

# Calibrating the Sick-Sicker model

Directed search using Nelder-mead

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: 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", "scatterplot3d")  
# 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 initial starting points
n_init <- 100

# 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 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_sick_sicker_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: "Prev"
# log likelihood
v_GOF[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_GOF[3] <- sum(dnorm(x = lst_targets$PropSick$value,
                     mean = model_res$PropSick,
                     sd = lst_targets$PropSick$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%)
scatterplot3d(x = m_calib_res[1:10, 1],
              y = m_calib_res[1:10, 2],
              z = m_calib_res[1:10, 3],
              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])

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

### Plot model-predicted output at best set vs targets ###
v_out_best <- run_sick_sicker_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: "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))

```