

# Calibrating a 3-state cancer model

## Incremental mixture importance sampling (IMIS)

The DARTH workgroup

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- 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/>

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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)
```

## 00 Calibration Specifications

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

Inputs to be calibrated: `p_Mets`, `p_DieMets`

Targets: `Surv`

Calibration method: Incremental mixture importance sampling (IMIS)

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", "IMIS", "matrixStats", "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

```

# - 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

```

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

# number of random samples
n_resamp <- 1000

# 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

```

# Write function to sample from prior
sample_prior <- function(n_samp){
  m_lhs_unit <- randomLHS(n = n_samp, k = n_param)
  m_param_samp <- matrix(nrow = n_samp, ncol = n_param)
  colnames(m_param_samp) <- v_param_names
  for (i in 1:n_param){
    m_param_samp[, i] <- qunif(m_lhs_unit[,i],
                              min = lb[i],
                              max = ub[i])

    # ALTERNATIVE prior using beta (or other) distributions
    # m_param_samp[, i] <- qbeta(m_lhs_unit[,i],
    #                             shape1 = 1,
    #                             shape2 = 1)
  }
  return(m_param_samp)
}

```

```

# view resulting parameter set samples
pairs.panels(sample_prior(1000))

### PRIOR ###
# Write functions to evaluate log-prior and prior

# function that calculates the log-prior
calc_log_prior <- function(v_params){
  if(is.null(dim(v_params))) { # If vector, change to matrix
    v_params <- t(v_params)
  }
  n_samp <- nrow(v_params)
  colnames(v_params) <- v_param_names
  lprior <- rep(0, n_samp)
  for (i in 1:n_param){
    lprior <- lprior + dunif(v_params[, i],
                           min = lb[i],
                           max = ub[i],
                           log = T)
    # ALTERNATIVE prior using beta distributions
    # lprior <- lprior + dbeta(v_params[, i],
    #                          shape1 = 1,
    #                          shape2 = 1,
    #                          log = T)
  }
  return(lprior)
}
calc_log_prior(v_params = v_params_test)
calc_log_prior(v_params = sample_prior(10))

# function that calculates the (non-log) prior
calc_prior <- function(v_params) {
  exp(calc_log_prior(v_params))
}
calc_prior(v_params = v_params_test)
calc_prior(v_params = sample_prior(10))

### LIKELIHOOD ###
# Write functions to evaluate log-likelihood and likelihood

# function to calculate the log-likelihood
calc_log_lik <- function(v_params){
  # par_vector: a vector (or matrix) of model parameters
  if(is.null(dim(v_params))) { # If vector, change to matrix
    v_params <- t(v_params)
  }
  n_samp <- nrow(v_params)
  v_llik <- matrix(0, nrow = n_samp, ncol = n_target)
  llik_overall <- numeric(n_samp)
  for(j in 1:n_samp) { # j=1

```

```

jj <- tryCatch( {
  ### Run model for parametr set "v_params" ###
  model_res <- run_crs_markov(v_params[j, ])

  ### Calculate log-likelihood of model outputs to targets ###
  # TARGET 1: Survival ("Surv")
  # log likelihood
  v_llik[j, 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_llik[j, 2] <- sum(dnorm(x = lst_targets$Target2$value,
  #                           mean = model_res$Target2,
  #                           sd = lst_targets$Target2$se,
  #                           log = T))

  # OVERALL
  llik_overall[j] <- sum(v_llik[j, ])
}, error = function(e) NA)
if(is.na(jj)) { llik_overall <- -Inf }
} # End loop over sampled parameter sets
# return LLIK
return(llik_overall)
}
calc_log_lik(v_params = v_params_test)
calc_log_lik(v_params = sample_prior(10))

# function to calculate the (non-log) likelihood
calc_likelihood <- function(v_params){
  exp(calc_log_lik(v_params))
}
calc_likelihood(v_params = v_params_test)
calc_likelihood(v_params = sample_prior(10))

### POSTERIOR ###
# Write functions to evaluate log-posterior and posterior

# function that calculates the log-posterior
calc_log_post <- function(v_params) {
  lpost <- calc_log_prior(v_params) + calc_log_lik(v_params)
  return(lpost)
}
calc_log_post(v_params = v_params_test)
calc_log_post(v_params = sample_prior(10))

# function that calculates the (non-log) posterior
calc_post <- function(v_params) {

```

```

    exp(calc_log_post(v_params))
  }
calc_post(v_params = v_params_test)
calc_post(v_params = sample_prior(10))

```

## 06 Calibrate!

```

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

#### Bayesian calibration using IMIS ####
# define three functions needed by IMIS: prior(x), likelihood(x), sample.prior(n)
prior <- calc_prior
likelihood <- calc_likelihood
sample.prior <- sample_prior

# run IMIS
fit_imis <- IMIS(B = 1000, # the incremental sample size at each iteration of IMIS
                B.re = n_resamp, # the desired posterior sample size
                number_k = 10, # the maximum number of iterations in IMIS
                D = 0)

# obtain draws from posterior
m_calib_res <- fit_imis$resample

# Calculate log-likelihood (overall fit) and posterior probability of each sample
m_calib_res <- cbind(m_calib_res,
                    "Overall_fit" = calc_log_lik(m_calib_res[,v_param_names]),
                    "Posterior_prob" = calc_post(m_calib_res[,v_param_names]))

# normalize posterior probability
m_calib_res[, "Posterior_prob"] <- m_calib_res[, "Posterior_prob"] / sum(m_calib_res[, "Posterior_prob"])

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

```

## 07 Exploring posterior distribution

```

# Plot the 1000 draws from the posterior
v_post_color <- scales::rescale(m_calib_res[, "Posterior_prob"])
plot(m_calib_res,
     xlim = c(lb[1], ub[1]), ylim = c(lb[2], ub[2]),
     xlab = v_param_names[1], ylab = v_param_names[2],
     col = scales::alpha("black", v_post_color))
# add center of Gaussian components
points(fit_imis$center, col = "red", pch = 8)
legend("topright", c("Draws from posterior", "Center of Gaussian components"),
     col = c("black", "red"), pch = c(1, 8))

```

```

# Plot the 1000 draws from the posterior with marginal histograms
pairs.panels(m_calib_res[,v_param_names])

# Compute posterior mean
v_calib_post_mean <- colMeans(m_calib_res[,v_param_names])
v_calib_post_mean

# Compute posterior median and 95% credible interval
m_calib_res_95cr <- colQuantiles(m_calib_res[,v_param_names], probs = c(0.025, 0.5, 0.975))
m_calib_res_95cr

# Compute maximum-a-posteriori (MAP) parameter set
v_calib_map <- m_calib_res[which.max(m_calib_res[, "Posterior_prob"]),]

### Model-predicted output at mode/MAP ###
v_out_best <- run_crs_markov(v_calib_map[v_param_names])

```

## 07.1 Model predicted outputs at maximum-a-posteriori (MAP)

```

### Plot model-predicted output at mode vs targets ###
# set plot margins (helps plotting)
par(mar=c(5,4,4,4))
# 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))

```

## 07.2 Distribution of model-predicted outputs

```
### Distribution of model-predicted output at mode vs targets ###
## Initialize matrix to store outputs
m_out_post <- matrix(NA,
                    nrow = n_resamp,
                    ncol = length(v_out_best$Surv))
## Iterate model over all parameter sets from posterior distribution
for(i in 1:n_resamp){
  l_out <- run_crs_markov(m_calib_res[i, ])
  m_out_post[i, ] <- l_out$Surv

  if(i/(n_resamp/10) == round(i/(n_resamp/10),0)) { # display progress every 10%
    cat('\r', paste(i/n_resamp * 100, "% done", sep = " "))
  }
}

## Compute model-predicted posterior summary statistics
# Model-predicted posterior mean
v_out_post_mean <- colMeans(m_out_post)
# Model-predicted posterior credible interval
m_out_post_intervals <- colQuantiles(m_out_post, probs = c(0.025, 0.975))
```

### 07.2.1 Plot model-predicted output at mode vs targets

```
# set plot margins (helps plotting)
par(mar=c(5,4,4,4))
# TARGET 1: Survival ("Surv")
plotrix::plotCI(x = lst_targets$Surv$time, y = lst_targets$Surv$value,
               ui = lst_targets$Surv$sub,
               li = lst_targets$Surv$lb,
               ylim = c(0, 1),
               xlab = "Time", ylab = "Pr Survive")
points(x = lst_targets$Surv$time,
       y = v_out_post_mean,
       pch = 8, col = "red")
lines(x = lst_targets$Surv$time,
      y = m_out_post_intervals[, 1],
      col = "blue")
lines(x = lst_targets$Surv$time,
      y = m_out_post_intervals[, 2],
      col = "blue")
legend("topright",
      legend = c("Target",
                  "Model-predicted posterior mean",
                  "Model-predicted 95% posterior CrI"),
      col = c("black", "red", "blue"),
      pch = c(1, 8, NA),
      lty = c(NA, NA, 1))

# 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))

```