

# Calibrating the Sick-Sicker model

## Random search using Latin-Hypercube Sampling

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.
- 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: Random search using Latin-Hypercube Sampling

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 random samples
n_samp <- 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 Calibrate!

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

### Generate a random sample of input values ###

# Sample unit Latin Hypercube
m_lhs_unit <- randomLHS(n_samp, n_param)
```

```

# Rescale to min/max of each parameter
m_param_samp <- matrix(nrow=n_samp,ncol=n_param)
for (i in 1:n_param){
  m_param_samp[,i] <- qunif(m_lhs_unit[,i],
                           min = lb[i],
                           max = ub[i])
}
colnames(m_param_samp) <- v_param_names

# view resulting parameter set samples
pairs.panels(m_param_samp)

### Run the model for each set of input values ###

# initialize goodness-of-fit vector
m_GOF <- matrix(nrow = n_samp, ncol = n_target)
colnames(m_GOF) <- paste0(v_target_names, "_fit")

# loop through sampled sets of input values
for (j in 1:n_samp){

  ### Run model for a given parameter set ###
  model_res <- run_sick_sicker_markov(v_params = m_param_samp[j, ])

  ### Calculate goodness-of-fit of model outputs to targets ###

  # TARGET 1: Survival ("Surv")
  # log likelihood
  m_GOF[j,1] <- sum(dnorm(x = lst_targets$Surv$value,
                        mean = model_res$Surv,
                        sd = lst_targets$Surv$se,
                        log = T))

  # weighted sum of squared errors (alternative to log likelihood)
  # w <- 1/(lst_targets$Surv$se^2)
  # m_GOF[j,1] <- -sum(w*(lst_targets$Surv$value - v_res)^2)

  # TARGET 2: "Prev"
  # log likelihood
  m_GOF[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
  m_GOF[j,3] <- sum(dnorm(x = lst_targets$PropSick$value,
                        mean = model_res$PropSick,
                        sd = lst_targets$PropSick$se,
                        log = T))
}

```

```

} # End loop over sampled parameter sets

### Combine fits to the different targets into single GOF ###
# can give different targets different weights
v_weights <- matrix(1, nrow = n_target, ncol = 1)
# matrix multiplication to calculate weight sum of each GOF matrix row
v_GOF_overall <- c(m_GOF%*%v_weights)
# Store in GOF matrix with column name "Overall"
m_GOF <- cbind(m_GOF,Overall_fit=v_GOF_overall)

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

```

## 06 Exploring best-fitting input sets

```

# Arrange parameter sets in order of fit
m_calib_res <- cbind(m_param_samp,m_GOF)
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 100 (top 10%)
scatterplot3d(x = m_calib_res[1:100, 1],
              y = m_calib_res[1:100, 2],
              z = m_calib_res[1:100, 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 100 sets
pairs.panels(m_calib_res[1:100,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))

```