**What is it about?**

The story behind this app comes from a real application inside departments evaluating clinical studies in diagnostics.

Due to fast recruiting for clinical studies the patient cohorts seemed to be inhomogenic. Therefore a researcher and a clinical study statistician wanted to find out, by which parameter they can find patients, that do not seem to fit their desired class. Maybe there was a mistake in the labeling of a patient’s disease status? Maybe one measurement or two measurements can be used to easily find such patients?

The example data used here is real data from a 1990’s study, known as the biopsy data set, [also hosted on UCI ML data repository](https://archive.ics.uci.edu/ml/datasets/breast+cancer+wisconsin+(original)). The app that should be build inside this tutorial is preliminary and was especially build for the tutorial. Pieces of it were applied in real world biostatistical applications.

**Starting point**

Please run the installation of dependencies in your R session:

install.packages(c("ape","dplyr","magrittr","igraph","viridisLite","MASS","shiny"))

if you have all the packages installed you will have one file to work on. This file is app.R. This app.R allows you to build a shiny application.

This file we will use to insert the right visualizations and the right table for the researcher to fullfil the task named above. To check what the app will finally look like you can already perform runApp() inside the console and your browser will open the app.

The app already contains:

A sideBarPanel that has all the inputs we need

* Slider for the # of patients
* Slider for the # of desired clusters/groups
* Empty input to choose measurements — shall be done by you
* Dropdown field for the clustering method

A server function that will provide

1. The empty input to choose measurments
2. A Heatmap to see the outcome of clustering
3. A Phylogenetic tree plot to see the outcome of clustering
4. A table to see the outcome of the clustering

It already contains a function to provide you with the input data sets biopsy and biopsy\_numeric(), as biopsy\_numeric.

In this tutorial we will go through steps 1–4 to enable building the app

**The input data set**

The patients inside the data set were obtained from the University of Wisconsin Hospitals, Madison from Dr. William H. Wolberg. [He assessed biopsies of breast tumours for 699 patients](http://rexa.info/paper/781d2581b297dad058cf6f1be2a009144b5306fb) up to 15 July 1992; each of nine attributes has been scored on a scale of 1 to 10, and the outcome is also known. There are 699 rows and 11 columns.

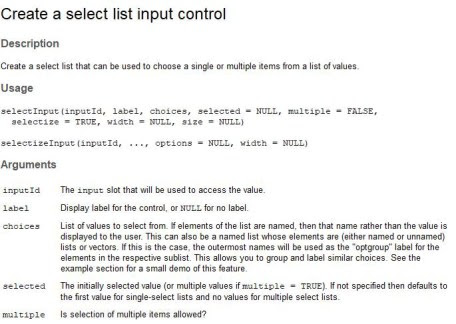
The data set can be called by the variable biopsy inside the app. The columns 2-10 were stored inside the reactive biopsy\_numeric() which is filtered by the input$patients input to not use all 699 patients, but between 1 and 100.

**1) Construction of a SelectInput**

The SelectInput shall allow the user to not use all 9 measured variables, but just the ones he desires. This shall help finding the measurement, that is necessary to classify patients. What is a shiny selectInput? We can therefore look at the description of the selectInput by

?shiny::selectInput

and see



We now need to build the choices as the column names of the biopsy data set from 2-10. the selected input will be the same. We shall allow multiple inputs, so multiple will be set to TRUE. Additionally we shall name the inputId "vars". So we can replace the part output$variables inside the app.R file with this:

output$variables <- renderUI({  
 selectInput(inputId="vars",   
 label = "Variables to use",   
 choices = names(biopsy)[2:10],  
 multiple = TRUE,  
 selected = names(biopsy)[2:10]  
 )  
 })

And you’re done.

**2) A Heatmap to see the outcome of clustering**

The basic heatmap function allows you to draw a heat map. In this case we would like to change a few things. We would like to change the clustering method inside the hclust function to a method defined by the user. We can grab the user defined method by using input$method as we already defined this input field as a drop down menu. We have to overwrite the default hclust method with our method by:

my\_hclust <- function(...){  
 hclust(method=my\_method,...)  
 }  
 my\_method <<- input$method

Be aware that you define a global variable my\_method here, which suffices within the scope of this tutorial. However, please keep in mind that global variables can be problematic in many other contexts and do your own research what best fits your application.

Now for the heatmap call we basically need to change a few inputs. Please see the result:

heatmap(x = t(as.matrix(biopsy\_numeric())), Rowv=NA, hclustfun=my\_hclust,  
 labCol =biopsy$"disease status",  
 col=viridis(15)  
 )

We need to transform the biopsy\_numeric matrix, as we would like to have the patients in columns. As there is just a one dimensional clustering, we can switch of row labels by setting Rowv to NA. The hclustfun is overwritten by our function my\_hclust.

For coloring of the plot we use the viridis palette as it is a color blind friendly palette. And the labels of our columns shall now not only the patient IDs but the disease status. You can see the names of all columns we defined in the file R/utils.R. There you see that the last column of biopsy is called "disease status". This will be used to label each patient. Now we got:

output$plot1 <- renderPlot({  
 my\_hclust <- function(...){  
 hclust(method=my\_method,...)  
 }  
 my\_method <<- input$method  
 heatmap(x = t(as.matrix(biopsy\_numeric())), Rowv=NA, hclustfun=my\_hclust,  
 labCol =biopsy$"disease status",  
 col=viridis(15)  
 )  
 })

Part 2 is done

**3) Plot a phylogenetic tree**

To allow plotting a phylogenetic tree we provided you with a function called phyltree. You can read the whole code of the function inside R/utils.R. This function takes as inputs

* a numeric matrix > biopsy\_numeric() CHECK
* The clustering method > input$method CHECK
* The number of clusters > input$nc CHECK
* A color function > viridis CHECK

The hard part are now the labels. The biopsy\_numeric data set is filtered by the # of patients. Therefore we have to filter the labels, too. Therefore we use

labels = biopsy %>% dplyr::select("disease status") %>%   
 filter(row\_number() <= input$patients) %>%   
 mutate\_all(as.character) %>%   
 pull("disease status")

This is a workflow using functional programming with the R-package dplyr. The function select allows us to just select the "disease status". The filter function filters the number of rows. The mutate\_all function applies the as.character function to all columns and finally we export the labels as a vector by using pull.

* labels for the tree nodes > biopsy %>% … CHECK

The final result looks like this

output$plot2 <- renderPlot({  
 phyltree( x = biopsy\_numeric(),  
 method = input$method,  
 nc = input$nc,  
 color\_func = "viridis",  
 labels = biopsy %>% dplyr::select("disease status") %>%   
 filter(row\_number() <= input$patients) %>%   
 mutate\_all(as.character)%>%   
 pull("disease status")  
 )  
 })

**4) Create a table from clustering results**

Now we would also like to see for each patient in which cluster she was assigned. Therefore we perform the clustering and tree cutting on our own:

clust <- hclust(dist(biopsy\_numeric()), method = input$method)  
cluster\_assigment = cutree(clust, k = input$nc) #cluster assignement

The cluster\_assignment is now a vector with numbers for the clusters for each patient such as c(1,2,1,1,1,2,2,1,…). This information can be helpful if we combine it with the patientID and the disease status that was named in the patients forms.

The task will be performed using the cbind function of R:

out\_table <- cbind(  
 cluster\_assigment,  
 biopsy %>% filter(row\_number() <= length(cluster\_assigment)) %>% select(c(1,11))  
 )# cbind

Now this table shall be sorted by the cluster\_assigment to get a faster view on which patients landed in the wrong cluster.

out\_table %>% arrange(cluster\_assigment)

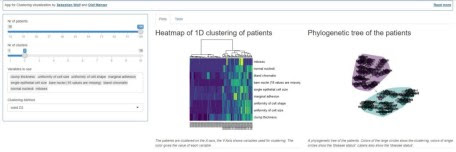
The final code:

output$cluster\_table <- renderTable({  
   
 # --------- perform clustering ----------------  
   
 # Clustering via Hierarchical Clustering  
 clust <- hclust(dist(biopsy\_numeric()), method = input$method)  
 cluster\_assigment = cutree(clust, k = input$nc) #cluster assignement  
   
 # Create a table with the clusters, Patient IDs and Disease status  
 out\_table <- cbind(  
 cluster\_assigment,  
 biopsy %>% filter(row\_number() <= length(cluster\_assigment)) %>% select(c(1,11))  
 )# cbind  
 # Order by cluster\_assigment  
 out\_table %>% arrange(cluster\_assigment)  
 }  
   
)

Done

**What to do now?**

Now you can run the runApp() function.



If you choose 100 patients, 2 clusters, “ward.D2” clustering and all variables you will see pretty fast, that the patients:

* 1002945
* 1016277
* 1018099
* 1096800

could be identified as the patients that were clustered wrong. Now you can go search for problems in clustering or look at the sheets of those patients. By changing the labeling e.g. using PatientIDs inside the phyltree function call, you can even check which other patients show close measurements to these patients. **Explore and play!**