Statistical methods for bioinformatics
Gene expression: case study (de Vijver et al.)

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1 Dataset exploration

The dataset under consideration consists of values of about 5000 gene expressions (obtained through a microarray technology) for 188 patients. Some of the patients developed distant metastases while some did not, and the goal is to see if we can use the information from the levels of gene expressions to predict the metatstases phenotype.
One thing to note from the dimensions of the dataset is that we are falling in the case of so-called high dimensionality with a number of observations n that is over an order of magnitude lower than that of predictors p. Among other things, this prevents the use of least square methods, common in linear models.
One of the risk when trying to come up with a gene panel that would predict the evolution of the cancer is that high levels of colinearity between the predictors likely exists. This renders the set of gene selected contingent on the particular analysis performed.

2 Predictive potential

Here are the libraries I used for this part, and the dataset:

```
library(glmnet)
library(polycor)
library(ROCR)
library(leaps)

load("VIJVER.Rdata")
```

As a first approach, I tried to search systematically through the dataset for variables that would correlate with the binary outcome with a correlation score above 0.45 (for a score of 0.5, the procedure returns only 2 results).

```
## Systematic identification of correlated genex/outcome
genes <- character()
i <- 1
for(gene in names(data)[2:length(data)]) {
    if(abs(hetcor(data$meta, data[gene])$correlations[1,2]) > 0.45){
        genes[i] <- gene
        i <- i + 1
    }
}
```

Here is the list of genes returned:

```
 [1] "NM_000987"      "NM_003258"      "NM_003295"      "NM_004119"
 [5] "NM_004203"      "NM_002808"      "NM_002811"      "NM_012291"
 [9] "NM_013277"      "NM_003981"      "NM_004701"      "M96577"
[13] "NM_007019"      "NM_007057"      "NM_007267"      "NM_007274"
[17] "NM_006607"      "NM_016185"      "Contig48913_RC" "NM_018410"
[21] "NM_001168"      "NM_002106"
```

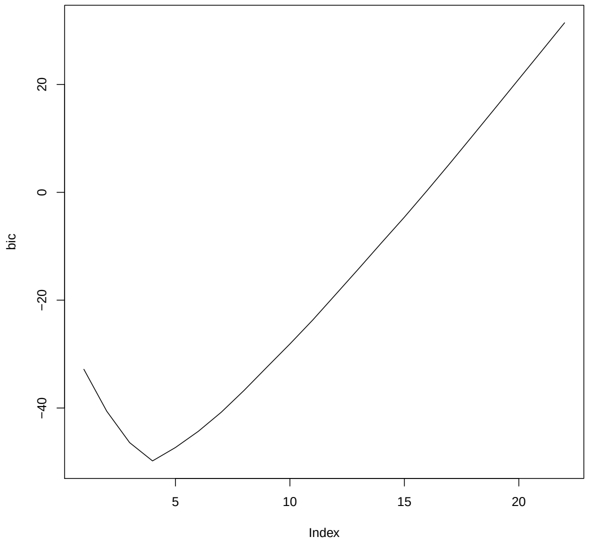
Which I then used to build a logistic model, with a best subset selection approach. For the selection, I used the BIC metric to select the subset of variable (see graphic)

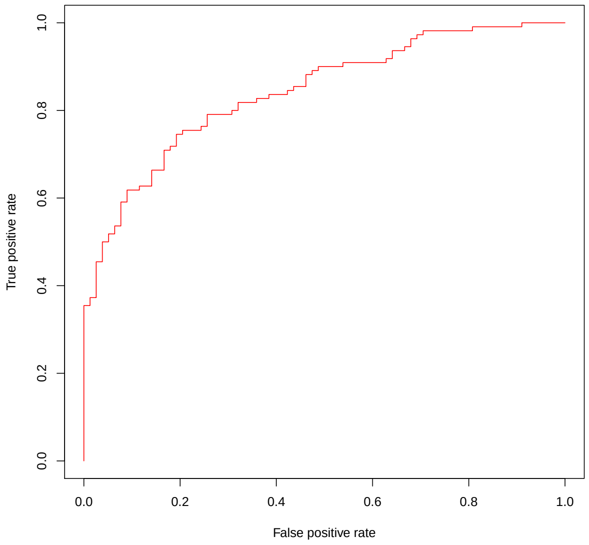
```
## Use the identified variables to create a model
regfit.full <- regsubsets(data.meta~., reduced.data, nvmax = length(genes))
reg.summary <- summary(regfit.full)

## fitting model with the 4 params
reg <- glm(meta~NM_000987+NM_003258+NM_004119+NM_002811, data=data,family = binomial(link=logi
summary(reg)
reg.probs <- predict(reg, type="response")
contrasts(data$meta)
table(data$meta, fitted(reg)>0.5)
predict <- fitted(reg)
pred <- prediction(predict, data$meta)
perf <- performance(pred, measure="tpr", x.measure = "fpr")
performance(pred, measure="auc")

## using bic to make a decision, n=4
which.min(reg.summary$bic)
coef(regfit.full,4)

## plotting the results
pdf("bic-auc.pdf", width = 16, height = 8)
par(mfrow = c(1,2))
plot(reg.summary$bic, ylab="bic", type="l")
plot(perf, col="red")
dev.off()
```



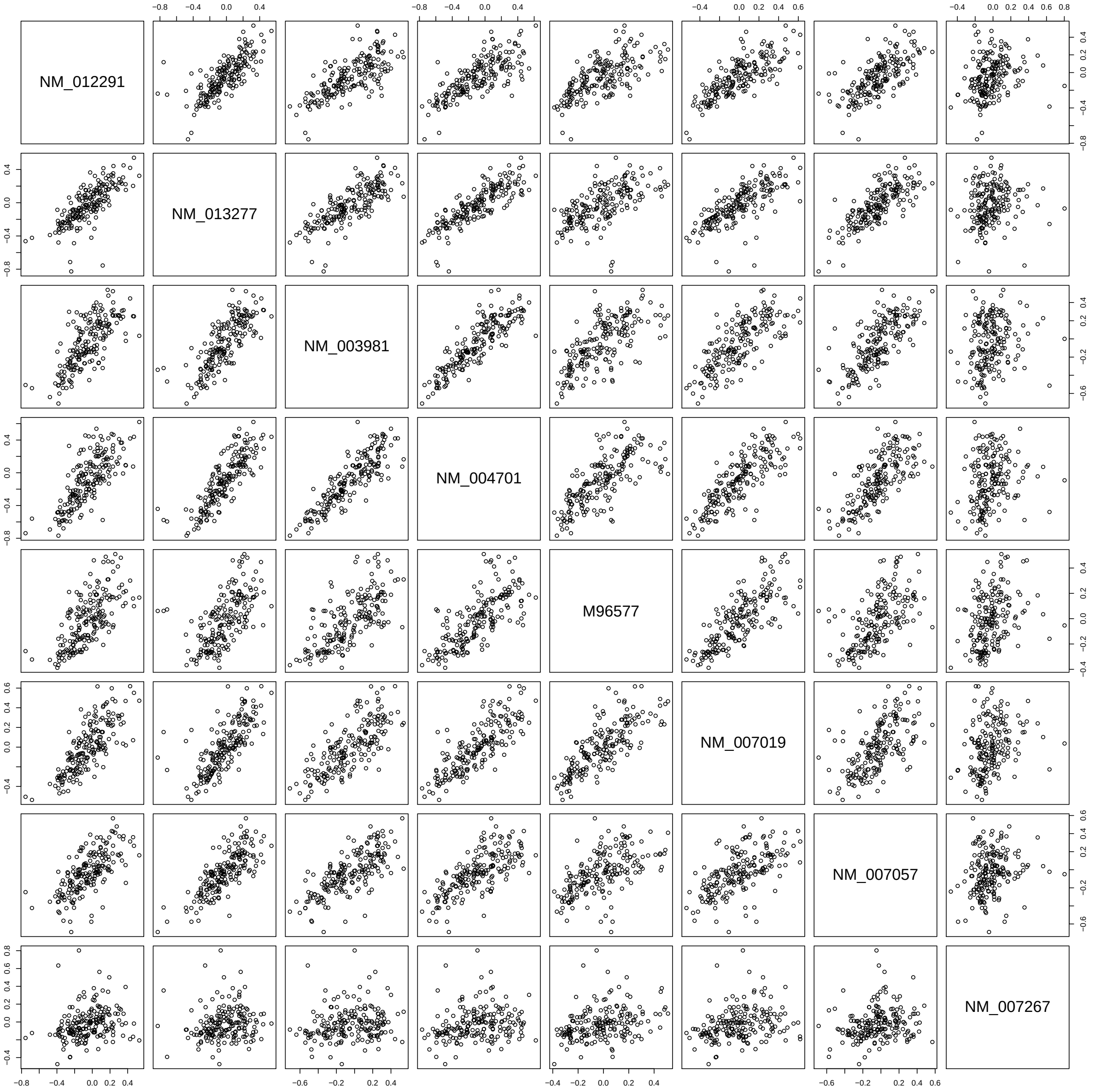


3 Collinearity structure

Given the size and the nature of the data collected (RNA expression), we can certainly expect colinearity between different transcripts. Working with the reduced dataset of 22 transcript levels created above, one can alreay show multiple examples of such colinearity:

```
pairs(reduced.data[,2:8])
cor(reduced.data$NM_002808,reduced.data$NM_002811)
pairs(reduced.data[,9:16])
cor(reduced.data$NM_003981,reduced.data$NM_004701)
```

```
> cor(reduced.data$NM_002808,reduced.data$NM_002811)
[1] 0.5072933
> cor(reduced.data$NM_003981,reduced.data$NM_004701)
[1] 0.8694202
```


NM_012291
NM_013277
NM_003981
NM_004701
M96577
NM_007019
NM_007057
NM_007267
−0.8 −0.4 0.0 0.4
−0.8 −0.4 0.0 0.4
−0.4 0.0 0.2 0.4 0.6
−0.4 0.0 0.2 0.4 0.6 0.8
−0.8 −0.4 0.0 0.2 0.4
−0.6 −0.2 0.2 0.4
−0.4 −0.2 0.0 0.2 0.4
−0.6 −0.2 0.2 0.4 0.6