Decision Analysis in R for Technologies in Health

Appendix A

Microsimulation modeling for health decision sciences using R: A tutorial.

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Appendix A - Microsimulation modeling for health decision sciences using R: A tutorial.

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This code forms the basis for the microsimulation model of the article: Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. Med Decis Making. 2018;38(3):400-22.

Please cite the article when using this code.

See GitHub for more information or code updates https://github.com/DARTH-git/Microsimulation-tutorial

To program this tutorial we made use of R: 3.3.0 GUI 1.68 Mavericks build (7202) RStudio: Version 1.0.136 2009-2016 RStudio, Inc.

Code of Appendix A

```r
#rm(list = ls())  # remove any variables in R's memory
```

Model input

```r
# Model input
n.i   <- 100000            # number of simulated individuals
n.t   <- 30                # time horizon, 30 cycles
v.n   <- c("H","S1","S2","D")  # the model states: Healthy (H), Sick (S1), Sicker (S2), Dead (D)
n.s   <- length(v.n)       # the number of health states
v.M_1 <- rep("H", n.i)     # everyone begins in the healthy state
d.c   <- d.e <- 0.03       # equal discounting of costs and QALYs by 3%
v.Trt <- c("No Treatment", "Treatment") # store the strategy names
```

Transition probabilities (per cycle)

```r
p.HD    <- 0.005              # probability to die when healthy
p.HS1   <- 0.15               # probability to become sick when healthy
p.S1H   <- 0.5                # probability to become healthy when sick
p.S1S2  <- 0.105              # probability to become sicker when sick
rr.S1   <- 3                  # rate ratio of death when sick vs healthy
rr.S2   <- 10                 # rate ratio of death when sicker vs healthy
r.HD    <- -log(1 - p.HD)     # rate of death when healthy
r.S1D   <- rr.S1 * r.HD       # rate of death when sick
r.S2D   <- rr.S2 * r.HD       # rate of death when sicker
```

```
p.S1D   <- 1 - exp(- r.S1D)    # probability to die when sick
p.S2D   <- 1 - exp(- r.S2D)    # probability to die when sicker
```

Cost and utility inputs

```
c.H     <- 2000                    # cost of remaining one cycle healthy
c.S1    <- 4000                    # cost of remaining one cycle sick
c.S2    <- 15000                   # cost of remaining one cycle sicker
c.Trt   <- 12000                   # cost of treatment (per cycle)

u.H     <- 1                       # utility when healthy
u.S1    <- 0.75                    # utility when sick
u.S2    <- 0.5                     # utility when sicker
u.Trt   <- 0.95                    # utility when sick(er) and being treated
```

Functions

The `MicroSim` function for the simple microsimulation of the 'Sick-Sicker' model keeps track of what happens to each individual during each cycle.

```
MicroSim <- function(v.M_1, n.i, n.t, v.n, d.c, d.e, TR.out = TRUE, TS.out =
TRUE, Trt = FALSE, seed = 1) {
# Arguments:
  # v.M_1:   vector of initial states for individuals
  # n.i:     number of individuals
  # n.t:     total number of cycles to run the model
  # v.n:     vector of health state names
  # d.c:     discount rate for costs
  # d.e:     discount rate for health outcome (QALYs)
  # TR.out:  should the output include a microsimulation trace? (default is T
RUE)
  # TS.out:  should the output include a matrix of transitions between states
? (default is TRUE)
  # Trt:     are the n.i individuals receiving treatment? (scalar with a Bool
ean value, default is FALSE)
  # seed:    starting seed number for random number generator (default is 1)
# Makes use of:
  # Probs:   function for the estimation of transition probabilities
  # Costs:   function for the estimation of cost state values
  # Effs:    function for the estimation of state specific health outcomes (Q
ALYs)

  v.dwc <- 1 / (1 + d.c) ^ (0:n.t)   # calculate the cost discount weight bas
ed on the discount rate d.c
  v.dwe <- 1 / (1 + d.e) ^ (0:n.t)   # calculate the QALY discount weight bas
ed on the discount rate d.e

 # create the matrix capturing the state name/costs/health outcomes for all i
ndividuals at each time point
```

```r
  m.M <- m.C <- m.E <-  matrix(nrow = n.i, ncol = n.t + 1,
                              dimnames = list(paste("ind", 1:n.i, sep = " ")
,
                                             paste("cycle", 0:n.t, sep = "
")))

  m.M[, 1] <- v.M_1                        # indicate the initial health state

  for (i in 1:n.i) {
    set.seed(seed + i)                    # set the seed for every individual f
or the random number generator
    m.C[i, 1] <- Costs(m.M[i, 1], Trt)  # estimate costs per individual for t
he initial health state conditional on treatment
    m.E[i, 1] <- Effs (m.M[i, 1], Trt)  # estimate QALYs per individual for t
he initial health state conditional on treatment

    for (t in 1:n.t) {
      v.p <- Probs(m.M[i, t])              # calculate the transition probabilit
ies at cycle t

      m.M[i, t + 1] <- sample(v.n, prob = v.p, size = 1)  # sample the next h
ealth state and store that state in matrix m.M
      m.C[i, t + 1] <- Costs(m.M[i, t + 1], Trt)   # estimate costs per indiv
idual during cycle t + 1 conditional on treatment
      m.E[i, t + 1] <- Effs( m.M[i, t + 1], Trt)   # estimate QALYs per indiv
idual during cycle t + 1 conditional on treatment

    } # close the loop for the time points
    if(i/100 == round(i/100,0)) {          # display the progress of the simu
lation
      cat('\r', paste(i/n.i * 100, "% done", sep = " "))
    }
  } # close the loop for the individuals

  tc <- m.C %*% v.dwc       # total (discounted) cost per individual
  te <- m.E %*% v.dwe       # total (discounted) QALYs per individual

  tc_hat <- mean(tc)        # average (discounted) cost
  te_hat <- mean(te)        # average (discounted) QALYs

  if (TS.out == TRUE) {  # create a  matrix of transitions across states
    TS <- paste(m.M, cbind(m.M[, -1], NA), sep = "->") # transitions from one
state to the other
    TS <- matrix(TS, nrow = n.i)
    rownames(TS) <- paste("Ind",   1:n.i, sep = " ")   # name the rows
    colnames(TS) <- paste("Cycle", 0:n.t, sep = " ")   # name the columns
  } else {
    TS <- NULL
  }
```

```
    if (TR.out == TRUE) { # create a trace from the individual trajectories
      TR <- t(apply(m.M, 2, function(x) table(factor(x, levels = v.n, ordered =
TRUE))))
      TR <- TR / n.i                                        # create a distribut
ion trace
      rownames(TR) <- paste("Cycle", 0:n.t, sep = " ")      # name the rows
      colnames(TR) <- v.n                                   # name the columns
    } else {
      TR <- NULL
    }

    results <- list(m.M = m.M, m.C = m.C, m.E = m.E, tc = tc, te = te, tc_hat =
tc_hat, te_hat = te_hat, TS = TS, TR = TR) # store the results from the simul
ation in a list
    return(results)  # return the results
}   # end of the MicroSim function
```

Probability function

The Probs function that updates the transition probabilities of every cycle is shown below.

```
Probs <- function(M_it) {
  # M_it:    health state occupied by individual i at cycle t (character vari
able)

  v.p.it <- rep(NA, n.s)      # create vector of state transition probabilitie
s
  names(v.p.it) <- v.n        # name the vector

  # update v.p.it with the appropriate probabilities
  v.p.it[M_it == "H"]  <- c(1 - p.HS1 - p.HD, p.HS1, 0, p.HD)
# transition probabilities when healthy
  v.p.it[M_it == "S1"] <- c(p.S1H, 1- p.S1H - p.S1S2 - p.S1D, p.S1S2, p.S1D)
# transition probabilities when sick
  v.p.it[M_it == "S2"] <- c(0, 0, 1 - p.S2D, p.S2D)
# transition probabilities when sicker
  v.p.it[M_it == "D"]  <- c(0, 0, 0, 1)
# transition probabilities when dead
  ifelse(sum(v.p.it) == 1, return(v.p.it), print("Probabilities do not sum to
1")) # return the transition probabilities or produce an error
}
```

Costs function

The Costs function estimates the costs at every cycle.

```
Costs <- function (M_it, Trt = FALSE) {
  # M_it: health state occupied by individual i at cycle t (character variabl
e)
```

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```
  # Trt:  is the individual being treated? (default is FALSE)

  c.it <- 0                                # by default the cost for everyo
ne is zero
  c.it[M_it == "H"]  <- c.H                # update the cost if healthy
  c.it[M_it == "S1"] <- c.S1 + c.Trt * Trt   # update the cost if sick condit
ional on treatment
  c.it[M_it == "S2"] <- c.S2 + c.Trt * Trt   # update the cost if sicker cond
itional on treatment
  return(c.it)                             # return the costs
}
```

Health outcome function

The `Effs` function to update the utilities at every cycle.

```
Effs <- function (M_it, Trt = FALSE, cl = 1) {
  # M_it: health state occupied by individual i at cycle t (character variabl
e)
  # Trt:  is the individual treated? (default is FALSE)
  # cl:   cycle length (default is 1)

  u.it <- 0                          # by default the utility for everyone is zer
o
  u.it[M_it == "H"]  <- u.H       # update the utility if healthy
  u.it[M_it == "S1"] <- Trt * u.Trt + (1 - Trt) * u.S1  # update the utility
if sick conditional on treatment
  u.it[M_it == "S2"] <- u.S2      # update the utility if sicker
  QALYs <-  u.it * cl              # calculate the QALYs during cycle t
  return(QALYs)                   # return the QALYs
}
```

Run the simulation

```
sim_no_trt  <- MicroSim(v.M_1, n.i, n.t, v.n, d.c, d.e, Trt = FALSE) # run fo
r no treatment
sim_trt     <- MicroSim(v.M_1, n.i, n.t, v.n, d.c, d.e, Trt = TRUE)  # run fo
r treatment
```

Cost-effectiveness analysis

```
# store the mean costs (and the MCSE) of each strategy in a new variable v.C
(vector costs)
v.C  <- c(sim_no_trt$tc_hat, sim_trt$tc_hat)
se.C <- c(sd(sim_no_trt$tc), sd(sim_trt$tc)) / sqrt(n.i)
# store the mean QALYs (and the MCSE) of each strategy in a new variable v.E
(vector health outcomes)
v.E  <- c(sim_no_trt$te_hat, sim_trt$te_hat)
se.E <- c(sd(sim_no_trt$te), sd(sim_trt$te)) / sqrt(n.i)
```

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```
delta.C <- v.C[2] - v.C[1]                  # calculate incremental costs
delta.E <- v.E[2] - v.E[1]                  # calculate incremental QALYs
se.delta.E <- sd(sim_trt$te - sim_no_trt$te) / sqrt(n.i) # Monte Carlo square
d error (MCSE) of incremental costs
se.delta.C <- sd(sim_trt$tc - sim_no_trt$tc) / sqrt(n.i) # Monte Carlo square
d error (MCSE) of incremental QALYs
ICER    <- delta.C / delta.E                # calculate the ICER
results <- c(delta.C, delta.E, ICER)        # store the values in a new vari
able
```

Create full incremental cost-effectiveness analysis table

```
table_micro <- data.frame(
  c(round(v.C, 0),   ""),         # costs per arm
  c(round(se.C, 0), ""),          # MCSE for costs
  c(round(v.E, 3),   ""),         # health outcomes per arm
  c(round(se.E, 3), ""),          # MCSE for health outcomes
  c("", round(delta.C, 0),    ""),  # incremental costs
  c("", round(se.delta.C, 0),""),   # MCSE for incremental costs
  c("", round(delta.E, 3),    ""),  # incremental QALYs
  c("", round(se.delta.E, 3),""),   # MCSE for health outcomes (QALYs) gained
  c("", round(ICER, 0),       "")   # ICER
)
rownames(table_micro) <- c(v.Trt, "* are MCSE values")  # name the rows
colnames(table_micro) <- c("Costs", "*",  "QALYs", "*", "Incremental Costs",
"*", "QALYs Gained", "*", "ICER") # name the columns

kable(table_micro)  # print the table
```

	Costs	*	QALYs	*	Incremental Costs	*	QALYs Gained	*	ICER
No Treatment	75996	183	15.823	0.016					
Treatment	141644	343	16.384	0.016	65648	164	0.561	0.001	117087

* are MCSE values