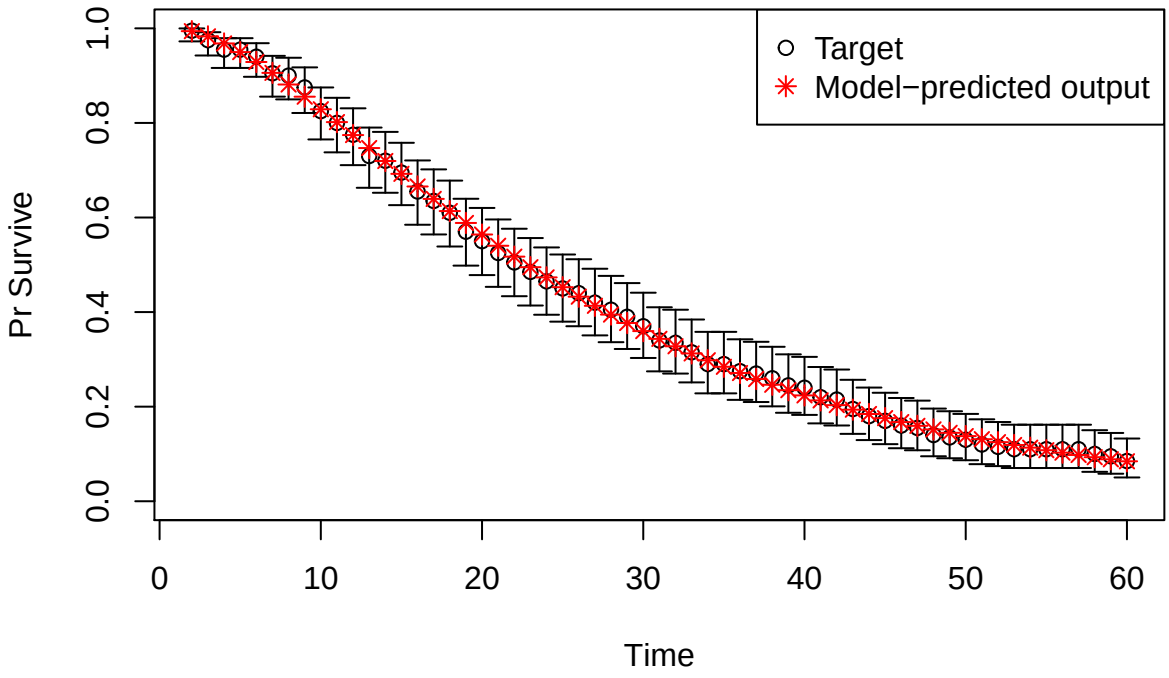
```
# Plot the top 10 (top 10%)
plot(m_calib_res[1:10,1],m_calib_res[1:10,2],
     xlim=c(lb[1],ub[1]),ylim=c(lb[2],ub[2]),
     xlab = colnames(m_calib_res)[1],ylab = colnames(m_calib_res)[2])
```




```
# 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))
```