

Calibrating the Sick-Sicker model

Incremental mixture importance sampling (IMIS)

The DARTH workgroup

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- Alarid-Escudero F, Macle hose 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.
- 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: Sick-Sicker 4-state Markov Model

Inputs to be calibrated: `p_S1S2`, `hr_S1`, `hr_S2`

Targets: Surv, Prev, PropSick

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", "plotrix", "psych", "scatterplot3d", "IMIS", "matrixStats")  
# install_github("DARTH-git/darthtools", force = TRUE) Uncomment if there is a newer version  
p_load_gh("DARTH-git/darthtools")
```

02 Load target data

```
load("SickSicker_CalibTargets.RData")  
lst_targets <- SickSicker_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: Prevalence ("Prev")  
plotrix::plotCI(x = lst_targets$Prev$time, y = lst_targets$Prev$value,  
                ui = lst_targets$Prev$ub,  
                li = lst_targets$Prev$lb,  
                ylim = c(0, 1),  
                xlab = "Time", ylab = "Prev")  
  
# TARGET 3: Proportion who are Sick ("PropSick"), among all those afflicted (Sick+Sicker)  
plotrix::plotCI(x = lst_targets$PropSick$time, y = lst_targets$PropSick$value,  
                ui = lst_targets$PropSick$ub,
```

```

li = lst_targets$PropSick$lb,
ylim = c(0, 1),
xlab = "Time", ylab = "PropSick")

```

03 Load model as a function

```

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

# creates the function run_sick_sicker_markov()
source("SickSicker_MarkovModel_Function.R")

# Check that it works
v_params_test <- c(p_S1S2 = 0.105, hr_S1 = 3, hr_S2 = 10)
run_sick_sicker_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_S1S2", "hr_S1", "hr_S2")
n_param <- length(v_param_names)

# range on input search space
lb <- c(p_S1S2 = 0.01, hr_S1 = 1.0, hr_S2 = 5) # lower bound
ub <- c(p_S1S2 = 0.50, hr_S1 = 4.5, hr_S2 = 15) # upper bound

# number of calibration targets
v_target_names <- c("Surv", "Prev", "PropSick")
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_sick_sicker_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: "Prev"
      # log likelihood
      v_llik[j, 2] <- sum(dnorm(x = lst_targets$Prev$value,
                               mean = model_res$Prev,
                               sd = lst_targets$Prev$se,
                               log = T))

      # TARGET 3: "PropSick"
      # log likelihood
      v_llik[j, 3] <- sum(dnorm(x = lst_targets$PropSick$value,
                               mean = model_res$PropSick,
                               sd = lst_targets$PropSick$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 best-fitting input sets

```
# Plot the 1000 draws from the posterior
v_post_color <- scales::rescale(m_calib_res[, "Posterior_prob"])
s3d <- scatterplot3d(x = m_calib_res[, 1],
                    y = m_calib_res[, 2],
                    z = m_calib_res[, 3],
                    color = scales::alpha("black", v_post_color),
                    xlim = c(lb[1], ub[1]), ylim = c(lb[2], ub[2]), zlim = c(lb[3], ub[3]),
                    xlab = v_param_names[1], ylab = v_param_names[2], zlab = v_param_names[3])

# add center of Gaussian components
s3d$points3d(fit_imis$center, col = "red", pch = 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"]),]

### Plot model-predicted output at best set vs targets ###
v_out_best <- run_sick_sicker_markov(v_calib_map[v_param_names])

# 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: "Prev"
plotrix::plotCI(x = lst_targets$Prev$time, y = lst_targets$Prev$value,
                ui = lst_targets$Prev$ub,
                li = lst_targets$Prev$lb,
```

```

        ylim = c(0, 1),
        xlab = "Time", ylab = "Prev")
points(x = lst_targets$Prev$time,
       y = v_out_best$Prev,
       pch = 8, col = "red")
legend("topright",
       legend = c("Target", "Model-predicted output"),
       col = c("black", "red"), pch = c(1, 8))

# TARGET 3: "PropSick"
plotrix::plotCI(x = lst_targets$PropSick$time, y = lst_targets$PropSick$value,
               ui = lst_targets$PropSick$ub,
               li = lst_targets$PropSick$lb,
               ylim = c(0, 1),
               xlab = "Time", ylab = "PropSick")
points(x = lst_targets$PropSick$time,
       y = v_out_best$PropSick,
       pch = 8, col = "red")
legend("topright",
       legend = c("Target", "Model-predicted output"),
       col = c("black", "red"), pch = c(1, 8))

```