Making Markov Models Shiny: A Tutorial

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Abstract

Health economic models have traditionally been built in spreadsheet software, but more sophisticated tools are increasingly being used as model complexity and computational requirements increase. Of all the programming languages there is a particular push towards the use of R because it is commonly used by statisticians, has a plethora of user created packages and is highly flexible, transparent and adaptable. However, the use of R requires some coding ability, as it does not have a simple point-and-click user interface. This might make the switch from spreadsheet software to R seem daunting, and it might make it difficult to directly communicate results with decisions makers and other stakeholders.

The R package 'shiny' resolves this limitation. It allows programmers to embed health economic models developed in R into interactive web-browser based user interfaces. Users can specify their own assumptions about model parameters and run different scenario analyses, which, in case of regular a Markov model, can be computed within seconds. This paper provides a tutorial on how to wrap R health economic models into shiny applications. We use the 4 state Markov model developed by the DARTH group as a case-study to demonstrate main principles and basic functionality.

A more extensive tutorial, all code and data are provided on a GitHub repository: https://robertasmith.github.io/healthecon_shiny/.

Introduction

As the complexity of health economics models increase, there is growing recognition of the advantages of high level programming languages to support statistical analysis (e.g. R, Python, C++).

Depending on the model that is being used, spreadsheet software can be relatively slow. Certain types of models (individual-level simulations) take very long times to run or become computationally infeasible, and some essential statistical methods can hardly be implemented at all, and rely on exporting results from other programs (e.g. survival modelling, network meta analysis, value of sample information, etc).

Of all the programming languages, R appears to be ahead of the competition for decision modelling in health economics (Jalal et al. 2017). R is open source, supported by a large community of statisticians, data scientists and health economists. There exists an extensive collection of (mostly free) online resources, including packages, tutorials, courses, and guidelines. Chunks of code, model functions, and entire models are shared by numerous authors, which allow R users to quickly adopt and adapt methods and code created by others. Importantly for the UK, R is also currently the only programming environment accepted by NICE for HTA submissions, the alternative submission formats Excel, DATA/Treeage, and WinBUGs are all software applications (NICE, 2014).

Despite the many strengths of the script based approach (e.g R) to decision modelling, an important limitation has been the lack of an easy-to-understand user-interface. While it is common practice for 'spreadsheet models' to have a structured front tab, which allows decision makers to manipulate model assumptions and change parameters to assess their impact on the results, up until recently, R models had to be adapted within script files or command lines.

Released in 2012, Shiny is an R-package which can be used to create a graphical, web browser based interface. The result looks like a website, and allows users to interact with underlying R models, without the need to manipulate the source code (Beely, 2013). Shiny has already been widely adopted in many different areas and by various organisations, to present the results of statistical analysis and to allow users to Use cases range from [example 1] and [example 2] to [example 3] and [example 4].

Using Shiny, it is possible to create flexible user interfaces which allow users to specify different assumptions, change parameters, run the underlying R code and display and explore in-depth the results. The primary benefit of this is that it makes script based computer models accessible to those with little or no programming knowledge - opening models up to critical inquiry from decision makers and other stakerholders (Jansen et al., 2019). Other benefits come from leveraging the power of R itself and other R packages, for example allowing for publication quality graphs and tables to be downloaded, user specific data uploaded, open-access data automatically updated and, perhaps most importantly, to efficiently run comprehensive probabilistic sensitivity analyses in a fraction of the time that it would take in spreadsheet software. Shiny web applications for R health economic models seem particularly useful in cases where model parameters are highly uncertain or unknown, and where model results need to be evaluated under various different assumptions. Once an R model and a shiny application have been created, they can also be easily adapted, making it possible to quickly update the model when new information becomes available.

While it is preferable that models constructed in R are made open-access to improve transparency, replicability and collaboration, it is not a requirement. Sensitive and proprietary data and/or models can be shared internally. or through secure, password-protected web applications, negating the need to email zipped folders.

Several authors postulated that there is considerable potential in using Shiny to support and improve health economic decision making. Incerti et al. (2019) identified web applications as being an essential part of modelling, stating that they "believe that the future of cost-effectiveness modeling lies in web apps, in which graphical interfaces are used to run script-based models" (p. 577). Similarly, Baio & Heath (2017) predicted that R Shiny web apps will be the "future of applied statistical modelling, particularly for cost-effectiveness analysis" (p.e5). Despite these potentially optimistic prognoses, adoption of R in health economics has been slow and the use of Shiny seems to have been limited to only a few cases. A reason for this might be the lack of accessible tutorials, tailored towards an economic modeller audience.

Here, we provide a simple example of a shiny web app, using a general 4-state Markov model. The model is based on the 'Sick-Sicker model', which has been described in detail in previous publications (Krijkamp et al., 2020; Alarid-Escudero et al., 2020) and in open source teaching materials by the DARTH workgroup (Decision Analysis in R for Technologies in Health, 2019). The model was slightly adapted to implement probabilistic sensitivity analysis.

Methods

While the focus of this tutorial is on the application of shiny for health economic models, it will be useful to have a basic understanding of the underlying 'sick-sicker-model'. In the following, we will provide a brief overview. For further details, readers are encouraged to consult Alarid-Escudero et al., 2019, Krijkamp et al., 2020 and the DARTH group website http://darthworkgroup.com/.

The Sick-Sicker model is a 4 state (Healthy, Sick, Sicker or Dead) Markov model. The cohort progresses through the model in cycles of equal duration, with the proportion of those in each health state in the next cycle being dependant on the proportion in each health state in the current cycle and the transition probability matrix.

The analysis incorporates probabilistic sensitivity analysis (PSA) by creating a data-frame of PSA inputs (one row being one set of model inputs) based on cost, utility and probability distributions using the function f_gen_psa and then running the model with each set of PSA inputs using the model function $f_MM_sicksicker$. We therefore begin by describing the two functions f_gen_psa and $f_MM_sicksicker$ in

more detail before moving on to demonstrate how to create a user-interface. Note that we adapt the coding framework from Alarid-Escudero et al., (2019) to use the f_{-} prefix for functions.

Functions

Creating PSA inputs.

The f_gen_psa function returns a data-frame of probabilistic sensitivity analysis inputs: transition probabilities between health states using a beta distribution, hazard rates using a log-normal distribution, costs using a gamma distribution and utilities using a truncnormal distribution.

NOTE: in order to use the *rtruncnorm* function the user must first install and load the 'truncnorm' package using *install.packages* and *library()*.

```
f gen psa <- function(n sim = 1000, c Trt = SI c Trt){
 df_psa <- data.frame(</pre>
    # Transition probabilities (per cycle)
   p HS1
           = rbeta(n sim, 30, 170),
                                           # prob Healthy -> Sick
   p S1H
           = rbeta(n_sim, 60, 60),
                                           # prob Sick
                                                        -> Healthy
   p_S1S2 = rbeta(n_sim, 84, 716),
                                          # prob Sick
                                                         -> Sicker
           = rbeta(n_sim, 10, 1990)
                                        , # prob Healthy -> Dead
   p_HD
           = rlnorm(n_sim, log(3), 0.01), # rate ratio death S1 vs healthy
   hr_S1
           = rlnorm(n_sim, log(10), 0.02), # rate ratio death S2 vs healthy
   hr_S2
   # Cost vectors with length n_sim
   c_H = rgamma(n_sim, shape = 100, scale = 20) , # cost p/cycle in state H
   c_S1 = rgamma(n_sim, shape = 177.8, scale = 22.5), # cost p/cycle in state S1
   c_S2 = rgamma(n_sim, shape = 225, scale = 66.7) , # cost p/cycle in state S2
   c D = 0
                                                     , # cost p/cycle in state D
   c_Trt = c_Trt,
                                                    # cost p/cycle of treatment
   # Utility vectors with length n_sim
   u_H = rtruncnorm(n_sim, mean = 1, sd = 0.01, b = 1), # utility when healthy
   u_S1 = rtruncnorm(n_sim, mean = 0.75, sd = 0.02, b = 1), # utility when sick
   u_S2 = rtruncnorm(n_sim, mean = 0.50, sd = 0.03, b = 1), # utility when sicker
   u_D = 0
                                                           , # utility when dead
   u_Trt = rtruncnorm(n_sim, mean = 0.95, sd = 0.02, b = 1) # utility when being treated
 return(df_psa)
}
```

Running the model for a specific set of PSA inputs

The function $f_MM_sicksicker$ makes use of the with function which applies an expression (in this case the rest of the code) to a dataset (in this case params, which will be a row of PSA-inputs). It uses the params (one row of PSA inputs) to create a transition probability matrix m_P , and then moves the cohort through the simulation one cycle at a time, recording the proportions in each health state in a markov trace m_TR and applying the transition matrix to calculate the proportions in each health state in the next period. The function returns a vector of five results: Cost with no treatment, Cost with treatment, QALYs with

no treatment and QALYs with treatment and an ICER. In this simple example treatment only influences utilities and costs, not transition probabilities

```
f_MM_sicksicker <- function(params) {</pre>
 with(as.list(params), {
   # compute internal paramters as a function of external parameter
           = - \log(1 - p_HD) # rate of death in healthy
   {	t r}_{	t HD}
   r S1D
         = hr_S1 * r_HD # rate of death in sick
                            # rate of death in sicker
   r_S2D = hr_S2 * r_HD
   p_S1D
         = 1 - exp(-r_S1D) # probability to die in sick
         = 1 - \exp(-r_S2D) # probability to die in sicker
   p_S2D
   # calculate discount weight for each cycle based on discount rate d_r
   v_dwe \leftarrow v_dwc \leftarrow 1 / (1 + d_r) ^ (0:n_t)
   # create transition probability matrix for NO treatment
   m P <- matrix(0,
                nrow = n_states, ncol = n_states,
                 dimnames = list(v_n, v_n))
   # fill in the transition probability array
   ### From Healthy
   m_P["H", "H"] <- 1 - (p_HS1 + p_HD)
   m_P["H", "S1"] <- p_HS1
   m_P["H", "D"] \leftarrow p_HD
   ### From Sick
   m_P["S1", "H"] <- p_S1H
   m_P["S1", "S1"] \leftarrow 1 - (p_S1H + p_S1S2 + p_S1D)
   m_P["S1", "S2"] <- p_S1S2
   m_P["S1", "D"] <- p_S1D
   ### From Sicker
   m_P["S2", "S2"] <- 1 - p_S2D
   m_P["S2", "D"] <- p_S2D
   ### From Dead
   m P["D", "D"] <- 1
   # create Markov trace (n t + 1 because R doesn't understand Cycle 0)
   m_TR <- matrix(NA, nrow = n_t + 1 , ncol = n_states,</pre>
                  dimnames = list(0:n_t, v_n))
   m_TR[1, ] \leftarrow c(1, 0, 0, 0)
                                    # initialize Markov trace
   for (t in 1:n_t){ # throughout the number of cycles
     # estimate the Markov trace for cycle the next cycle (t + 1)
     m_TR[t + 1, ] <- m_TR[t, ] %*% m_P
   }
   # create vectors of utility and costs for each state
   v_u_trt <- c(u_H, u_Trt, u_S2, u_D)
```

```
v_u_no_trt <- c(u_H, u_S1, u_S2, u_D)</pre>
             <- c(c_H, c_S1 + c_Trt, c_S2 + c_Trt, c_D)
   v_c_trt
   v_c_no_trt <- c(c_H, c_S1, c_S2, c_D)</pre>
   # estimate mean QALys and costs
   v_E_no_trt <- m_TR %*% v_u_no_trt</pre>
            v E trt
   v_C_no_trt <- m_TR %*% v_c_no_trt</pre>
           v_C_trt
   ### discount costs and QALYs
   te_no_trt <- t(v_E_no_trt) %*% v_dwe # 1x31 %*% 31x1 -> 1x1
           tc_no_trt <- t(v_C_no_trt) %*% v_dwc
          <- t(v_C_trt)
   tc_trt
                          %*% v_dwc
   results <- c("Cost_NoTrt" = tc_no_trt,
                          = tc_trt,
                "Cost_Trt"
               "QALY_NoTrt" = te_no_trt,
                "QALY Trt"
                          = te trt,
                "ICER"
                           = (tc_trt - tc_no_trt)/(te_trt - te_no_trt))
   return(results)
 }
}
```

Creating a Wrapper

When using a web application it is likely that the user will want to be able to change parameter inputs and re-run the model. In order to make this simple, we recommend wrapping the entire model into a function. We call this function $f_wrapper$, using the prefix $f_$ to denote that this is a function.

The wrapper function has as its inputs all the things which we may wish to vary using R-Shiny. We set the default values to those of the base model in any report/publication. The model then generates PSA inputs using the f_gen_psa function, creates a table of results, and finally loops through the PSA, running the model with each set of PSA inputs (a row from df_psa) in turn. The function then returns the results in the form of a dataframe with n=5 columns and n=psa rows. The columns contain the costs and qalys for treatment and no treatment for each PSA run, as well as an ICER for that PSA run.

```
){
                       Non-shiny inputs
#-----
n_t <- n_age_max - n_age_init # time horizon, number of cycles
v_n <- c("H", "S1", "S2", "D") # the 4 health states of the model:
n states <- length(v n) # number of health states
                       Create PSA Inputs
df_psa <- f_gen_psa(n_sim = n_sim, c_Trt)</pre>
                       Run PSA
#-----
# Initialize matrix of results outcomes
df_out <- matrix(NaN,</pre>
             nrow = n_sim,
             ncol = 5,
             dimnames = list(1:n_sim,c("Cost_NoTrt", "Cost_Trt",
                                     "QALY_NoTrt", "QALY_Trt",
                                     "ICER")))
# loop through psa inputs running the model for each.
for(i in 1:n_sim){
  # store results in one row of results matrix
 df_out[i,] <- f_MM_sicksicker(df_psa[i, ])</pre>
  # display the progress of the simulation
  cat('\r', paste(round(i/n_sim * 100), "% done", sep = " "))
}
df_out <- as.data.frame(df_out) # convert matrix to dataframe</pre>
return(df out) # output the dataframe from the function
}
```

Integrating into R-Shiny

The method so far has involved wrapping the model into a function, which takes some inputs and returns a single data-frame output. The next step is to integrate the model function into a shiny web-app. This is done within a single R file, which we call *app.R*. This can be found here: https://github.com/RobertASmith/healthecon_shiny/tree/master/App.

The app.R script has three main parts, each are addressed in turn below: - set-up (getting everything ready so the ui and server can be created) - user interface (what people will see) - server (stuff going on in the background)

Set-up

The set-up is relatively simple, load the R-Shiny package from your library so that you can use the R-Shiny function. The next step is to use the *source* function in baseR to run the script which creates the *f_wrapper* function, being careful to ensure your relative path is correct ('./wrapper.R' should work if the app.R file is within the same folder). The function *shinyApp* at the end of the app file is reliant on the *shiny* package so please ensure that the shiny package is installed, using *install-packages*("*shiny*") if it is not.

```
# install.packages("shiny") # necessary if you don't already have the function 'shiny' installed.
# we need the function shiny installed, this loads it from the library.
library(shiny)
# source the wrapper function.
source("./wrapper.R")
```

User Interface

The user interface is extremely flexible, we show the code for a very simple structure (fluidpage) with a sidebar containing inputs and a main panel containing outputs. We have done very little formatting in order to minimize the quantity of code while maintaining basic functionality. In order to get an aesthetically pleasing application we would have much more sophisticated formatting, relying on CSS, HTML and Javascript.

This example user interface below is made up of two components, a titlepanel and a sidebar layout display. The sidebar Layout display has within it a sidebar and a main panel. These are all contained within the *fluidpage* function which creates the ui.

The title panel contains the title "Sick Sicker Model in Shiny", the sidebar panel contains two numeric inputs and a slider input ("Treatment Cost", "PSA runs", "Initial Age") and an Action Button ("Run / update model").

The values of the inputs have ids which are used by the server function, we denote these with the prefix "SI" to indicate they are 'Shiny Input' objects $(SI_c_Trt,SI_n_sim,SI_n_age_init)$, and distiguish them from the non-Shiny inputs in the server (e.g. c_Trt). Note that this is an addition of the coding framework provided by Alarid-Escudero et al., (2019).

The action button also has an id, this is not an input into the model wrapper (f_wrapper) so we leave out the SI and call it "run model".

The main panel contains two objects which have been output from the server: $tableOutput("SO_icer_table")$ is a table of results, and $plotOutput("SO_CE_plane")$ is a cost-effectiveness plane plot. It is important that the format (e.g. tableOutput) matches the format of the object from the server (e.g. SO_icer_table). Again, the SO prefix reflects the fact that these are Shiny Outputs. The two h3() functions are simply headings which appear as "Results Table" and "Cost-effectiveness Plane".

```
sidebarPanel( # open sidebar panel
 numericInput(inputId = "SI_c_Trt",
                                    # id of input, used in server
              label = "Treatment Cost", # label next to numeric input
                                        # initial value
              value = 200,
              min = 0,
                                        # minimum value allowed
              \max = 400),
                                        # maximum value allowed
 numericInput(inputId = "SI_n_sim", # id of input, used in server
              label = "PSA runs",
                                        # label next to numeric input
              value = 1000,
                                       # initial value
              min = 0,
                                       # minimum value allowed
              \max = 400),
                                        # maximum value allowed
 sliderInput(inputId = "SI_n_age_init", # id of input, used in server
             label = "Initial Age",
                                       # label next to numeric input
                                        # initial value
             value = 25,
             min = 10,
                                       # minimum value allowed
             max = 80),
                                       # maximum value allowed
 actionButton(inputId = "run_model",
                                    # id of action button, used in server
              label = "Run model")
                                       # action button label (on button)
             ), # close sidebarPanel
mainPanel(
                                        # open main panel
 h3("Results Table"),
                                        # heading (results table)
 tableOutput(outputId = "SO_icer_table"), # tableOutput id = icer_table, from server
 h3("Cost-effectiveness Plane"),
                                 # heading (Cost effectiveness plane)
 plotOutput(outputId = "SO_CE_plane")
                                          # plotOutput id = CE_plane, from server
         ) # close mainpanel
   ) # close sidebarlayout
) # close UI fluidpage
```

Server

The server is marginally more complicated than the user interface. It is created by a function with inputs and outputs. The observe event indicates that when the action button (run_model) is pressed the code within the curly brackets is run. The code wil be re-run if the button is pressed again.

The first thing that happens when the run_model button is pressed is that the model wrapper function $f_wrapper$ is called, with the user interface inputs $(SI_c_Trt,SI_n_age_init,SI_n_sim)$ as inputs to the function. The input\$ prefix indicates that the objects have come from the user interface. The results of the model are stored as the dataframe object df_model_res .

The ICER table is then created and output (note the prefix output\$) in the object SO_icer_table. See previous section on the user interface and note that the tableOutput function was reliant on SO_icer_table. The function renderTable rerenders the table continuously so that the table always reflects the values from the data-frame of results created above. In this simple example we have created a table of results using code within the script. In reality we would generally use a custom function which creates a publication quality table which is aesthetically pleasing. There are numerous packages which provide this functionality (e.g. BCEA, Darthpack, Heemod)

The cost-effectiveness plane is created in a similar process, using the renderPlot function to continuously update a plot which is created using baseR plot function using ICERs calculated from the results dataframe df_model_res . For aesthetic purposes we recommend this is replaced by a ggplot plot which has much improved functionality.

```
#
                        Create Server Function
server <- function(input, output){</pre>
                                    # server = function with two inputs
 observeEvent(input$run model,
                                      # when action button pressed ...
              ignoreNULL = F, {
  # Run model wrapper function with the Shiny inputs and store as data-frame
  df_model_res = f_wrapper(c_Trt = input$SI_c_Trt,
                           n_age_init = input$SI_n_age_init,
                           n_sim = input$SI_n_sim)
    #--- CREATE COST EFFECTIVENESS PLANE ---#
    output$SO_icer_table <- renderTable({ # this continuously updates table
      df_res_table <- data.frame( # create dataframe</pre>
        Option = c("Treatment", "No Treatment"),
        QALYs = c(mean(df_model_res$QALY_Trt), mean(df_model_res$QALY_NoTrt)),
        Costs = c(mean(df_model_res$Cost_Trt), mean(df_model_res$Cost_NoTrt)),
        Inc.QALYs = c(mean(df model res$QALY Trt) - mean(df model res$QALY NoTrt), NA),
        Inc.Costs = c(mean(df_model_res$Cost_Trt) - mean(df_model_res$Cost_NoTrt), NA),
        ICER = c(mean(df_model_res$ICER),NA)
      )
      # round the dataframe to two digits so looks tidier
      df_res_table[,2:6] <- round(df_res_table[,2:6],digits = 2)</pre>
      #print the dataframe
      df_res_table
      }) # table plot end.
```

```
#--- CREATE COST EFFECTIVENESS PLANE ---#
   output$SO_CE_plane <- renderPlot({ # render plot repeatedly updates.
     # calculate incremental costs and galys from results dataframe
     df model res$inc C <- df model res$Cost Trt - df model res$Cost NoTrt
     df_model_res$inc_Q <- df_model_res$QALY_Trt - df_model_res$QALY_NoTrt
     # create cost effectiveness plane plot
     plot(x = df_model_res$inc_Q, # x axis incremental QALYS
          y = df_model_res$inc_C, # y axis incremental Costs
          #label axes
          xlab = "Incremental QALYs",
          ylab = "Incremental Costs",
          # set xlimits and ylimits for plot.
          xlim = c(min(df_model_res$inc_Q,df_model_res$inc_Q*-1),
                   max(df_model_res$inc_Q,df_model_res$inc_Q*-1)),
          ylim = c(min(df_model_res$inc_C,df_model_res$inc_C*-1),
                   max(df_model_res$inc_C,df_model_res$inc_C*-1)),
          # include y and y axis lines.
          abline(h = 0, v=0)
         ) # plot end
   }) # renderplot end
}) # Observe Event End
 } # Server end
```

Running the app

The app can be run within the R file using the function *shinyApp* which depends on the *ui* and *server* which have been created and described above. Running this creates a shiny application in the local environment (e.g. your desktop). In order to deploy the application onto the web the app needs to be *published* using the publish button in the top right corner of the R-file in RStudio (next to run-app).

```
## ---- run app-----
shinyApp(ui, server)
```

Discussion

With the movement to make economic models more transparent and reproducible gaining traction, the shift to the use of script based models written in programming languages seems inevitable. This move will be gradual, but will nevertheless require upskilling of health economists used to working in excel through short courses, and the introduction of new courses at universities. It is our opinion that these new courses should include some instruction on the creation of user interfaces and web applications for script based economic models. Since the most predominant script based programming environment in health economics is currently R, we recommend including a tutorial in R-Shiny within these courses.

As demonstrated in this tutorial, creating a web application for an economic model created in R programming environment is relatively straightforward. The authors' experience of creating these web apps has led us to

the conclusion that the most efficient method is to work iteratively, first ensuring that the model is working as intended before making small incremental changes to the UI and server one item at a time. While experienced programmers can make substantial time savings by combining multiple steps we have found that the time taken to correct mistakes far outweighs the time savings associated with combining steps.

From our experience in working with stakeholders from a variety of sectors, there is still a concern about the process of deploying code and data to an external server. While providers such as ShinyIO provide assurances of SSR encryption and user authentication clients with particularly sensitive data may still have concerns. This problem can be avoided in two ways: firstly if clients have their own server and the ability to deploy applications they can maintain control of all data and code, and secondly the application could simply not be deployed, and instead simply created during a meeting using code and data shared in a zip file.

The movement towards script based health economic models with web based user interfaces is particularly useful in situations where a general model structure has been created with a variety of stakeholders in mind, each of which may have different input parameters and wish to conduct sensitivity analysis specific to their decision. For example the World Health Organisation Department of Sexual and Reproductive Health and Research recently embedded a shiny application into their website. The application runs a heemod model in R in an external server, and allows users to select their country and change country specific input parameters, run the model and display results. The process of engagement, the ability to 'play' with the model and test the extremes of the decision makers' assumptions gives stakeholders more control over models, making them feel less like black boxes, and provides some engagement with the process. While there is a danger that a mis-informed stakeholder may make a mistake in their choice of parameter, we should remember that the role of the model is to inform decision-makers not instruct them . . . and besides: it is simple to limit the range that parameter inputs can take.

Conclusion

The aim of this tutorial was to provide a useful reference for those hoping to create a user interface for a health economic model created in R. It is our hope that more health economic models will be created open source, and open access so that other economists can critique, learn from and adapt these models. The creation of user interfaces for these apps should improve transparency further, allowing stakeholders and third parties to conduct their own sensitivity analysis. The future is bright, maybe even shiny.

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