The University of Texas Rio Grande Valley

School of Mathematical and Statistical Science

Statistical Learning (MATH 6392)

Case Study 1

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1. Introduction

Tinnitus is a conscious awareness of a sound in the ears or head that is not due to an external noise. People who experience this symptom described the noise as a roaring, buzzing, hissing or whizzing noise. Tinnitus affect 10-15% of the world's population; and is especially common in people over age 55 as well as it is associated with hearing loss [1]. A significant number of people who experience tinnitus symptoms do become severely distressed by the sounds as it significantly affect quality of life. Unfortunately, there is no cure for chronic tinnitus, but there are several ways to help tune out the noise and minimize its impact. The aim of this study is to investigate the outcome of a new treatment for Tinnitus and its influence on the person's quality of life.

2. Literature Review

Causes

A common cause of tinnitus is inner ear hair cell damage. Tiny, delicate hairs in your inner ear move in relation to the pressure of sound waves. This triggers cells to release an electrical signal through a nerve from your ear (auditory nerve) to your brain. Your brain interprets these signals as sound. If the hairs inside your inner ear are bent or broken, they can "leak" random electrical impulses to your brain, causing tinnitus [2].

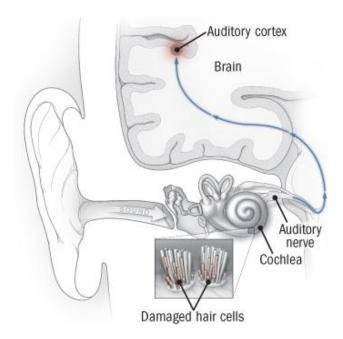


Fig. 1 Sound waves travel through the ear canal to the middle and inner ear, where hair cells in part of the cochlea help transform sound waves into electrical signals that then travel to the brain's auditory cortex via the auditory nerve. When hair cells are damaged — by loud noise or ototoxic drugs, for example — the circuits in the brain don't receive the signals they're expecting. This stimulates abnormal activity in the neurons, which results in the illusion of sound, or tinnitus. [1]

Risk factors and complications

Anyone can experience tinnitus, but some factors may increase your risk of experiencing it. For example:

- Loud noise exposure. Prolonged exposure to loud noise can damage the hair cells in your ear. People who work in noisy environments, like factories, or construction workers, musicians, and soldiers are particularly at risk.
- Age. The number of functioning nerve fibers in your ears decline as you age.
- Sex. Men are more likely to experience tinnitus.
- Smoking. Smokers have higher risk of developing tinnitus.
- Cardiovascular problems. Conditions that affect blood flow, such as blood pressure or narrowed arteries.

Although, tinnitus can affect people in different ways, the most common side effects or complications include fatigue, stress, sleep problems, trouble concentrating, memory problems, depression, anxiety and irritability.

Because of these complications, several studies have been done and found out a strong association between hearing loss (which is a strong predictor of tinnitus) and mental illnesses [3].

Preventions

In many cases, tinnitus is the result that something that can't be prevented. However, some precautions can help prevent certain kind of tinnitus. For example, using hearing protection equipment (especially if working in a industry that uses loud machinery or firearms), turn down the volume (especially if exposed to amplified music or thought headphones), and taking care of your cardiovascular health, as healthy blood vessels can prevent tinnitus linked to blood vessels disorders [2].

Treatment

There is currently no scientifically proven cure for chronic tinnitus. The search for a definitive cure is ongoing and real progress is being made, but there is currently no clinically proven way to fully eliminate the perception of tinnitus [4]. In fact the most effective approaches are behavioral strategies and sound-generating devices, often used in combination. [1]

There are, however, excellent tools to help patients manage their condition; treatments that reduce the perceived intensity, omnipresence, and burden of tinnitus. These currently available treatments are not "cures", they neither repair the underlying causes of tinnitus, nor eliminate the tinnitus signal in the brain. Instead, they address the attentional, emotional, and cognitive impact of tinnitus. They help patients live better, more fulfilling, and more productive lives, even if the perception of tinnitus remains [4].

The treatments that are available, however, receive a lot of criticism, because of the different methods used to assess patients. The challenge medical practitioners faced when assessing the effectiveness of treatments is very straightforward: how can you accurately assess a patient response to a treatment if the symptoms are mostly based on the patient's perception.

The most effective tinnitus treatment tools address the aspects of tinnitus that so often make the condition feel burdensome: anxiety, stress, social isolation, sound sensitivity, hearing difficulties, and perceived volume.

One of the most used treatments approaches include the use of surveys with questions relating to hearing, attitude, emotion and sleep to gauge the severity, or perceived level of distress from their tinnitus. These questionnaires contain a series of questions from which patients select a response from the given choices which is usually recorded as a grade scale. In this way the severity of the tinnitus is graded. However, some questionnaires were not designed to measure the effectiveness of tinnitus interventions and treatments.

Most recently, in 2012, a group of researchers from the Oregon Health and Science University proposed a new self-report type of questionnaire called the Tinnitus Functional Index (TFI) which scales the severity and negative impact of tinnitus. This new questionnaire emphasizes on the effect sizes, content validly and response scaling which enables the detection of changes in condition of the patients during treatment [5].

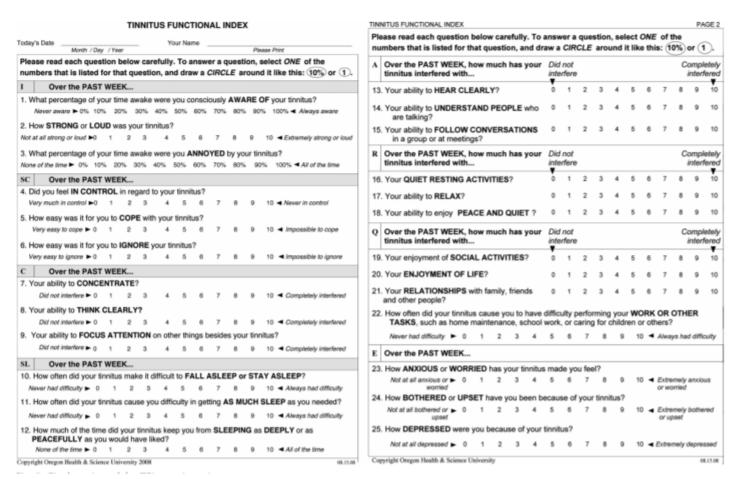


Fig. 2 Final version of the TFI questionnaire proposed by a group of researches from the Oregon Health and Science University in 2012.

3. Methods and Analysis

In this case study we will investigate the effectiveness of an internet based cognitive behavioral therapy (referred as the *Treatment* in the data set) intervention which has been developed in UK to improve the access to evidence-based tinnitus treatment. The Tinnitus Functional Index (**TFI_Scores**) has been used as the primary assessment measure to quantify tinnitus distress prior and after the treatment. We will be performing a Multiple Linear Regression and a KNN Regression Analysis on a dataset ("CaseStudy1.csv)" containing the **pre** and **post TFI_Scores**, and clinical and demographic factors related to a pre-post interventional study of 142 subjects with tinnitus. For the computations we will be using R. The specific column details of the data set are the following:

Column	Name	Description
A	Subject_ID	Subject ID of the participant
В	Group	Subject's Treatment / Control group details
С	HHI_Score	Hearing survey- overall score- 0-40 (higher score more severe)
D	Generalized Anxiety Disorder (GAD)	Anxiety sum: 0-21 (higher score more severe)
E	Patient Health Questionnaire (PHQ)	Depression sum: 0-28 (higher score more severe)
F	Insomnia Severity Index (ISI)	Insomnia total: 0-28 (higher score more severe)
G	Satisfaction with Life Scales (SWLS)	Overall score, satisfaction with life, like Quality of Life (QOF). Higher scores BETTER QOL (opposite to all other scales)
H	Hyperacusis	0-42 (higher score more severe)
I	Cognitive failures (CFQ)	0-100 (higher score more severe)
J	Gender	1-Male, 2-Female
K	Age	In Years
L	Duration_of_tinnitus	In Years
M	Pre_TFI_Score	TFI score at the beginning of the study: Tinnitus score out of 100, higher more severe
N	Post_TFI_Score	TFI score after the completion of the study: Tinnitus score out of 100, higher more severe (TFI)

Table 1. Complete list of variables for the data set "CaseStudy1.csv"

We begin our analysis by looking at the data gathered. From the 142 surveyed patients, 73 were in the control group and 69 were in the treatment group. Also, 80 identified themselves as males and 62 as females.



Fig. 3 Pie charts for Control vs Treatment and Male vs Female

In Fig. 4, we can observe the different values of TFI: before treatment (left plot), after treatment (middle) and the difference between the two (right plot). These graphs were obtained after the initial data cleaning. The dataset was missing 86 values from the **Post_TFI_Score** predictor and to fix this situation we proceed to a data imputation with mean. Also, the variable **TFI_Reduction** was created and added to the dataset to serve as the variable response for the upcoming analysis.

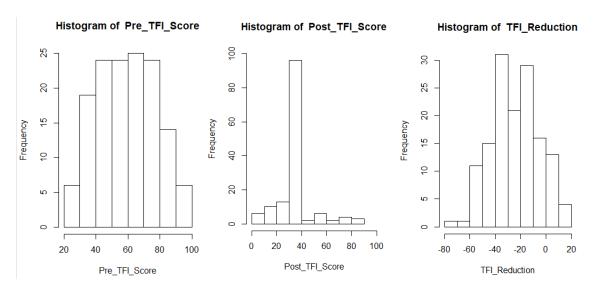


Fig. 4. Perceibable values of TFI from patients before treatment, after treatment and their difference.

Multiple Regression Analysis

To proceed with the Multiple Regression Analysis mix the dataset, remove the **Pre_TFI_Score**, **Post_TFI_Score** and **Subject_ID** predictors from the analysis and partition the dataset using the caret package. The partition of the data splits the 142 observation into two subgroups randomly. One group of observations represent the 80% and it represents the training set. The remaining 20% becomes the subgroup called the testing set.

We perform the Multiple Linear Regression Analysis on the training set (80% observations) using variables B,C,D,E,F,G,H,I,J,K,L as the predictors (see Table.1) and **TFI_Reduction** as the response to the model. We obtain the following coefficient results:

```
lm(formula = TFI_Reduction ~ . - Subject_ID, data = train.data)
Coefficients:
                 (Intercept)
                                             GroupTreatment
                                                                                  HHI Score
                                                                                                                                                   0.0283
                     -20.6238
                                                     -0.8862
                                                                                    -0.1115
                                                                                                                    -0.7691
                                                                                Hyperacusis
                                                                                                                                                    Gender
                          ISI
                                                        SWLS
                                                                                                                       CFO
                      -0.8050
                                                      0.3100
                                                                                    -0.0917
                                                                                                                     0.0306
                                                                                                                                                    2.7897
                               Duration_of_tinnitus.years.
                          Age
                      0.1078
                                                     -0.0867
```

Table 2 Coefficients for the Multiple Linear Regression Analysis.

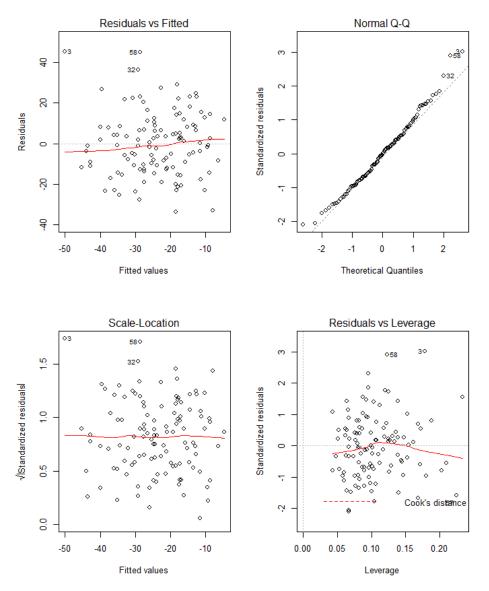


Fig. 5. Plots of Residuals vs Fitted (or predicted) values (top and bottom left) show little pattern in the residuals, which is ideally what we want for the linear model. The linearity of the normal Q-Q plot (top right) suggests the data is normally distributed. Observation 3 seems to be a high leverage point. In the Residual vs Leverage (bottom right) plot we see observation 3 and 58 are three standard deviations away from the mean.

We will leave observations 3 and 58 in our analysis since they are a natural part of the population we are studying. The observations are well within the range of each individual's predictor's values, but they are an unusual combination in term of the full set of predictors. Ideally, we would have to perform a series of analysis on the impact of the outliners (leverage statistic) to figure out the true impact on the least square fit.

We will now use an alternative model to least square fit, because our dataset contains p=10 predictors. A model with a high number of variables might include irrelevant predictors which can lead to a needlessly complex model. The purpose of using another fitting procedure is to yield a better prediction accuracy and model interpretability [6].

Forward and Backward Selection

The analysis of forward and backward selections yield the same result. The best model for both approaches contain predictors **ISI**, **GAD** and **SWLS** which represent the factors that highly influence the reduction in TFI_Score. In mathematical terms, the predicted response, \hat{y} (or **TFI_Response**) that best fits the model according to forward and backward selection is:

$$\widehat{\mathbf{y}} = \widehat{\beta_0} + \widehat{\beta_1}(\mathbf{ISI}) + \widehat{\beta_2}(\mathbf{GAD}) + \widehat{\beta_3}(\mathbf{SWLS})$$
 (1)

Where $\widehat{\beta_0}$ is the predicted y-intercept of the model, $\widehat{\beta_1}$ is the predicted coefficient of **ISI**, $\widehat{\beta_2}$ is the predicted coefficient of **SWLS**.

Model Summary									
R	0.507	RMSE	16.172						
R-Squared	0.257	Coef. Var	-68.145						
Adj. R-Squared	0.237	MSE	261.545						
Pred R-Squared	0.201	MAE	12.862						
DUCE: Doot Moon Co									

RMSE: Root Mean Square Error MSE: Mean Square Error MAE: Mean Absolute Error

Parameter Estimates

model	Beta	Std. Error	Std. Beta	t	Sig	lower	upper
(Intercept) ISI GAD SWLS	-16.070 -0.773 -0.826 0.401	5.961 0.238 0.322 0.211	-0.295 -0.234 0.161	-2.696 -3.252 -2.562 1.906	0.008 0.002 0.012 0.059	-27.884 -1.244 -1.465 -0.016	-4.257 -0.302 -0.187 0.819

Table 3 Model Summary and Parameter Estimates of Forward and Backward Selection alike. Both methods yielded the same results.

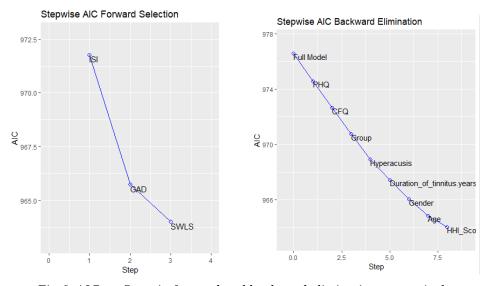


Fig.6 AIC vs. Steps in forward and backward elimination respectively.

Now, that we know which are the predictors that highly influence the reduction in **TFI_Score**, we perform and linear regression analysis considering only the predictors: **ISI**, **GAD** and **SWLS**.

The summary of the linear regression model and diagnostic graphs are shown below.

```
call:
lm(formula = TFI_Reduction ~ ISI + GAD + SWLS, data = train.data)
Residuals:
                         3Q
   Min
           1Q Median
                                Max
-33.18 -11.58
               -0.66
                        9.49
                              40.91
Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)
             -16.070
                           5.961
                                   -2.70
                                           0.0081
                                   -3.25
                                           0.0015
ISI
              -0.773
                           0.238
              -0.826
                           0.322
                                   -2.56
                                           0.0117
GAD
SWLS
               0.401
                           0.211
                                    1.91
                                           0.0592
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Residual standard error: 16.2 on 110 degrees of freedom
Multiple R-squared: 0.257,
                                 Adjusted R-squared:
F-statistic: 12.7 on 3 and 110 DF, p-value: 0.000000348
```

Table 4. Summary of the linear regression including ISI,GAD and SWLS as the only predictors and TFI_Score as the response; p-values (below 0.05) show high correlation between predictors and response.

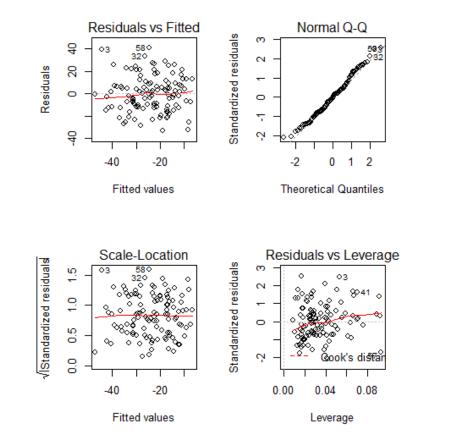


Fig. 7. Graphs show a very similar outcome as the graphs from Fig. 5.

Then, we make predictions on the test dataset (20% observations) to compare how accurate was the proposed model that we found using the training dataset (80% observations). To compare both models we run a Mean Square Error (MSE) calculations on both datasets.

Multiple Linear Regression MSE:

$$MSE_{training} = 252.4$$

 $MSE_{testing} = 256$

K- Mean Regression

We will now perform a K-Mean Regression analysis using the *caret* package in R. For the analysis, we first perform the training of the model by using the same training dataset (80%) that we used for the Multiple Regression Analysis. The predictors used for this analysis included C,D,E,F,G,H,I,J,K,L (Table.1) and **TFI_Reduction** for the response.

We run a KNN regression analysis for different values of k, which represent the number of nearest neighbor's labels used to assign a label to the current point. We perform the analysis for k = 2,4,6,8,10.

The K-nearest neighbors analysis tells us that for our particular sample, k = 6 results in the lowest RMSE (Root Mean Square Error), so we will use this to run a prediction on the testing dataset.

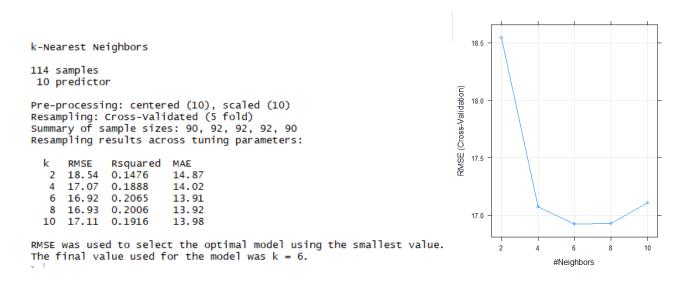


Fig. 8. KNN analysis for k values of 2,4,6,8,10. Graph shows that k=6 and k=8 have pretty much the same RMSE. Summary (left) shows that RMSE for k=6 is 16.92 and RMSE for k=8 is 16.93.

We run the prediction on the testing dataset (20%) and calculate the MSE for the training and testing dataset.

K-Nearest Neighbors MSE:

$$MSE_{training} = 286.4$$

 $MSE_{testing} = 306.2$

4. Conclusion

On the basis of the findings, several conclusions concerning the interaction between a reduction in TFI and some quality life indicators can be drawn. The findings of this study suggest that the Multiple Regression Analysis results in a more accurate model than the KNN Regression Analysis by comparing both model's MSE. The results of the Multiple Regression Analysis indicate strong correlation of three particular variables with the reduction of TFI. These variables are the Insomnia Severity Index (ISM), the Generalized Anxiety Disorder (GAD), and the Satisfaction with Life Scales (SWLS). The study suggest than by focusing in therapies and treatments for variables mentioned above will translate in a reduction of TFI and a better quality of life for the patient.

5. Appendix

Appendix A. References

- [1] Harvard Health Publishing Harvard Medical School. (2020, April 8). *Tinnitus: Ringing in the ears and what to do about it.* Retrieved June 29, 2020, from https://www.health.harvard.edu/diseases-and-conditions/tinnitus-ringing-in-the-ears-and-what-to-do-about-it
- [2] Mayo Foundation for Medical Education and Research (MFMER). (n.d.). *Tinnitus*. Retrieved June 29th, 2020, from https://www.mayoclinic.org/diseases-conditions/tinnitus/symptoms-causes/syc-20350156
- [3] Adeyi A. Adoga and Taiwo J. Obindo (January 16th 2013). *The Association Between Tinnitus and Mental Illnesses*, Mental Disorders Theoretical and Empirical Perspectives, Robert Woolfolk and Lesley Allen, IntechOpen, DOI: 10.5772/52755. Available from: https://www.intechopen.com/books/mental-disorders-theoretical-and-empirical-perspectives/the-association-between-tinnitus-and-mental-illnesses
- [4] American Tinnitus Association. (n.d.). *Managing your tinnitus*. Retrieved June 29th, 2020, from https://www.ata.org/managing-your-tinnitus/treatment-options
- [5] Meikle MB, Stewart BJ, Griest SE, Henry JA.Tinnitus Outcomes Assessments, Trends, Amplif..2008; 12: 223-235.
- [6] G. James et al., An Introduction to Statistical Learning: with Applications in R, Springer Texts in Statistics, DOI 10.1007/978-1-4614-7138-7, Springer Science+Business Media New York 2013.

Appendix B. Code

```
# clear plots
if(!is.null(dev.list())) dev.off()
# clear console
cat("\014")
# clean workspace
rm(list=ls())
setwd("C:/Users/Checo/Desktop/Statistical Learning/Case Study")
getwd()
#library(RColorBrewer)
tin.rdata = read.csv("CaseStudy1.csv", header=T)
fix(tin.rdata)
#### Multiple Linear Regression Analysis
## 1 - Descriptive Analysis of the data
# Data cleaning - Combining levels (the categories) in the "Group" predictor
levels(tin.rdata$Group) = c("Control", "Control", "Treatment")
# Pie chart
pie.GROUP = pie(table(tin.rdata$Group), labels=c('Control', 'Treatment'))
pie.GENDER = pie(table(tin.rdata$Gender), labels=c('Male','Female'))
#Histograms
hist.GROUP= plot(as.factor(tin.rdata$Group), xlab = names(tin.rdata)[2], main =
paste("Histogram of ", names(tin.rdata)[2]), ylim=c(0,80) )
hist.HHI = hist(as.numeric(tin.rdata[,3]), xlab = names(tin.rdata)[3], main =
paste("Histogram of ", names(tin.rdata)[3]) )
hist.GAD = hist(as.numeric(tin.rdata[,4]), xlab = names(tin.rdata)[4], main =
paste("Histogram of ", names(tin.rdata)[4]) )
hist.PHQ= hist(as.numeric(tin.rdata[,5]), xlab = names(tin.rdata)[5], main =
paste("Histogram of ", names(tin.rdata)[5]), ylim=c(0,60))
hist.ISI= hist(as.numeric(tin.rdata[,6]), xlab = names(tin.rdata)[6], main =
paste("Histogram of ", names(tin.rdata)[6]))
hist.SWLS= hist(as.numeric(tin.rdata[,7]), xlab = names(tin.rdata)[7], main =
paste("Histogram of ", names(tin.rdata)[7]), ylim=c(0,40))
hist.HYP= hist(as.numeric(tin.rdata[,8]), xlab = names(tin.rdata)[8], main =
paste("Histogram of ", names(tin.rdata)[8]), ylim=c(0,40))
hist.CFQ= hist(as.numeric(tin.rdata[,9]), xlab = names(tin.rdata)[9], main =
paste("Histogram of ", names(tin.rdata)[9]), ylim=c(0,40))
hist.GENDER= plot(as.factor(tin.rdata$Gender),xlab =
paste(names(tin.rdata)[10],"(1 = Man , 2 = Female)"), main = paste("Histogram
of ", names (tin.rdata) [10]) )
hist.AGE= hist(as.numeric(tin.rdata[,11]), xlab = names(tin.rdata)[11], main =
paste("Histogram of ", names(tin.rdata)[11]), ylim=c(0,35))
hist.DURATION= hist(as.numeric(tin.rdata[,12]), xlab = names(tin.rdata)[12],
main = paste("Histogram of ", names(tin.rdata)[12]))
hist.PRE= hist(as.numeric(tin.rdata[,13]), xlab = names(tin.rdata)[13], main =
paste("Histogram of ", names(tin.rdata)[13]))
#Summary
summary(tin.rdata)
```

```
## 2 - Data cleaning
# Data imputation with mean for Pre and Post TFI scores
tin.rdata$Post TFI Score[is.na(tin.rdata$Post TFI Score)] =
mean(tin.rdata$Post_TFI_Score, na.rm = TRUE)
# Create response variable "TFI Reduction"
TFI_Reduction = tin.rdata$Post_TFI_Score - tin.rdata$Pre_TFI_Score
tin.rdata$TFI Reduction = TFI Reduction
View(tin.rdata)
# Histogram of Post TFI Score and TFI Reduction
hist.POST= hist(as.numeric(tin.rdata[,14]), xlab = names(tin.rdata)[14], main =
paste ("Histogram of ", names (tin.rdata) [14]), ylim=c(0,100), xlim=c(0,100))
hist.RED= hist(as.numeric(tin.rdata[,15]), xlab = names(tin.rdata)[15], main =
paste("Histogram of ", names(tin.rdata)[15]))
par(mfrow=c(1,1))
## 3
# Data imputation for numerical values using mean and data imputation for
categorical values using mode
## 4 - Partition the data set
# Mix Data Set
set.seed(123)
mix.data = runif(nrow(tin.rdata)) # Randomly genertes 142 values
tin.rdata mix = tin.rdata[order(mix.data),]
sset.data1 = subset(tin.rdata mix,select = -c(Pre TFI Score,Post TFI Score))
#Removing Pre and Post TFI variables
#Partition the data set into a trainning set (80%) and test set (20%)
library(caret)
set.seed(123)
train.index =createDataPartition(sset.data1$TFI Reduction, p=.8, list = F,
times=1)
train.data = sset.data1[train.index,]
test.data = sset.data1[-train.index,]
names(sset.data1)
## 5 - Multiple Regression Analysis
# Remove the "Subject ID" indicator column and perform Multiple regression
analysis
data.fit = lm(TFI Reduction ~ . -Subject ID ,data = train.data)
options(scipen="100", digits = "4")
summary(data.fit)
par(mfrow=c(2,2))
plot(data.fit)
# Forward selection model
# Forward Selection (Approach A)
# install.packages("olsrr")
library(olsrr)
fws a.aic = ols step forward aic(data.fit,details=T)
plot(fws a.aic)
```

```
#Forward Selection (Approach B)
# fit.start = lm(TFI Reduction ~ 1 , data = train.data) # Specify Starting
list of coefficients
# fws b = step(fit.start, direction ="forward", scope=formula(data.fit))
# summary(fws b)
# Backward selection model
# Backward selection (Approach A)
bws a.aic = ols step backward aic(data.fit, details=T)
bws a.aic
plot(bws a.aic)
betas = bws a.aic$model$coefficients
betas
# Backward Selection (Approach B)
# bws_b = step(data.fit, direction ="backward")
# summary(bws b)
## 6 - Model diagnostic and correcttion of the model assumptions (if needed)
## 7 - Factors that influence the reduction in TFI
train.response = lm(TFI Reduction ~ ISI+GAD+SWLS , data = train.data )
summary(train.response)
plot(train.response)
summary(influence.measures(train.response))
## 8 - Make predictions on the test data set and calculate the mean square
error
test.response = predict(train.response, newdata = test.data)
test.response
summary(test.response)
plot(test.response)
# Train Model Mean square error
sum((train.data$TFI Reduction - train.response$fitted)^2)/nrow(train.data)
#Test Model Mean Square Error
sum((test.data$TFI Reduction - test.response)^2)/nrow(test.data)
#### K-mean Regression
\#\# 9,10,11,12 - K-mean regression to train several regression models (k=
2, 4, 6, 8, 10)
set.seed(123)
model.knn = train(train.data[,3:12],train.data[,13], method ="knn" ,
                  trControl=trainControl (method="cv", number =5),
                  preProcess = c("center", "scale"),
                  tuneGrid = expand.grid(k=seq(2,10, by =2)))
model.knn
plot (model.knn)
model.knn$bestTune
# Make prediction on the testing data set and find the Mean Square Error
prediction.knn = predict(object=model.knn ,newdata = test.data[,2:12])
prediction.knn
summary(prediction.knn)
if(!is.null(dev.list())) dev.off()
plot(prediction.knn)
```

```
# Calculate RMSE and MSE
library(Metrics)
rmse = model.knn$results$RMSE
rmse.train = min(rmse)
rmse.train
mse.train = (rmse.train)^2
mse.train

rmse.test = rmse(test.data[,13],prediction.knn)
rmse.test
mse.test = (rmse.test)^2
mse.test
```