Data Simulation

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Title: Glycated Albumin and Hemoglobin in Controlling Complications of Infants of Diabetic Mothers During Pregnancy

References:

- Complications in Infants of Diabetic Mothers Related to Glycated Albumin and Hemoglobin Levels
 During Pregnancy. content source: http://www.ncbi.nlm.nih.gov/pubmed/27131880
 (http://www.ncbi.nlm.nih.gov/pubmed/27131880)
- Analysis of the method for conversion between levels of HbA1c and glycated albumin by linear regression analysis using a measurement error model. content source: http://www.ncbi.nlm.nih.gov/pubmed/19380169 (http://www.ncbi.nlm.nih.gov/pubmed/19380169)

Introduction:

Infants of diabetic mothers (IDMs) often have complications associated with maternal hyperglycemia. Glycated Albumin(GA) and Hemoglobin(HbA1c) are usully used as markers in diabetic patients. However, the HbA1c level is affected by an abnormal erythrocyte life span, which may occur in iron deficiency anemia. Pregnant women with diabetes mellitus or gestational diabetes mellitus (GDM) often develop iron deficiency anemia; therefore, HbA1c may be insufficient for assessing glycemic control in these women.

In this project, I simulated a dateset from the paper "Complications in Infants of Diabetic Mothers Related to Glycated Albumin and Hemoglobin Levels During Pregnancy"[1] which suggests to use GA as a marker to control diabeties during pregnancy in order to lower the incidence of compliations ammoun IDMs. In the end, I build a logistic model to predice the probability of having complications given a GA value.

Part1 Data Simulation

1.Data set to simulate:

*Observations: In the research article, Daisuke Sugawara observed 42 infants of diabetics mothers(IDMs) 25 of which have at least 1 complication after birth. 17 of the IDMs has no complications. In order to reduce the bias of simulating a small dataset(less than 50), I decided to simulate a data set that contains 420 observations.

*Attributes There are 10 attributes for each observation in this dataset:

Complications/ Labs	Column name	Туре	probability of having the condition
1.Hypoglycemia	Hypo_glc	Logic: T/F	13/42
2. Respiratory disorder	Resp_dis	Logic: T/F	11/42
3. Hypocalcemia	Hypo_cal	Logic: T/F	9/42
4. Hypervolemia	Hype_vol	Logic: T/F	4/42
5. Hyperbilirubinemia	Hype_bil	Logic: T/F	6/42
6. Myocardial hypertrophy	Hype_myocar	Logic: T/F	17/42
7. Large for date	Large_for_date	Logic: T/F	8/42
8. Glycated albumin	GA	Logic: T/F	NA
HbA1C	HbA1C	Logic: T/F	NA
Complications	complication	Logic: T/F	0.595

2. Creation of the data set and associated code:

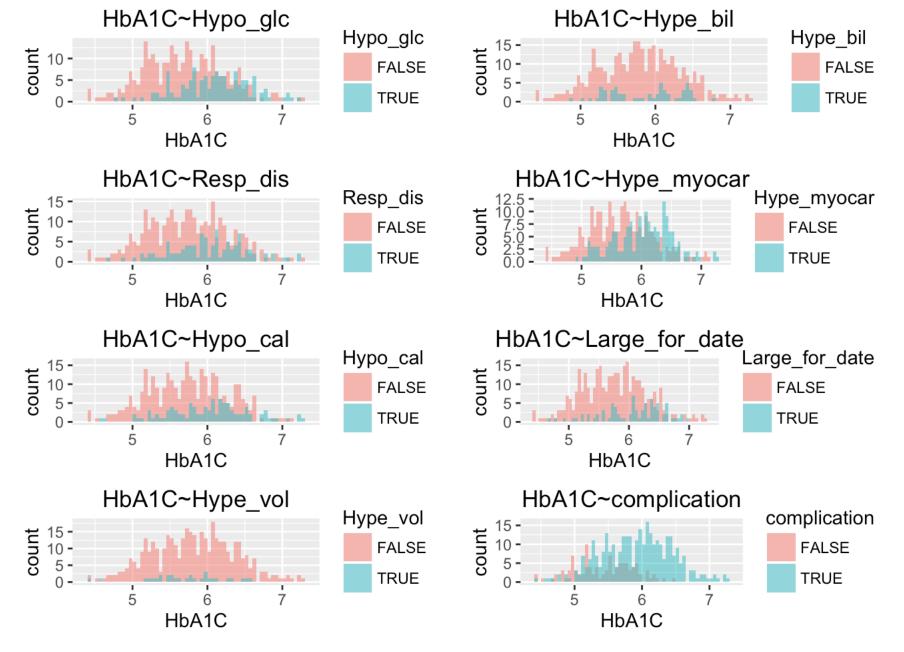
- In the research paper, means and stander deviations(sd) of GA and HbA1C for patients with/without complications are given. However, the mean and sd of GA and HbA1C for all patients are not specified in the paper. So I first created vector 'temp' to hold to classes (Complications, NoComplications). Then use temp to help stimulating the distribution of GA for all patients.
- "Hb temp" is created to help to simulate a temporary Hb vectors for both patients with/without complications. This temporary Hb vector later is used to calculate the mean and sd for all the patients. However, a further research on correlations between HbA1C and GA indicates these 2 variables are strongly correlated (0.747)[2], a linear model using GA to predict HbA1C is HbA(1c)=1.73+0.245GA [2]. I used this model along with the mean and sd calculated from Hb_temp to simulate HbA1C for each patient.
- "Hypo_glc, Resp_dis, Hypo_cal, Hype_vol, Hype_bil, Hype_myocar, Large_for_date" are 7 common complications for IDMs. The paper[1] discovered that GA and HbA1C for mothers of IDMs who have Hype_vol, Hype_bil are not significantly different with those without these 2 conditions.
- "Hypo_glc, Resp_dis, Hypo_cal, Hype_myocar, Large_for_date" are simulated using logistic function with the probability specified(refer to attributes).
- "Hype_vol, Hype_bil" are simulated randomly with the probability specified(refer to attributes).

```
##############################
set.seed(123)
logistic \leftarrow function(t) 1 / (1 + exp(-t))
generate dataset <- function(N){</pre>
  temp <- sample(c("Complication", "NoComplication"), N, replace=TRUE, prob=c(0.595,</pre>
0.415))
  GA_mean <- c(Complication= 15.3, NoComplication = 13.3)
  GA sd <- c(Complication = 1.6, NoComplication = 1.1)
  GA <- rnorm(N, mean = GA mean[temp], sd = GA sd[temp])</pre>
  Hb temp mean <- c(Complication = 5.9, NoComplication = 5.6)
  Hb temp sd < c(Complication = 0.3, NoComplication = 0.4)
  Hb temp <- rnorm(N, mean = Hb temp mean[temp], sd = Hb temp sd[temp])</pre>
  HbA1C \leftarrow 0.245 * (GA-mean(GA)) + mean(Hb temp) + rnorm(N, sd = sd(Hb temp))
  Hypo glc \leftarrow runif(N) \leftarrow (13/42)*2*logistic(GA-mean(GA))
  Resp dis \leftarrow runif(N) \leftarrow (11/42)*2*logistic(GA-mean(GA))
  Hypo cal <- runif(N) < (9/42)*2*logistic(GA-mean(GA))
  Hype vol <- sample(c(TRUE, FALSE), N,replace=TRUE, prob=c(4/42, 1-4/42))</pre>
  Hype bil <- sample(c(TRUE, FALSE), N,replace=TRUE, prob=c(6/42, 1-6/42))</pre>
  Hype myocar <- runif(N) < (17/42)*2*logistic(GA-mean(GA))</pre>
  Large for date \leftarrow runif(N) < (8/42)*2*logistic(GA-mean(GA))
  df <- data.frame(Hypo glc,Resp dis,Hypo cal,Hype vol,Hype bil,Hype myocar,Large for</pre>
date)
  df$complication <- ifelse(apply(df[,c(1:7)],1,sum) != 0, TRUE, FALSE)</pre>
  df$GA <- GA
  df$HbA1C <- HbA1C
  return(df)
}
N < -420
mydata <- generate dataset(N)</pre>
```

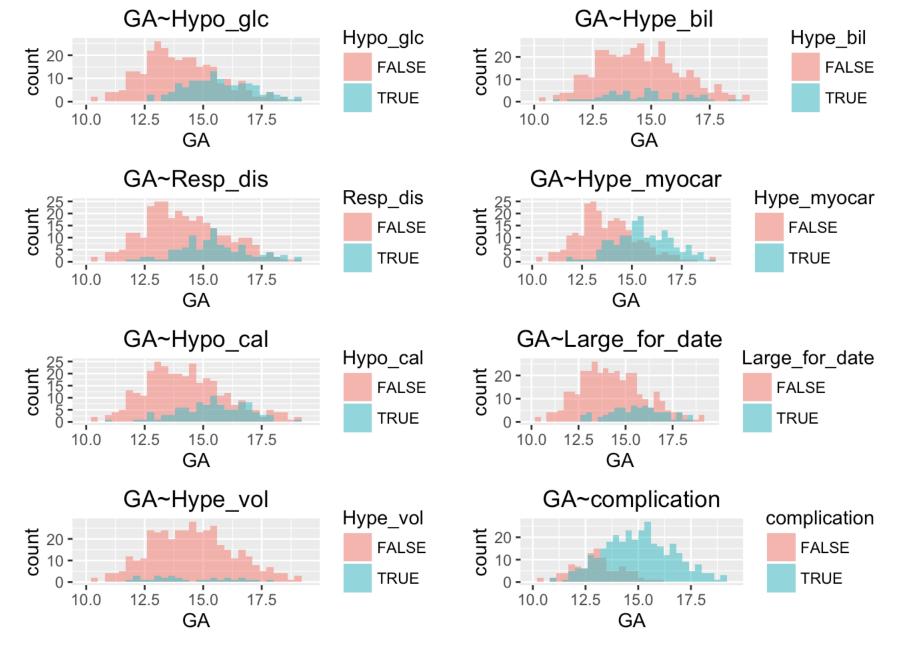
Part2 Data Exploration

1.Distributions of GA and HbA1C for each complication

```
# 3 will go all the way across the bottom.
multiplot <- function(..., plotlist=NULL, file, cols=1, layout=NULL) {
  library(grid)
  # Make a list from the ... arguments and plotlist
  plots <- c(list(...), plotlist)</pre>
  numPlots = length(plots)
  # If layout is NULL, then use 'cols' to determine layout
  if (is.null(layout)) {
    # Make the panel
    # ncol: Number of columns of plots
    # nrow: Number of rows needed, calculated from # of cols
    layout <- matrix(seq(1, cols * ceiling(numPlots/cols)),</pre>
                     ncol = cols, nrow = ceiling(numPlots/cols))
  }
  if (numPlots==1) {
    print(plots[[1]])
    } else {
    # Set up the page
    grid.newpage()
    pushViewport(viewport(layout = grid.layout(nrow(layout), ncol(layout))))
    # Make each plot, in the correct location
    for (i in 1:numPlots) {
      # Get the i, j matrix positions of the regions that contain this subplot
      matchidx <- as.data.frame(which(layout == i, arr.ind = TRUE))</pre>
      print(plots[[i]], vp = viewport(layout.pos.row = matchidx$row,
                                       layout.pos.col = matchidx$col))
    }
  }
}
Hb1 <- ggplot(data = mydata) + geom histogram(aes(x = HbA1C, fill = Hypo glc), binwid
th = 0.05, alpha = 0.5, position = "identity" )+ggtitle('HbA1C~Hypo_glc')
Hb2 <- ggplot(data = mydata) + geom histogram(aes(x = HbA1C, fill = Resp dis), binwid
th = 0.05, alpha = 0.5, position = "identity")+ggtitle('HbA1C~Resp_dis')
Hb3 <- ggplot(data = mydata) + geom_histogram(aes(x = HbA1C, fill = Hypo_cal), binwid</pre>
th = 0.05, alpha = 0.5, position = "identity")+ggtitle('HbA1C~Hypo_cal')
Hb4 <- ggplot(data = mydata) + geom_histogram(aes(x = HbA1C, fill = Hype_vol), binwid</pre>
th = 0.05, alpha = 0.5, position = "identity")+ggtitle('HbA1C~Hype vol')
Hb5 <- ggplot(data = mydata) + geom histogram(aes(x = HbA1C, fill = Hype bil), binwid
th = 0.05, alpha = 0.5, position = "identity")+ggtitle('HbA1C~Hype bil')
Hb6 <- ggplot(data = mydata) + geom_histogram(aes(x = HbA1C, fill = Hype_myocar), bin</pre>
width = 0.05, alpha = 0.5, position = "identity")+ggtitle('HbA1C~Hype myocar')
Hb7 <- ggplot(data = mydata) + geom_histogram(aes(x = HbA1C, fill = Large_for_date),</pre>
binwidth = 0.05, alpha = 0.5, position = "identity")+ggtitle('HbA1C~Large_for_date')
Hb8 <- ggplot(data = mydata) + geom_histogram(aes(x = HbA1C, fill = complication), bi
nwidth = 0.05, alpha = 0.5, position = "identity")+ggtitle('HbA1C~complication')
multiplot(Hb1,Hb2,Hb3,Hb4,Hb5,Hb6,Hb7,Hb8, cols = 2)
```



```
GA1 \leftarrow ggplot(data = mydata) + geom_histogram(aes(x = GA, fill = Hypo glc), binwidth
= 0.3, alpha = 0.5, position = "identity" )+ggtitle('GA~Hypo glc')
GA2 \leftarrow ggplot(data = mydata) + geom histogram(aes(x = GA, fill = Resp dis), binwidth
= 0.3, alpha = 0.5, position = "identity")+ggtitle('GA~Resp dis')
GA3 \leftarrow ggplot(data = mydata) + geom histogram(aes(x = GA, fill = Hypo cal), binwidth
= 0.3, alpha = 0.5, position = "identity")+ggtitle('GA~Hypo_cal')
GA4 \leftarrow ggplot(data = mydata) + geom histogram(aes(x = GA, fill = Hype vol), binwidth
= 0.3, alpha = 0.5, position = "identity")+ggtitle('GA~Hype_vol')
GA5 <- ggplot(data = mydata) + geom_histogram(aes(x = GA, fill = Hype_bil), binwidth
= 0.3, alpha = 0.5, position = "identity")+ggtitle('GA~Hype_bil')
GA6 \leftarrow ggplot(data = mydata) + geom histogram(aes(x = GA, fill = Hype myocar), binwid
th = 0.3, alpha = 0.5, position = "identity")+ggtitle('GA~Hype_myocar')
GA7 \leftarrow ggplot(data = mydata) + geom histogram(aes(x = GA, fill = Large for date), bin
width = 0.3, alpha = 0.5, position = "identity")+ggtitle('GA~Large for date')
GA8 <- ggplot(data = mydata) + geom_histogram(aes(x = GA, fill = complication), binwi
dth = 0.3, alpha = 0.5, position = "identity")+ggtitle('GA~complication')
multiplot(GA1,GA2,GA3,GA4,GA5,GA6,GA7,GA8, cols = 2)
```



- Each plot delivers the stories of the distributions of GA/HbA1C between patients with/without a
 particular complication.
- There are no significant differences of mean and sd of GA/HbA1C for infants with/without Hype_bil and Hype_vol.

2.2-sample T test between case and control for each complication

```
## [1] "======GA~Hypo glc"
##
##
   Welch Two Sample t-test
##
## data: data$GA by data[[col]]
## t = -10.538, df = 269.88, p-value < 2.2e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
  -1.981569 -1.357686
##
## sample estimates:
## mean in group FALSE mean in group TRUE
            14.04067
##
                              15.71030
##
## [1] "=======HbA1C~Hypo glc"
##
##
   Welch Two Sample t-test
##
## data: data$HbA1C by data[[col]]
## t = -7.6515, df = 263.03, p-value = 3.767e-13
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
## -0.5009189 -0.2958736
## sample estimates:
## mean in group FALSE mean in group TRUE
            5.682429
                             6.080826
##
##
======"
## [1] "======GA~Resp dis"
##
##
   Welch Two Sample t-test
##
## data: data$GA by data[[col]]
## t = -6.9277, df = 197.75, p-value = 5.876e-11
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##
  -1.5864138 -0.8833704
## sample estimates:
## mean in group FALSE mean in group TRUE
            14.22990
                             15.46479
##
##
## [1] "=======HbA1C~Resp dis"
##
##
   Welch Two Sample t-test
##
## data: data$HbA1C by data[[col]]
## t = -4.8378, df = 192.74, p-value = 2.681e-06
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
  -0.3912847 -0.1646387
##
```

```
## sample estimates:
## mean in group FALSE mean in group TRUE
           5.731796
##
##
======"
## [1] "======GA~Hypo cal"
##
##
   Welch Two Sample t-test
##
## data: data$GA by data[[col]]
## t = -6.0848, df = 190.03, p-value = 6.302e-09
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
## -1.4390518 -0.7344548
## sample estimates:
## mean in group FALSE mean in group TRUE
##
           14.28281
                           15.36956
##
##
##
   Welch Two Sample t-test
##
## data: data$HbA1C by data[[col]]
## t = -4.4017, df = 160.18, p-value = 1.954e-05
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##
  -0.3959575 -0.1506940
## sample estimates:
## mean in group FALSE mean in group TRUE
##
           5.736871
                           6.010196
##
## [1] "======GA~Hype vol"
##
##
   Welch Two Sample t-test
##
## data: data$GA by data[[col]]
## t = 0.36192, df = 33.582, p-value = 0.7197
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##
  -0.5559425 0.7967276
## sample estimates:
## mean in group FALSE mean in group TRUE
##
           14.55016
##
## [1] "=======HbA1C~Hype vol"
##
##
   Welch Two Sample t-test
```

```
##
## data: data$HbA1C by data[[col]]
## t = 0.99375, df = 34.333, p-value = 0.3273
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
  -0.1005431 0.2931010
##
## sample estimates:
## mean in group FALSE mean in group TRUE
##
           5.808825
                            5.712546
##
======"
## [1] "======GA~Hype bil"
##
##
   Welch Two Sample t-test
##
## data: data$GA by data[[col]]
## t = -1.0004, df = 71.077, p-value = 0.3205
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
  -0.7599918 0.2521702
##
## sample estimates:
## mean in group FALSE mean in group TRUE
##
           14.50831
                            14.76222
##
##
##
   Welch Two Sample t-test
##
## data: data$HbA1C by data[[col]]
## t = -1.0598, df = 77.646, p-value = 0.2925
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
## -0.21467557 0.06552705
## sample estimates:
## mean in group FALSE mean in group TRUE
##
           5.792182
##
======="
## [1] "======GA~Hype myocar"
##
##
  Welch Two Sample t-test
##
## data: data$GA by data[[col]]
## t = -11.903, df = 386.28, p-value < 2.2e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##
  -2.059970 -1.475912
## sample estimates:
```

```
## mean in group FALSE mean in group TRUE
##
          13.81334
                          15.58128
##
##
##
  Welch Two Sample t-test
##
## data:
       data$HbA1C by data[[col]]
## t = -7.7701, df = 394.54, p-value = 6.859e-14
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
## -0.4816397 -0.2871266
## sample estimates:
## mean in group FALSE mean in group TRUE
          5.643619
##
                          6.028002
##
========"
## [1] "======GA~Large for date"
##
##
  Welch Two Sample t-test
##
## data:
       data$GA by data[[col]]
## t = -7.0505, df = 132.09, p-value = 8.958e-11
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
  -1.7094919 -0.9604189
##
## sample estimates:
## mean in group FALSE mean in group TRUE
##
          14.29046
                          15.62542
##
##
##
   Welch Two Sample t-test
##
## data: data$HbA1C by data[[col]]
## t = -4.9143, df = 120.88, p-value = 2.83e-06
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##
  -0.4425054 -0.1883570
## sample estimates:
## mean in group FALSE mean in group TRUE
##
          5.742617
                          6.058048
##
## [1] "=======GA~complication"
##
##
   Welch Two Sample t-test
##
```

```
## data: data$GA by data[[col]]
## t = -13.396, df = 246.85, p-value < 2.2e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##
   -2.248112 -1.671758
## sample estimates:
## mean in group FALSE mean in group TRUE
##
             13.06694
                               15.02688
##
##
##
   Welch Two Sample t-test
##
## data: data$HbA1C by data[[col]]
## t = -9.337, df = 205.58, p-value < 2.2e-16
## alternative hypothesis: true difference in means is not equal to 0
## 95 percent confidence interval:
##
   -0.5885134 - 0.3833073
## sample estimates:
## mean in group FALSE mean in group TRUE
##
             5.436358
                               5.922269
```

• The results of 2 sample t-test justified what we saw from the plots above that Hype_vol and Hype_bil are not significantly different between control and case groups.

3. The linear relation between GA and HbA1C

```
cor(mydata[,c(9,10)])

## GA HbA1C

## GA 1.0000000 0.7577657

## HbA1C 0.7577657 1.0000000
```

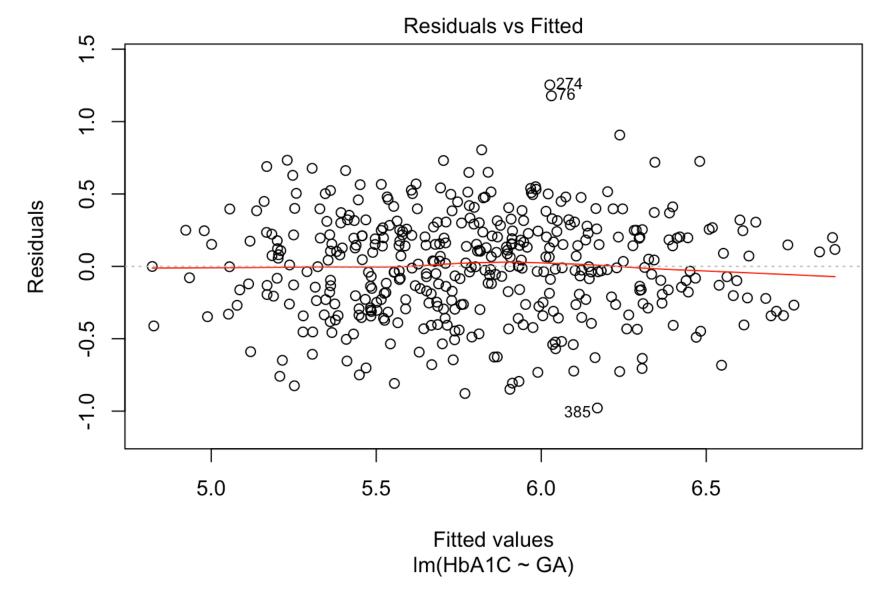
• GA and HbA1C are positively correlated, with a correlation of 0.758 very close to 0.747[2]

```
fit_Hb <- lm(HbA1C~GA,data = mydata)
pred_HB <- predict(fit_Hb)
summary(fit_Hb)</pre>
```

```
##
## Call:
## lm(formula = HbA1C ~ GA, data = mydata)
##
## Residuals:
##
       Min
              1Q Median
                                  3Q
                                          Max
## -0.97841 -0.25337 0.00078 0.24092 1.25351
##
## Coefficients:
##
              Estimate Std. Error t value Pr(>|t|)
## (Intercept) 2.381311
                        0.145108 16.41 <2e-16 ***
## GA
              0.235232 0.009908 23.74 <2e-16 ***
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.3545 on 418 degrees of freedom
## Multiple R-squared: 0.5742, Adjusted R-squared: 0.5732
## F-statistic: 563.7 on 1 and 418 DF, p-value: < 2.2e-16
```

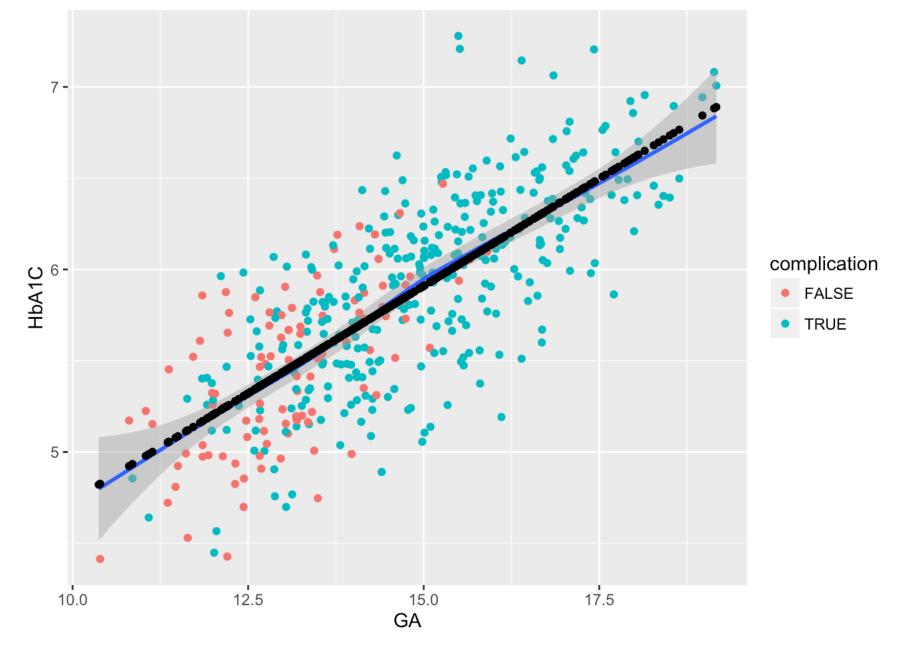
- Hb = 0.235*GA + 2.38 vary close to the linear model HbA(1c)=1.73+0.245GA [2]
- $R^2 = 0.5742$, P-value < 2.2e-16

```
plot(fit Hb,1)
```



• The residuals are randomly distributed

 $ggplot(data=mydata)+geom_point(aes(x=GA,y=HbA1C,color = complication))+ geom_smooth(aes(x=GA,y=HbA1C))+geom_point(aes(x=GA,y=pred_HB))$

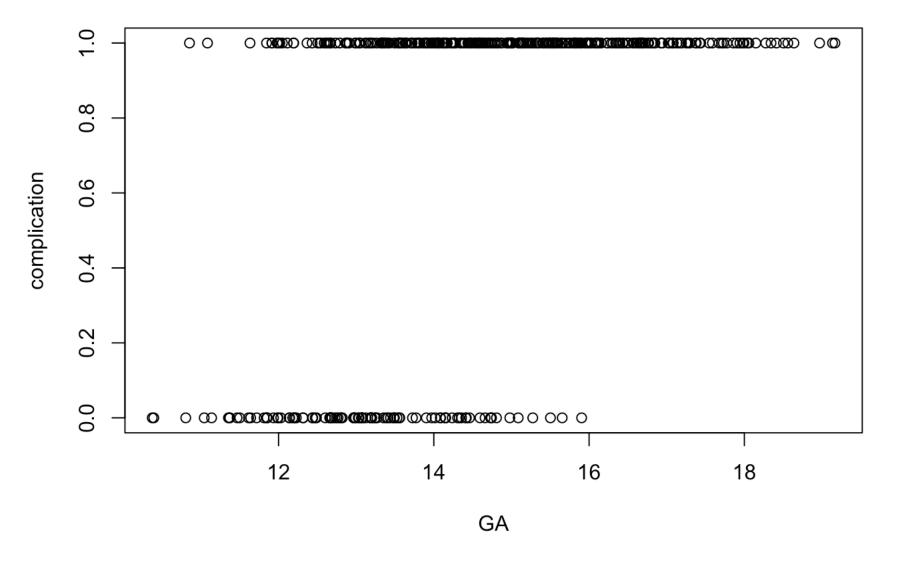


• this plot indicates the model is significant, although R^2 is 0.5742, this may due to the data is pretty spread out

Part3 Data modeling

1.Let's plot complications vs GA again

```
mydata1 <- data.frame(apply(mydata,2,as.numeric)) # change the T/F to 1/0
plot(complication~GA, data = mydata1)</pre>
```



- The plot indicates babies with complications their moms have higher GA.
- Babies without complications their moms have lower GA.

2.Let's fit a logistic regression model

```
logisticPseudoR2s <- function(LogModel) {</pre>
  dev <- LogModel$deviance</pre>
  nullDev <- LogModel$null.deviance</pre>
  modelN <- length(LogModel$fitted.values)</pre>
  R.l \leftarrow 1 - dev / nullDev
  R.cs <- 1- exp ( -(nullDev - dev) / modelN)</pre>
  R.n \leftarrow R.cs / (1 - (exp (-(nullDev / modelN))))
  cat("Pseudo R^2 for logistic regression\n")
  cat("Hosmer and Lemeshow R^2 ", round(R.1, 3), "\n")
  cat("Cox and Snell R^2
                                   ", round(R.cs, 3), "\n")
  cat("Nagelkerke R^2
                                   ", round(R.n, 3),
}
fit Com <- glm(complication~GA,family=binomial, data = mydata1)</pre>
pred com <- predict(fit Com, type="response")</pre>
summary(fit Com)
```

```
##
## Call:
## glm(formula = complication ~ GA, family = binomial, data = mydata1)
##
## Deviance Residuals:
##
        Min
                   10
                         Median
                                        30
                                                 Max
\#\# -2.44778
              0.07026
                        0.35904
                                   0.67551
                                             1.98682
##
## Coefficients:
##
               Estimate Std. Error z value Pr(>|z|)
## (Intercept) -12.069
                             1.499 -8.051 8.22e-16 ***
## GA
                  0.944
                             0.110
                                      8.584 < 2e-16 ***
## ---
## Signif. codes:
                   0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
##
       Null deviance: 470.15 on 419 degrees of freedom
## Residual deviance: 350.86 on 418 degrees of freedom
## AIC: 354.86
##
## Number of Fisher Scoring iterations: 5
```

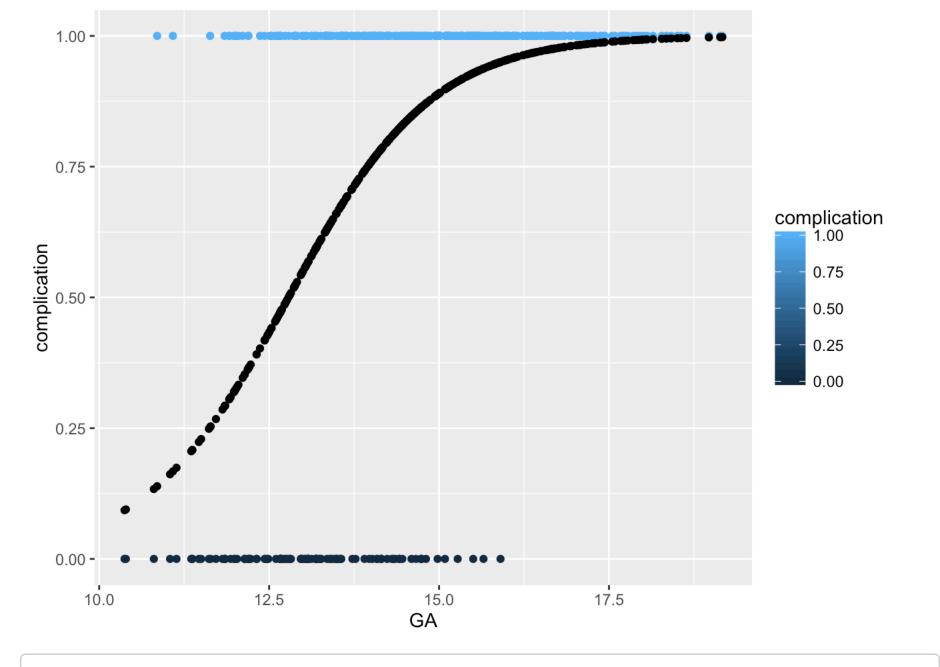
```
logisticPseudoR2s(fit Com)
```

```
## Pseudo R^2 for logistic regression
## Hosmer and Lemeshow R^2  0.254
## Cox and Snell R^2  0.247
## Nagelkerke R^2  0.367
```

- Log(Have Complications/no Complications) = 0.944*GA 12.069
- pseudoR^2:
- 1. Hosmer and Lemeshow R^2 0.254
- 2. Cox and Snell R^2 0.247
- 3. Nagelkerke R^2 0.367
- AIC: 354.86

3. Let's plot out the model we just built

```
ggplot(data=mydata1)+geom_point(aes(x=GA,y=complication,color = complication))+
  geom_point(aes(x=GA,y= pred_com))
```



library(scatterplot3d)

s3d <-scatterplot3d(mydata\$GA[mydata\$complicatio==1], mydata\$HbA1C[mydata\$complicatio ==1], mydata\$complication[mydata\$complicatio==1],

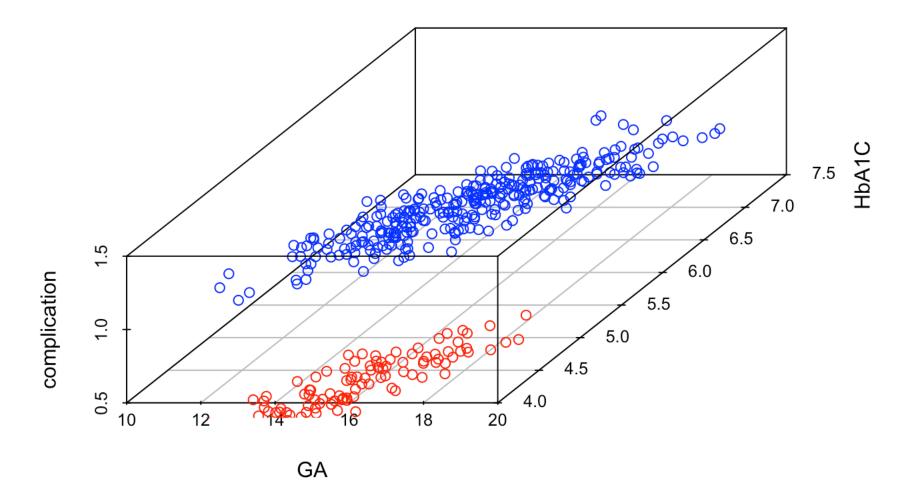
color = "blue",

xlab= "GA",ylab= "HbA1C",zlab="complication",

main="GA VS HbA1C VS complication")

s3d\$points3d(mydata\$GA[mydata\$complicatio==0],mydata\$HbA1C[mydata\$complicatio==0],myd
ata\$complication[mydata\$complicatio==0], col = "red")

GA VS HbA1C VS complication



Conlusion

- Patients having higher GA their babies will have a higher chance to have complications after birth.
- The model to predic the probablity of have conditions is Log(p/(1-p)) = 0.944*GA 12.069.
- HbA1C is correlated with GA, the linear relation can be described as HbA1C = 0.235*GA + 2.38
- HbA1C can be affected by diabeties condition during pragnency. GA can be used to control diabeties in order to lower the incidence of complications in IDMs.