Building meaningful machine learning models for disease prediction

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Webinar for the ISDS R Group

This document presents the code used to produce the example analysis and figures shown in my webinar on building meaningful machine learning models for disease prediction.

My webinar slides are available on Github

> **Description:** Dr Shirin Glander will go over her work on building machine-learning models to predict the course of different diseases. She will go over building a model, evaluating its performance, and answering or addressing different disease related questions using machine learning. Her talk will cover the theory of machine learning as it is applied using R.

Setup

All analyses are done in R using RStudio. For detailed session information including R version, operating system and package versions, see the `sessionInfo()` output at the end of this document.

All figures are produced with ggplot2.

The dataset

The dataset I am using in these example analyses, is the **Breast Cancer Wisconsin (Diagnostic) Dataset**. The data was downloaded from the UC Irvine Machine Learning Repository.

The first dataset looks at the predictor classes:

- malignant or
- benign breast mass.

The features characterise cell nucleus properties and were generated from image analysis of fine needle aspirates (FNA) of breast masses:

- Sample ID (code number)
- Clump thickness
- Uniformity of cell size
- Uniformity of cell shape
- Marginal adhesion
- Single epithelial cell size
- Number of bare nuclei
- Bland chromatin
- Number of normal nuclei
- Mitosis
- Classes, i.e. diagnosis

```r
bc_data <- read.table("datasets/breast-cancer-wisconsin.data.txt", header = FALSE, sep = ",")
colnames(bc_data) <- c("sample_code_number",
                       "clump_thickness",
                       "uniformity_of_cell_size",
                       "uniformity_of_cell_shape",
                       "marginal_adhesion",
                       "single_epithelial_cell_size",
                       "bare_nuclei",
                       "bland_chromatin",
                       "normal_nucleoli",
                       "mitosis",
                       "classes")

bc_data$classes <- ifelse(bc_data$classes == "2", "benign",
                          ifelse(bc_data$classes == "4", "malignant", NA))
```

Missing data

```r
bc_data[bc_data == "?"] <- NA

# how many NAs are in the data
length(which(is.na(bc_data)))
```

```
## [1] 16
```

```r
# how many samples would we loose, if we removed them?
nrow(bc_data)
```

```
## [1] 699
```

```r
nrow(bc_data[is.na(bc_data), ])
```

```
## [1] 16
```

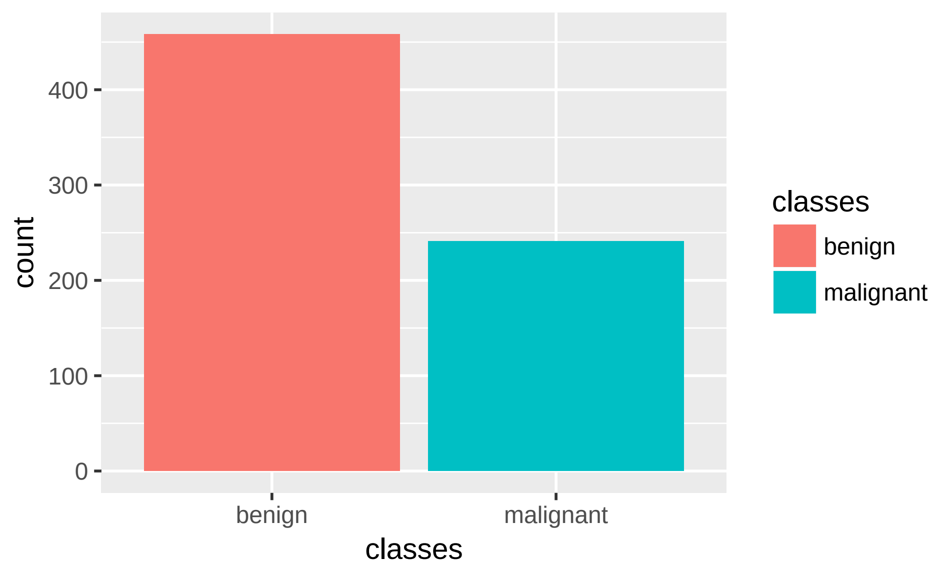
Missing values are imputed with the *mice* package.

```r
# impute missing data
library(mice)

bc_data[,2:10] <- apply(bc_data[, 2:10], 2, function(x) as.numeric(as.character(x)))
dataset_impute <- mice(bc_data[, 2:10],  print = FALSE)
bc_data <- cbind(bc_data[, 11, drop = FALSE], mice::complete(dataset_impute, 1))

bc_data$classes <- as.factor(bc_data$classes)

# how many benign and malignant cases are there?
summary(bc_data$classes)
```

Data exploration

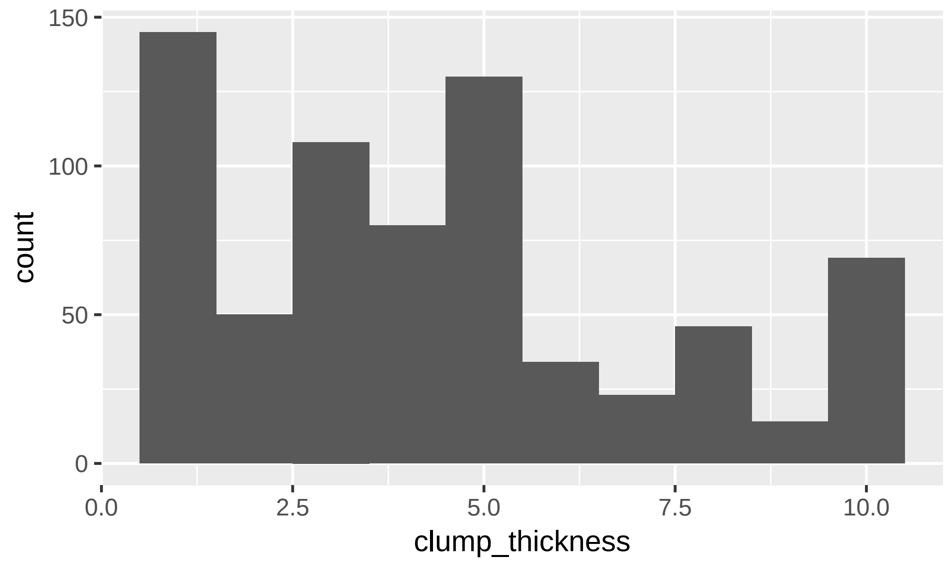
- Response variable for classification

```r
library(ggplot2)

ggplot(bc_data, aes(x = classes, fill = classes)) +
  geom_bar()
```



- Response variable for regression

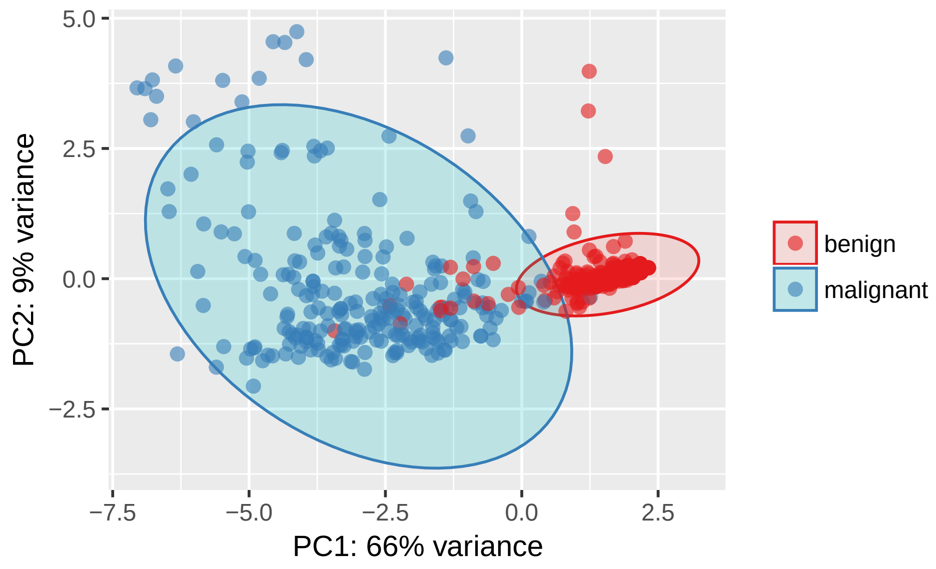
```r
ggplot(bc_data, aes(x = clump_thickness)) +
  geom_histogram(bins = 10)
```



- Principal Component Analysis

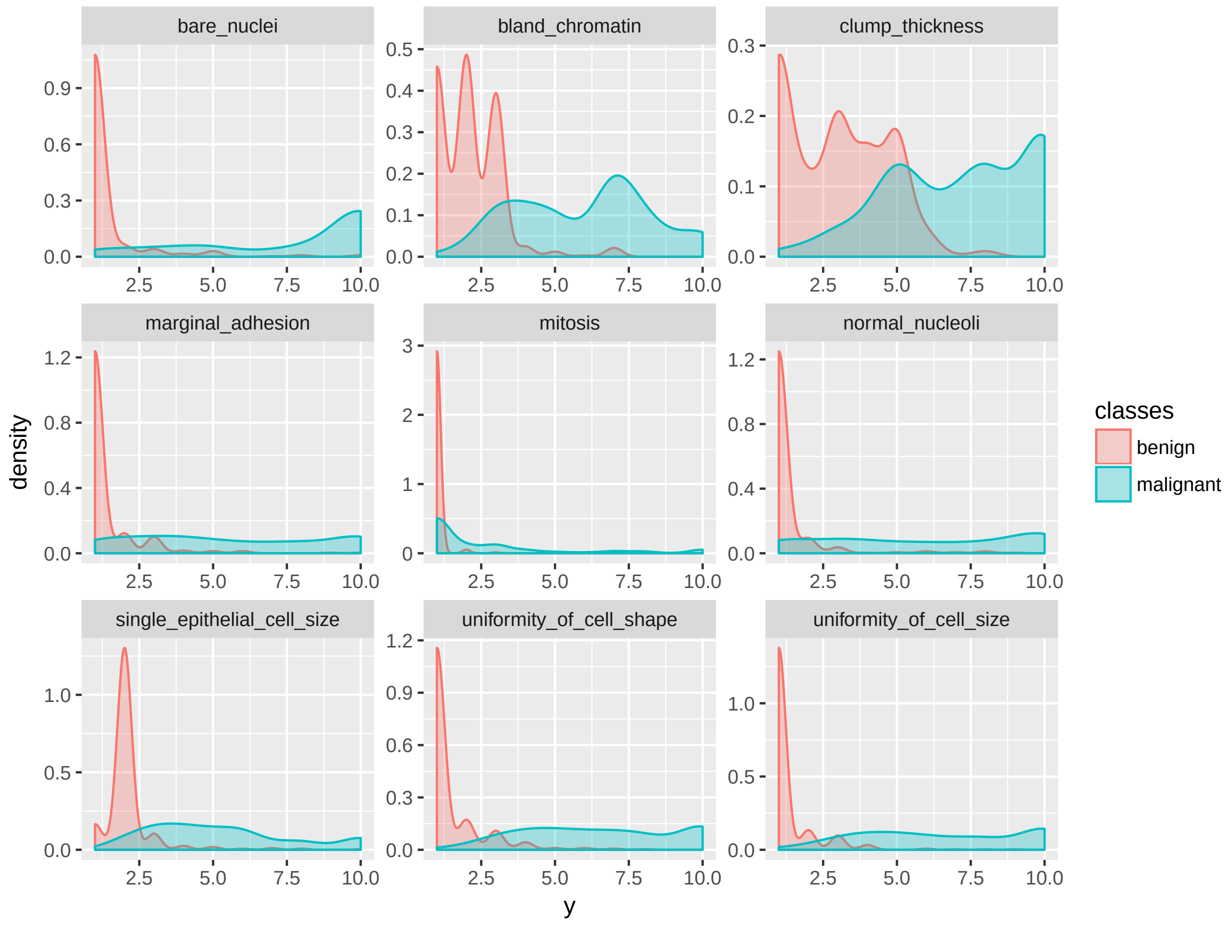
```r
library(pcaGoPromoter)
library(ellipse)

# perform pca and extract scores
pcaOutput <- pca(t(bc_data[, -1]), printDropped = FALSE, scale = TRUE, center = TRUE)
pcaOutput2 <- as.data.frame(pcaOutput$scores)

# define groups for plotting
pcaOutput2$groups <- bc_data$classes

centroids <- aggregate(cbind(PC1, PC2) ~ groups, pcaOutput2, mean)
```

```
conf.rgn  <- do.call(rbind, lapply(unique(pcaOutput2$groups), function(t)
  data.frame(groups = as.character(t),
             ellipse(cov(pcaOutput2[pcaOutput2$groups == t, 1:2]),
                   centre = as.matrix(centroids[centroids$groups == t, 2:3]),
                   level = 0.95),
             stringsAsFactors = FALSE)))

ggplot(data = pcaOutput2, aes(x = PC1, y = PC2, group = groups, color = groups)) +
    geom_polygon(data = conf.rgn, aes(fill = groups), alpha = 0.2) +
    geom_point(size = 2, alpha = 0.6) +
    scale_color_brewer(palette = "Set1") +
    labs(color = "",
         fill = "",
         x = paste0("PC1: ", round(pcaOutput$pov[1], digits = 2) * 100, "% variance"),
         y = paste0("PC2: ", round(pcaOutput$pov[2], digits = 2) * 100, "% variance"))
```



- Features

```
library(tidyr)

gather(bc_data, x, y, clump_thickness:mitosis) %>%
  ggplot(aes(x = y, color = classes, fill = classes)) +
    geom_density(alpha = 0.3) +
    facet_wrap( ~ x, scales = "free", ncol = 3)
```



Machine Learning packages for R

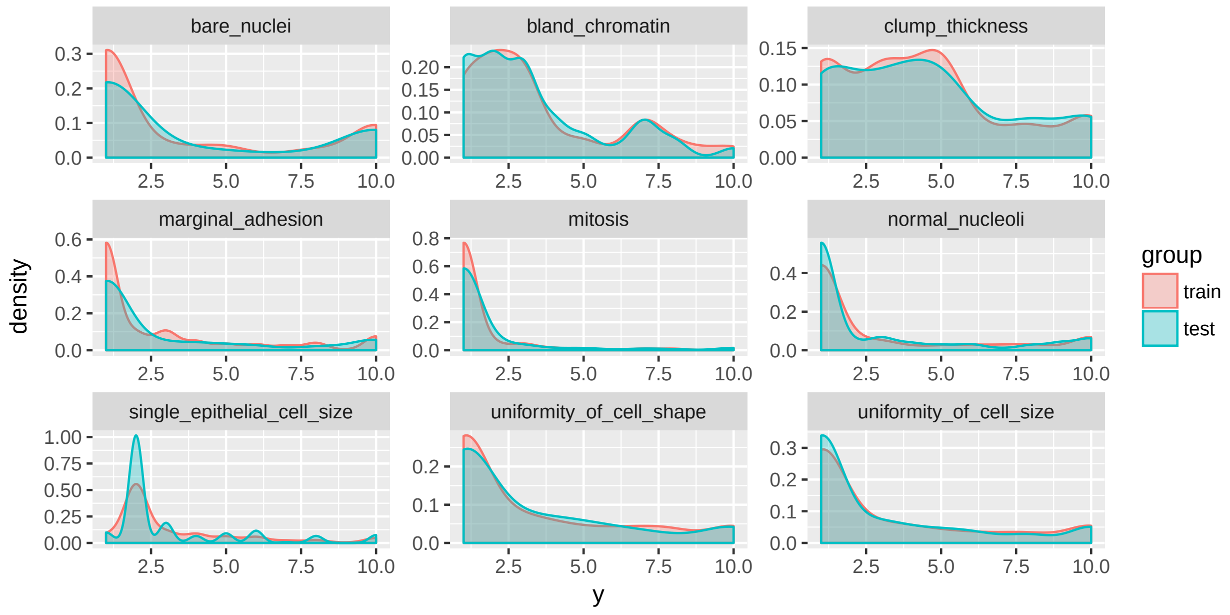
caret

```
library(caret)
```

Training, validation and test data

```
set.seed(42)
index <- createDataPartition(bc_data$classes, p = 0.7, list = FALSE)
train_data <- bc_data[index, ]
test_data  <- bc_data[-index, ]
```

```
library(dplyr)

rbind(data.frame(group = "train", train_data),
      data.frame(group = "test", test_data)) %>%
  gather(x, y, clump_thickness:mitosis) %>%
  ggplot(aes(x = y, color = group, fill = group)) +
    geom_density(alpha = 0.3) +
    facet_wrap( ~ x, scales = "free", ncol = 3)
```

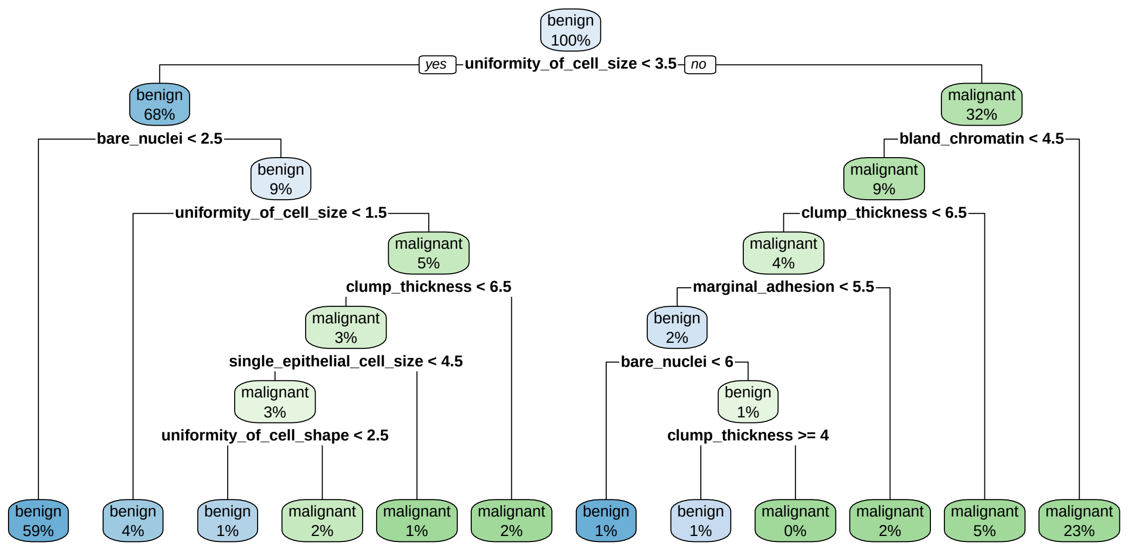


Classification

Decision trees

rpart

```
library(rpart)
library(rpart.plot)

set.seed(42)
fit <- rpart(classes ~ .,
            data = train_data,
            method = "class",
            control = rpart.control(xval = 10,
                                    minbucket = 2,
                                    cp = 0),
             parms = list(split = "information"))

rpart.plot(fit, extra = 100)
```



Random Forests

Random Forests predictions are based on the generation of multiple classification trees. They can be used for both, classification and regression tasks. Here, I show a classification task.

```
set.seed(42)
model_rf <- caret::train(classes ~ .,
                         data = train_data,
                         method = "rf",
                         preProcess = c("scale", "center"),
                         trControl = trainControl(method = "repeatedcv",
                                                  number = 10,
                                                  repeats = 10,
                                                  savePredictions = TRUE,
                                                  verboseIter = FALSE))
```

When you specify `savePredictions = TRUE`, you can access the cross-validation resuls with `model_rf$pred`.

```
model_rf$finalModel$confusion
```

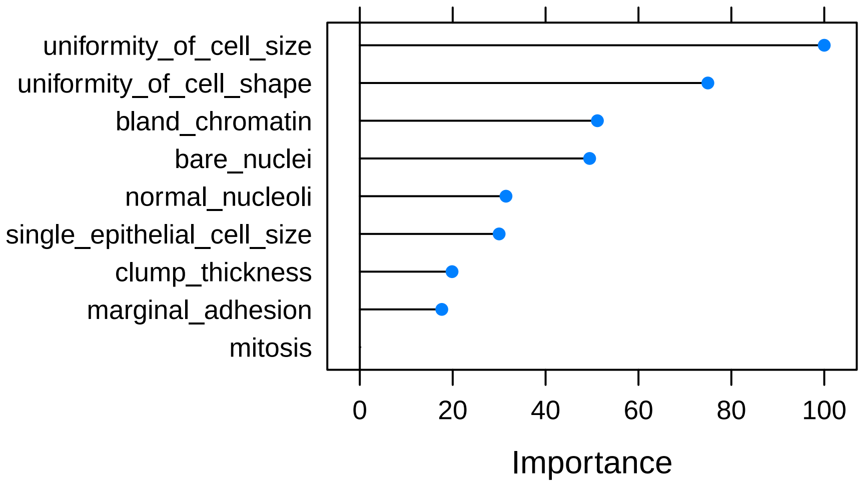
```
##           benign malignant class.error
## benign       313         8  0.02492212
## malignant      4       165  0.02366864
```

- Feature Importance

```
imp <- model_rf$finalModel$importance
imp[order(imp, decreasing = TRUE), ]
```

```
##     uniformity_of_cell_size    uniformity_of_cell_shape
##                   54.416003                   41.553022
##             bland_chromatin                 bare_nuclei
##                   29.343027                   28.483842
##             normal_nucleoli single_epithelial_cell_size
##                   19.239635                   18.480155
##              clump_thickness           marginal_adhesion
##                    13.276702                   12.143355
##                      mitosis
##                     3.081635
```

```
# estimate variable importance
importance <- varImp(model_rf, scale = TRUE)
plot(importance)
```



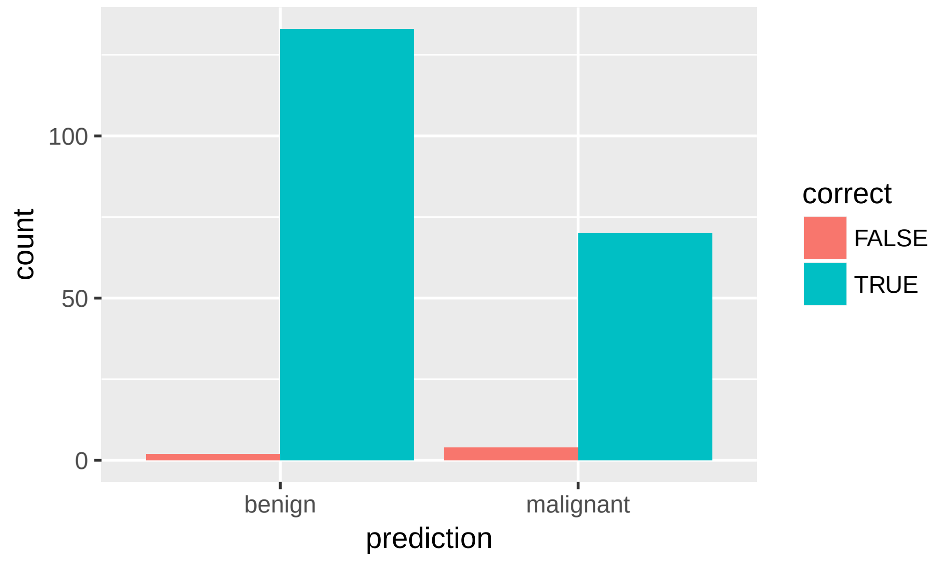
- predicting test data

```
confusionMatrix(predict(model_rf, test_data), test_data$classes)
```

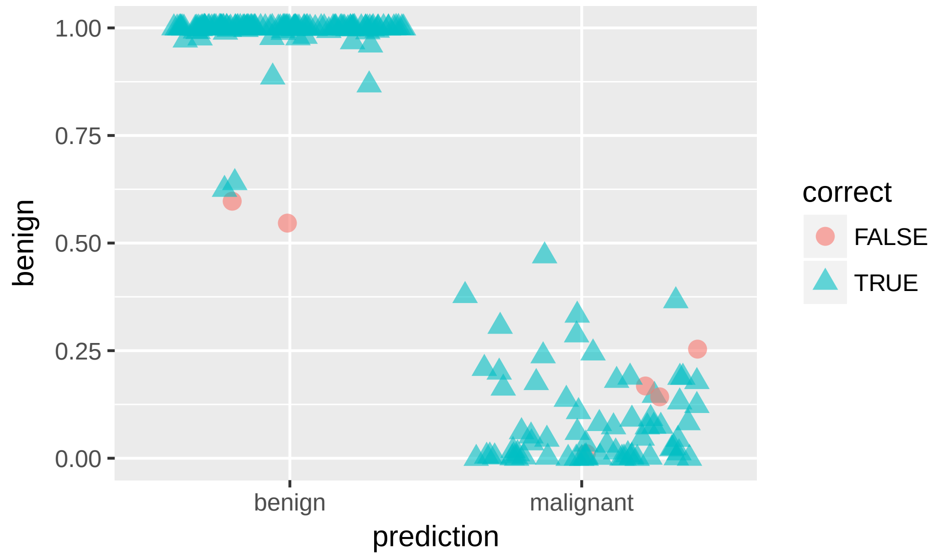
```
## Confusion Matrix and Statistics
##
##            Reference
## Prediction  benign malignant
##   benign       133         2
##   malignant      4        70
##
##                Accuracy : 0.9713
##                  95% CI : (0.9386, 0.9894)
##     No Information Rate : 0.6555
##     P-Value [Acc > NIR] : <2e-16
##
##                   Kappa : 0.9369
##  Mcnemar's Test P-Value : 0.6831
##
##             Sensitivity : 0.9708
##             Specificity : 0.9722
##          Pos Pred Value : 0.9852
##          Neg Pred Value : 0.9459
##              Prevalence : 0.6555
##          Detection Rate : 0.6364
##    Detection Prevalence : 0.6459
##       Balanced Accuracy : 0.9715
##
```

```
##        'Positive' Class : benign
##
```

```
results <- data.frame(actual = test_data$classes,
                      predict(model_rf, test_data, type = "prob"))

results$prediction <- ifelse(results$benign > 0.5, "benign",
                             ifelse(results$malignant > 0.5, "malignant", NA))

results$correct <- ifelse(results$actual == results$prediction, TRUE, FALSE)

ggplot(results, aes(x = prediction, fill = correct)) +
  geom_bar(position = "dodge")
```



```
ggplot(results, aes(x = prediction, y = benign, color = correct, shape = correct)) +
  geom_jitter(size = 3, alpha = 0.6)
```



Extreme gradient boosting trees

Extreme gradient boosting (XGBoost) is a faster and improved implementation of gradient boosting for supervised learning.

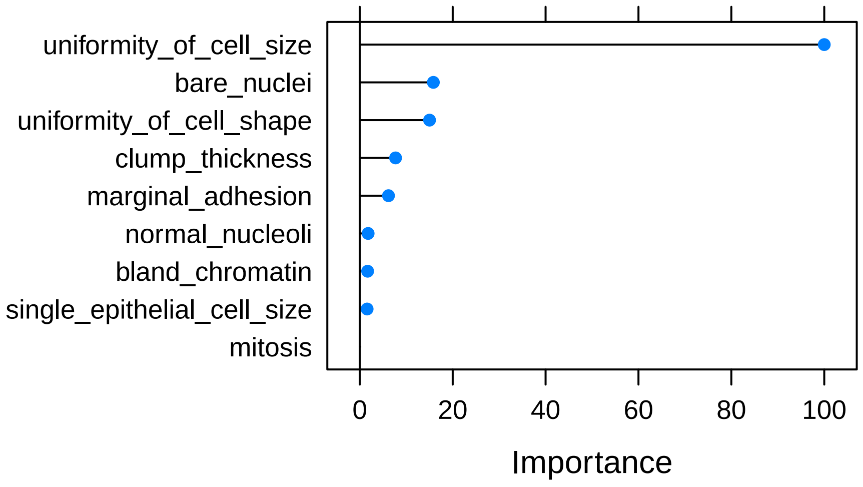
> "XGBoost uses a more regularized model formalization to control over-fitting, which gives it better performance." Tianqi Chen, developer of xgboost

XGBoost is a tree ensemble model, which means the sum of predictions from a set of classification and regression trees (CART). In that, XGBoost is similar to Random Forests but it uses a different approach to model training. Can be used for classification and regression tasks. Here, I show a classification task.

```r
set.seed(42)
model_xgb <- caret::train(classes ~ .,
                          data = train_data,
                          method = "xgbTree",
                          preProcess = c("scale", "center"),
                          trControl = trainControl(method = "repeatedcv",
                                                   number = 10,
                                                   repeats = 10,
                                                   savePredictions = TRUE,
                                                   verboseIter = FALSE))
```

- Feature Importance

```r
importance <- varImp(model_xgb, scale = TRUE)
plot(importance)
```



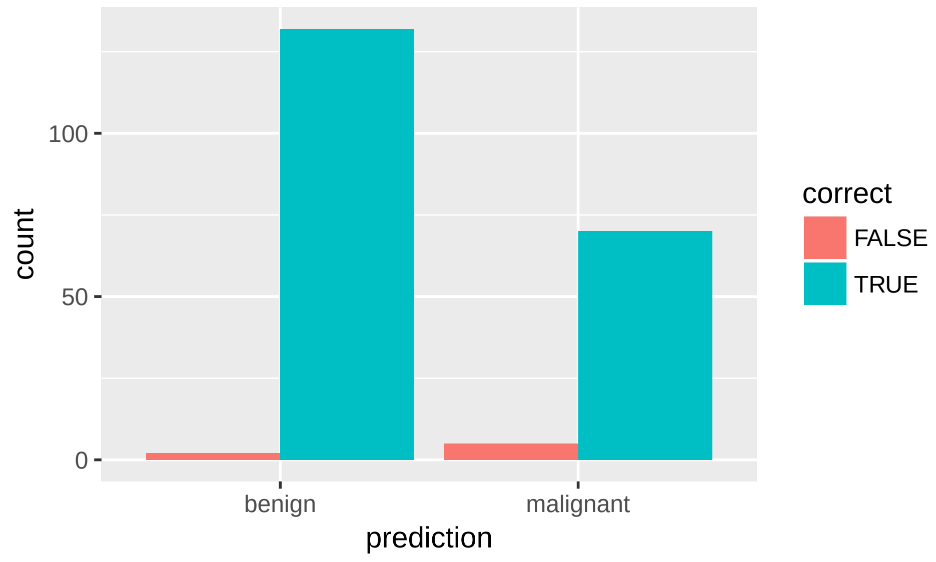
- predicting test data

```r
confusionMatrix(predict(model_xgb, test_data), test_data$classes)
```

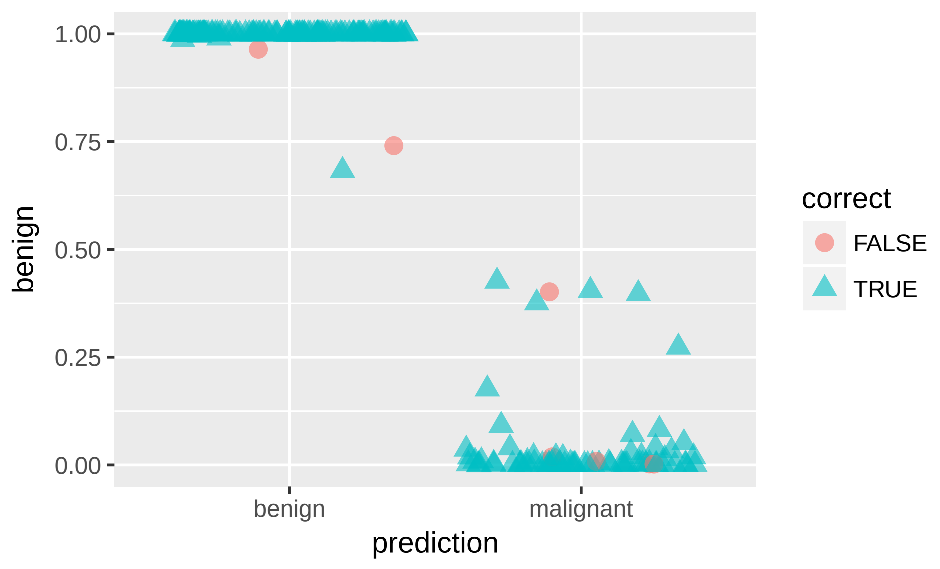
```
## Confusion Matrix and Statistics
##
##            Reference
## Prediction  benign malignant
##   benign       132         2
##   malignant      5        70
##
```

```
##                Accuracy : 0.9665
##                  95% CI : (0.9322, 0.9864)
##     No Information Rate : 0.6555
##     P-Value [Acc > NIR] : <2e-16
##
##                   Kappa : 0.9266
##  Mcnemar's Test P-Value : 0.4497
##
##             Sensitivity : 0.9635
##             Specificity : 0.9722
##          Pos Pred Value : 0.9851
##          Neg Pred Value : 0.9333
##              Prevalence : 0.6555
##          Detection Rate : 0.6316
##    Detection Prevalence : 0.6411
##       Balanced Accuracy : 0.9679
##
##        'Positive' Class : benign
##
```

```
results <- data.frame(actual = test_data$classes,
                      predict(model_xgb, test_data, type = "prob"))

results$prediction <- ifelse(results$benign > 0.5, "benign",
                             ifelse(results$malignant > 0.5, "malignant", NA))

results$correct <- ifelse(results$actual == results$prediction, TRUE, FALSE)

ggplot(results, aes(x = prediction, fill = correct)) +
  geom_bar(position = "dodge")
```



```
ggplot(results, aes(x = prediction, y = benign, color = correct, shape = correct)) +
  geom_jitter(size = 3, alpha = 0.6)
```



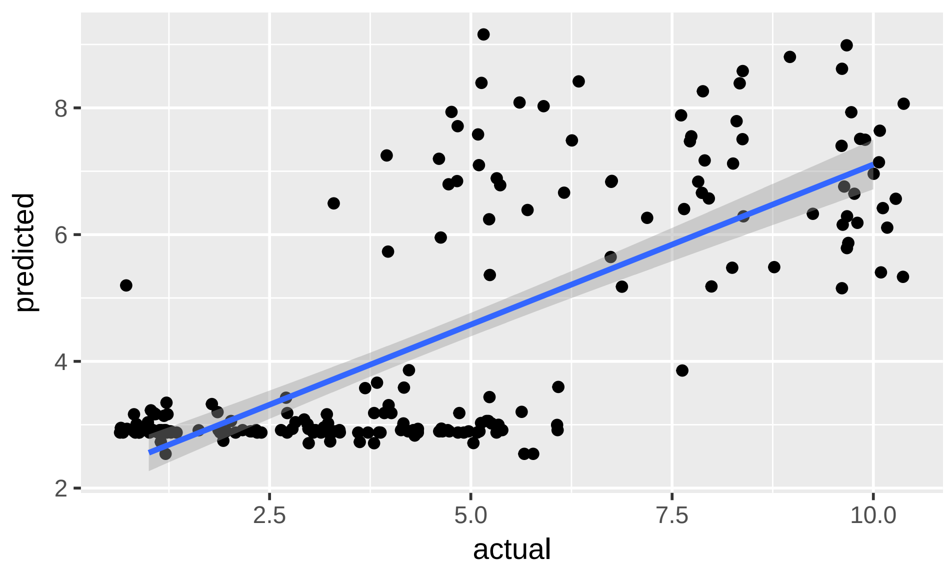
Regression

```
set.seed(42)
model_glm <- caret::train(clump_thickness ~ .,
                          data = train_data,
                          method = "glm",
                          preProcess = c("scale", "center"),
                          trControl = trainControl(method = "repeatedcv",
                                                   number = 10,
                                                   repeats = 10,
                                                   savePredictions = TRUE,
                                                   verboseIter = FALSE))
```

```
model_glm
```

```
## Generalized Linear Model
##
## 490 samples
##   9 predictor
##
## Pre-processing: scaled (9), centered (9)
## Resampling: Cross-Validated (10 fold, repeated 10 times)
## Summary of sample sizes: 441, 441, 440, 442, 441, 440, ...
## Resampling results:
##
##   RMSE      Rsquared
##   1.974296  0.5016141
##
##
```

```
data.frame(actual = test_data$clump_thickness,
           predicted = predict(model_glm, test_data)) %>%
  ggplot(aes(x = actual, y = predicted)) +
    geom_jitter() +
    geom_smooth(method = "lm")
```



Feature Selection

Machine learning uses so called features (i.e. variables or attributes) to generate predictive models. Using a suitable combination of features is essential for obtaining high precision and accuracy. Because too many (unspecific) features pose the problem of overfitting the model, we generally want to restrict the features in our models to those, that are most relevant for the response variable we want to predict. Using as few features as possible will also reduce the complexity of our models, which means it needs less time and computer power to run and is easier to understand.

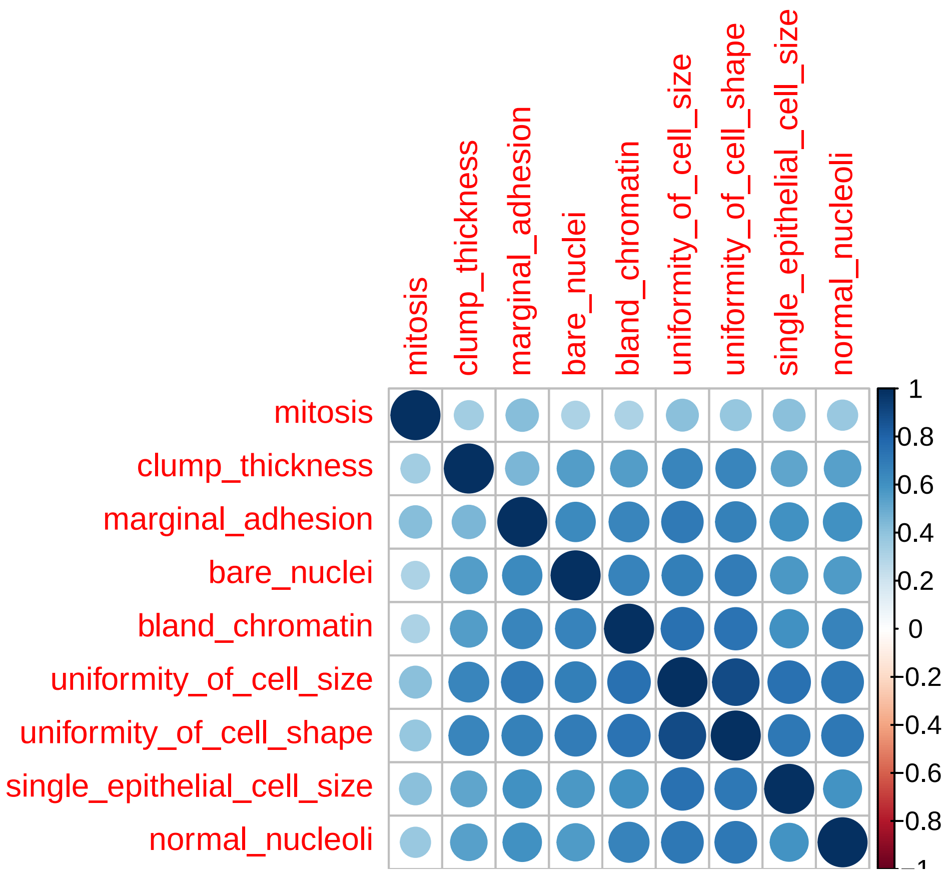
Performing feature selection on the whole dataset would lead to prediction bias, we therefore need to run the whole modeling process on the training data alone!

- Correlation

Often we have features that are highly correlated and thus provide redundant information. By eliminating highly correlated features we can avoid a predictive bias for the information contained in these features. This also shows us, that when we want to make statements about the biological/ medical importance of specific features, we need to keep in mind that just because they are suitable to predicting an outcome they are not necessarily causal - they could simply be correlated with causal factors.

Correlations between all features are calculated and visualised with the *corrplot* package. I am then removing all features with a correlation higher than 0.7, keeping the feature with the lower mean.

```r
library(corrplot)

# calculate correlation matrix
corMatMy <- cor(train_data[, -1])
corrplot(corMatMy, order = "hclust")
```



```r
#Apply correlation filter at 0.70,
highlyCor <- colnames(train_data[, -1])[findCorrelation(corMatMy, cutoff = 0.7, verbose = TRUE)]
```

```
## Compare row 2  and column  3 with corr  0.899
##   Means:  0.696 vs 0.575 so flagging column 2
## Compare row 3  and column  7 with corr  0.736
##   Means:  0.654 vs 0.55 so flagging column 3
## All correlations <= 0.7
```

```r
# which variables are flagged for removal?
highlyCor
```

```
## [1] "uniformity_of_cell_size"  "uniformity_of_cell_shape"
```

```r
#then we remove these variables
train_data_cor <- train_data[, which(!colnames(train_data) %in% highlyCor)]
```

- Recursive Feature Elimination (RFE)

Another way to choose features is with Recursive Feature Elimination. RFE uses a Random Forest algorithm to test combinations of features and rate each with an accuracy score. The combination with the highest score is usually preferential.

```r
# chosen features
predictors(results_rfe)
```

```
## [1] "bare_nuclei"                 "uniformity_of_cell_size"
## [3] "clump_thickness"             "uniformity_of_cell_shape"
## [5] "bland_chromatin"             "marginal_adhesion"
## [7] "normal_nucleoli"             "single_epithelial_cell_size"
## [9] "mitosis"
```

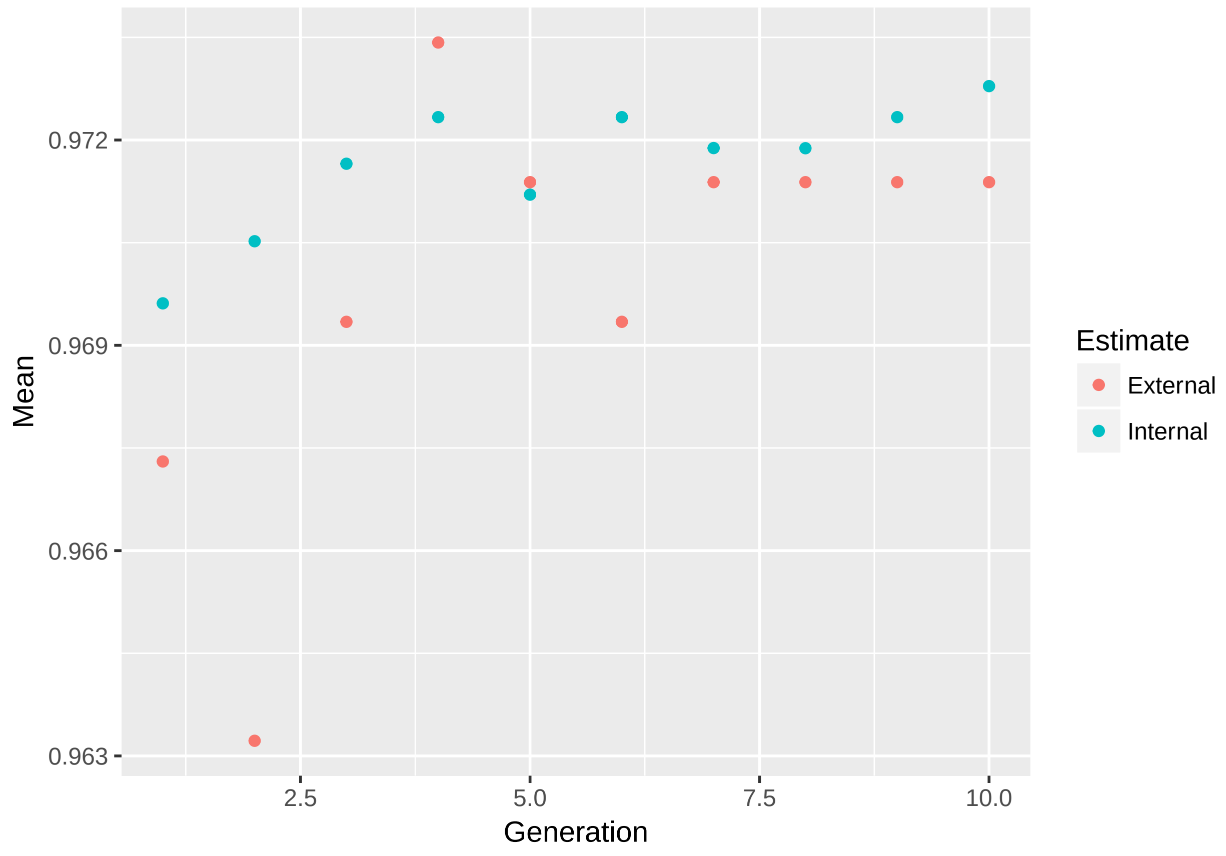
```
train_data_rfe <- train_data[, c(1, which(colnames(train_data) %in% predictors(results_rfe)))]
```

- Genetic Algorithm (GA)

The Genetic Algorithm (GA) has been developed based on evolutionary principles of natural selection: It aims to optimize a population of individuals with a given set of genotypes by modeling selection over time. In each generation (i.e. iteration), each individual's fitness is calculated based on their genotypes. Then, the fittest individuals are chosen to produce the next generation. This subsequent generation of individuals will have genotypes resulting from (re-) combinations of the parental alleles. These new genotypes will again determine each individual's fitness. This selection process is iterated for a specified number of generations and (ideally) leads to fixation of the fittest alleles in the gene pool.

This concept of optimization can be applied to non-evolutionary models as well, like feature selection processes in machine learning.

```
plot(model_ga) # Plot mean fitness (AUC) by generation
```



```
train_data_ga <- train_data[, c(1, which(colnames(train_data) %in% model_ga$ga$final))]
```

Grid search with h2o

The R package h2o provides a convenient interface to H2O, which is an open-source machine learning and deep learning platform. H2O distributes a wide range of common machine learning algorithms for classification, regression and deep learning.

```r
library(h2o)
h2o.init(nthreads = -1)
```

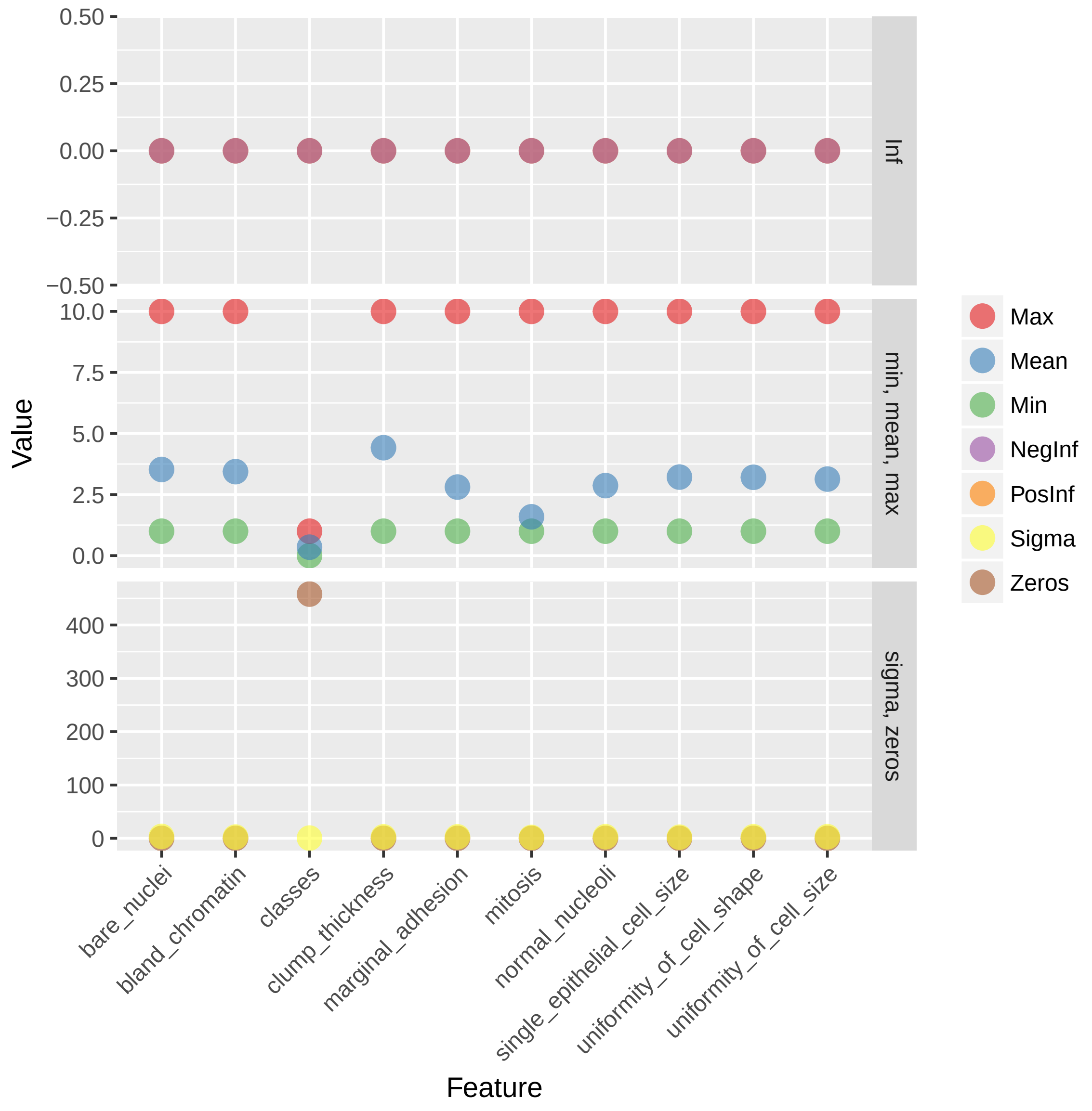
```
##  Connection successful!
## 
## R is connected to the H2O cluster: 
##     H2O cluster uptime:         1 minutes 50 seconds 
##     H2O cluster version:        3.10.3.6 
##     H2O cluster version age:    22 days  
##     H2O cluster name:           H2O_started_from_R_s_glan02_pzm476 
##     H2O cluster total nodes:    1 
##     H2O cluster total memory:   3.21 GB 
##     H2O cluster total cores:    8 
##     H2O cluster allowed cores:  8 
##     H2O cluster healthy:        TRUE 
##     H2O Connection ip:          localhost 
##     H2O Connection port:        54321 
##     H2O Connection proxy:       NA 
##     R Version:                  R version 3.3.3 (2017-03-06)
```

```r
bc_data_hf <- as.h2o(bc_data)
```

```
## 
  |                                                                       
  |                                                                 |   0%
  |                                                                       
  |=================================================================| 100%
```

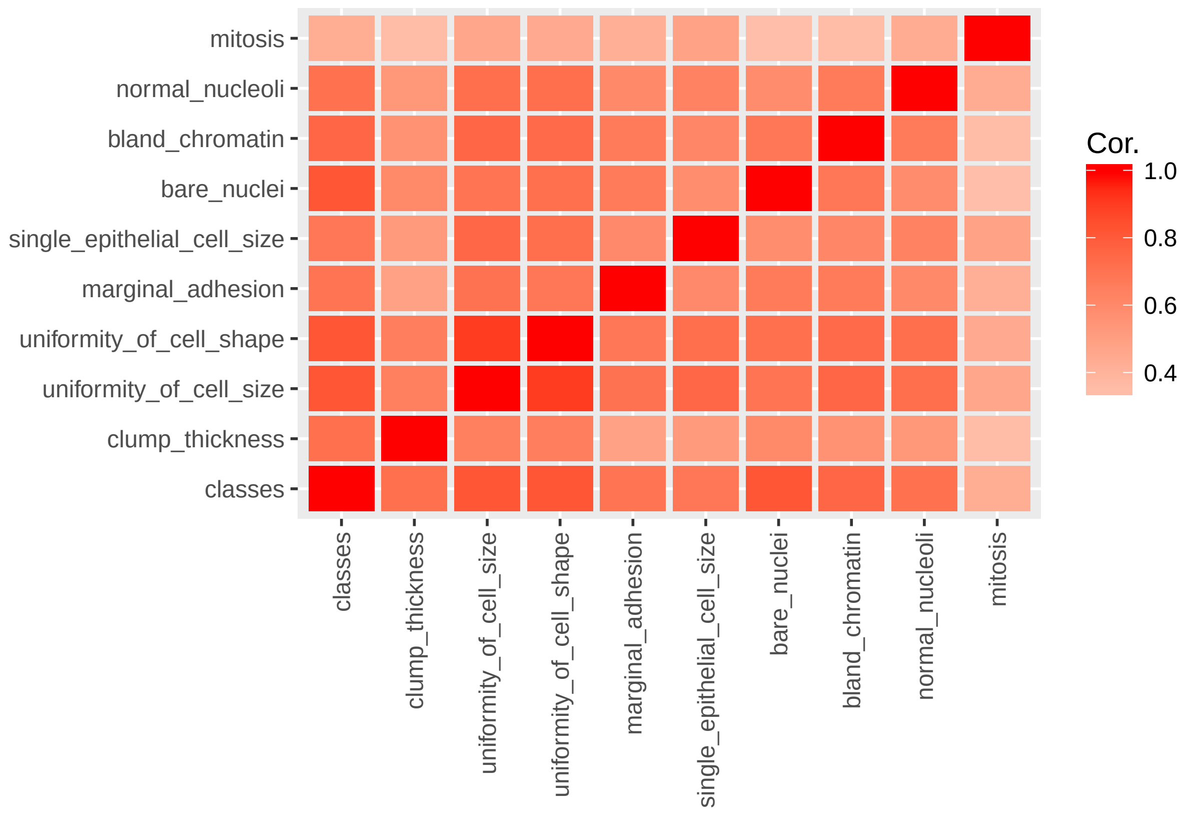
We can now access all functions from the **h2o** package that are built to work on H2O Frames. A useful such function is *h2o.describe()*. It is similar to base R's *summary()* function but outputs many more descriptive measures for our data. To get a good overview about these measures, I am going to plot them.

```r
h2o.describe(bc_data_hf) %>%
  gather(x, y, Zeros:Sigma) %>%
  mutate(group = ifelse(x %in% c("Min", "Max", "Mean"), "min, mean, max", 
                        ifelse(x %in% c("NegInf", "PosInf"), "Inf", "sigma, zeros"))) %>% 
  ggplot(aes(x = Label, y = as.numeric(y), color = x)) +
    geom_point(size = 4, alpha = 0.6) +
    scale_color_brewer(palette = "Set1") +
    theme(axis.text.x = element_text(angle = 45, vjust = 1, hjust = 1)) +
    facet_grid(group ~ ., scales = "free") +
    labs(x = "Feature",
         y = "Value",
         color = "")
```



I am also interested in the correlation between features and the output. We can use the *h2o.cor()* function to calculate the correlation matrix. It is again much easier to understand the data when we visualize it, so I am going to create another plot.

```
library(reshape2) # for melting

bc_data_hf[, 1] <- h2o.asfactor(bc_data_hf[, 1])

cor <- h2o.cor(bc_data_hf)
rownames(cor) <- colnames(cor)

melt(cor) %>%
  mutate(Var2 = rep(rownames(cor), nrow(cor))) %>%
  mutate(Var2 = factor(Var2, levels = colnames(cor))) %>%
  mutate(variable = factor(variable, levels = colnames(cor))) %>%
  ggplot(aes(x = variable, y = Var2, fill = value)) +
    geom_tile(width = 0.9, height = 0.9) +
    scale_fill_gradient2(low = "white", high = "red", name = "Cor.") +
    theme(axis.text.x = element_text(angle = 90, vjust = 0.5, hjust = 1)) +
    labs(x = "",
         y = "")
```



Training, validation and test data

Now we can use the *h2o.splitFrame()* function to split the data into training, validation and test data. Here, I am using 70% for training and 15% each for validation and testing. We could also just split the data into two sections, a training and test set but when we have sufficient samples, it is a good idea to evaluate model performance on an independent test set on top of training with a validation set. Because we can easily overfit a model, we want to get an idea about how generalizable it is - this we can only assess by looking at how well it works on previously unknown data.

I am also defining response and feature column names now.

```
splits <- h2o.splitFrame(bc_data_hf,
                         ratios = c(0.7, 0.15),
                         seed = 1)

train <- splits[[1]]
valid <- splits[[2]]
test <- splits[[3]]

response <- "classes"
features <- setdiff(colnames(train), response)
```

```r
summary(train$classes, exact_quantiles = TRUE)
```

```
##  classes
##  benign   :317
##  malignant:174
```

```r
summary(valid$classes, exact_quantiles = TRUE)
```

```
##  classes
##  benign   :71
##  malignant:35
```

```r
summary(test$classes, exact_quantiles = TRUE)
```

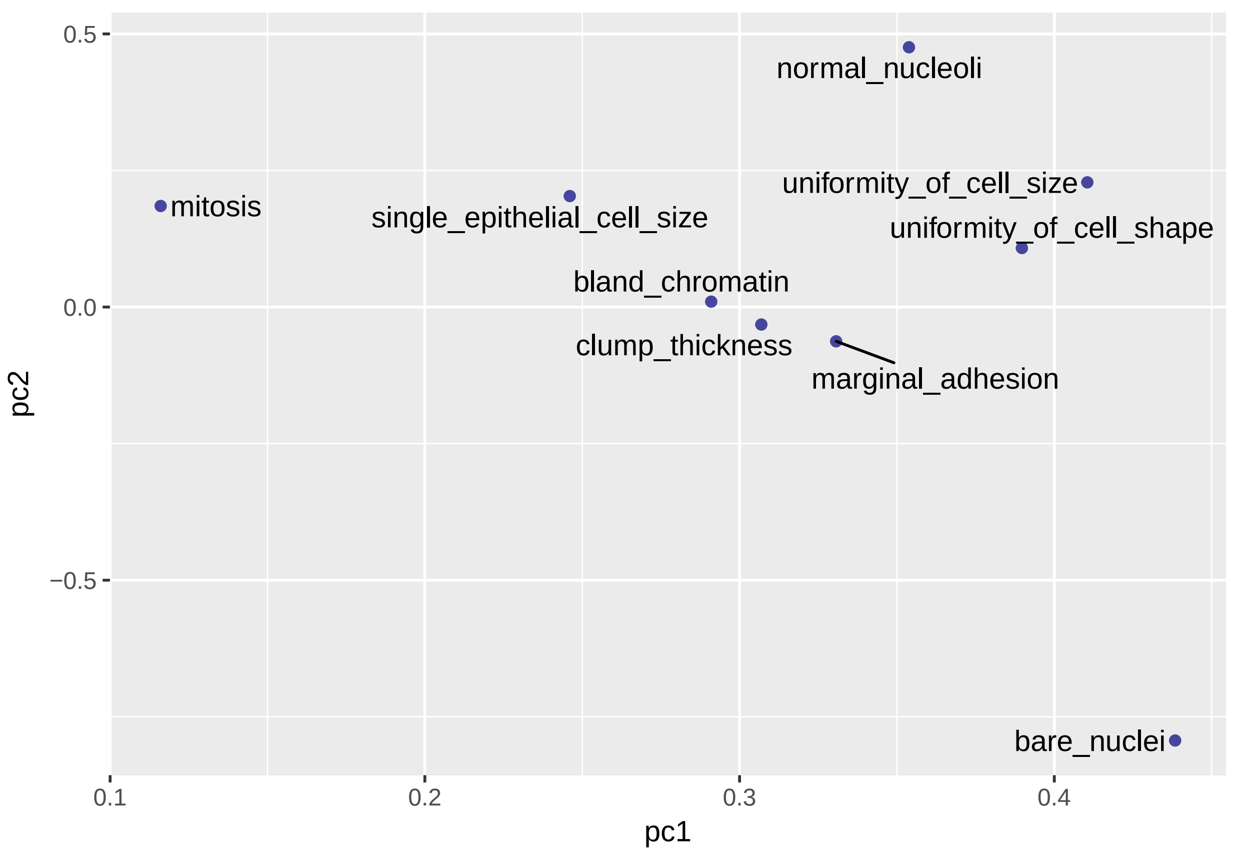
```
##  classes
##  benign   :70
##  malignant:32
```

We can also run a PCA on the training data, using the *h2o.prcomp()* function to calculate the singular value decomposition of the Gram matrix with the power method.

```r
pca <- h2o.prcomp(training_frame = train,
           x = features,
           validation_frame = valid,
           transform = "NORMALIZE",
           impute_missing = TRUE,
           k = 3,
           seed = 42)
```

```
##
  |
  |                                                                 |   0%
  |
  |=================================================================| 100%
```

```r
eigenvec <- as.data.frame(pca@model$eigenvectors)
eigenvec$label <- features

library(ggrepel)
ggplot(eigenvec, aes(x = pc1, y = pc2, label = label)) +
  geom_point(color = "navy", alpha = 0.7) +
  geom_text_repel()
```



Classification

Of course, you need quite a bit of experience and intuition to hit on a good combination of parameters. That's why it usually makes sense to do a grid search for hyper-parameter tuning. Hyper-parameter tuning with grid search allows us to test different combinations of hyper-parameters and find one with improved accuracy.

Keep in mind though, that hyper-parameter tuning can only improve the model so much without overfitting. If you can't achieve sufficient accuracy, the input features might simply not be adequate for the predictions you are trying to model. It might be necessary to go back to the original features and try e.g. feature engineering methods.

We can use the `h2o.grid()` function to perform a Random Grid Search (RGS). We could also test all possible combinations of parameters with Cartesian Grid or exhaustive search, but RGS is much faster when we have a large number of possible combinations and usually finds sufficiently accurate models.

For RGS, we first define a set of hyper-parameters and search criteria to fine-tune our models. Because there are many hyper-parameters, each with a range of possible values, we want to find an (ideally) optimal combination to maximize our model's accuracy. We can also specify how long we want to run the grid search for. Based on the results of each model tested in the grid, we can choose the one with the highest accuracy or best performance for the question on hand.

Random Forest

```
hyper_params <- list(
                     ntrees = c(25, 50, 75, 100),
                     max_depth = c(10, 20, 30),
                     min_rows = c(1, 3, 5)
                     )

search_criteria <- list(
                        strategy = "RandomDiscrete",
                        max_models = 50,
                        max_runtime_secs = 360,
                        stopping_rounds = 5,
                        stopping_metric = "AUC",
                        stopping_tolerance = 0.0005,
                        seed = 42
                        )
```

```
rf_grid <- h2o.grid(algorithm = "randomForest", # h2o.randomForest,
                                                # alternatively h2o.gbm for Gradient boosting trees
                    x = features,
                    y = response,
                    grid_id = "rf_grid",
                    training_frame = train,
                    validation_frame = valid,
                    nfolds = 25,
                    fold_assignment = "Stratified",
                    hyper_params = hyper_params,
                    search_criteria = search_criteria,
                    seed = 42
                    )
```

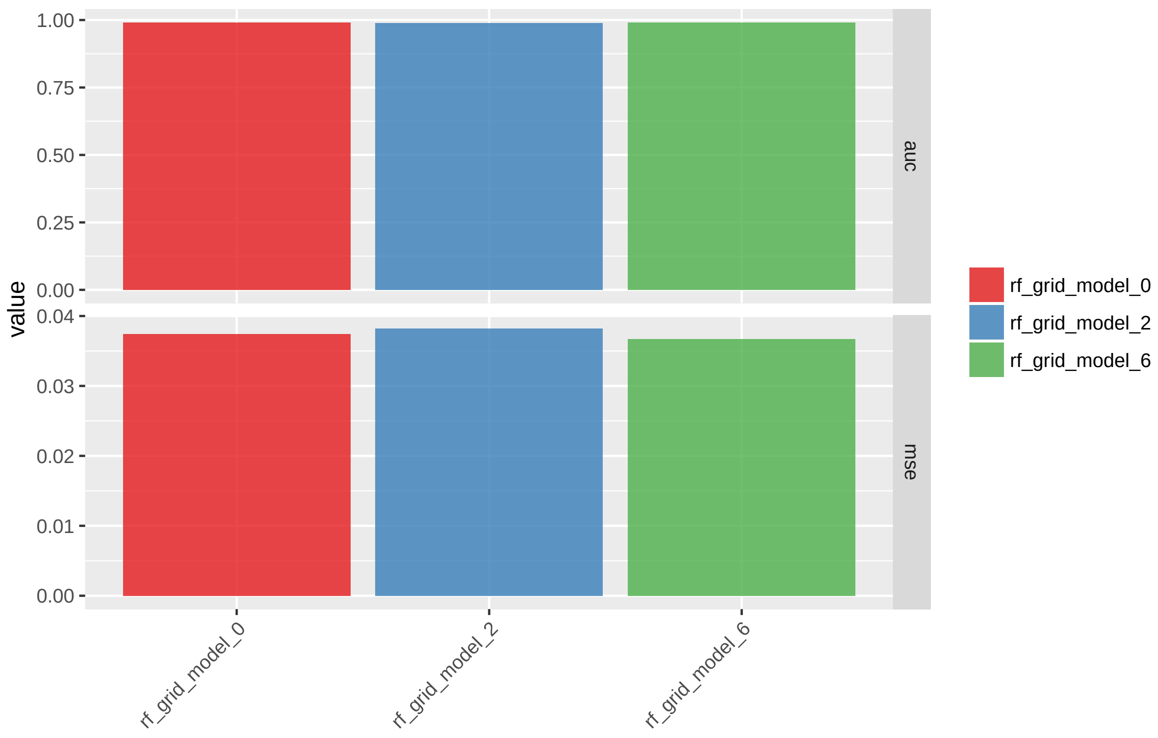
We now want to extract the best model from the grid model list. What makes a model *the best* depends on the question you want to address with it: in some cases, the model with highest AUC is the most suitable, or the one with the lowest mean squared error, etc. We first use the `h2o.getGrid()` function to sort all models by the quality metric we choose (depending on the metric, you want it ordered by descending or ascending values). We can then get the model that's the first in the list to work with further. This model's hyper-parameters can be found with `best_model@allparameters`. You can now work with your best model as with any regular model in **h2o**.

```
# performance metrics where smaller is better -> order with decreasing = FALSE
sort_options_1 <- c("mean_per_class_error", "mse", "err", "logloss")

for (sort_by_1 in sort_options_1) {

  grid <- h2o.getGrid("rf_grid", sort_by = sort_by_1, decreasing = FALSE)

  model_ids <- grid@model_ids
  best_model <- h2o.getModel(model_ids[[1]])

  h2o.saveModel(best_model, path="models", force = TRUE)

}


# performance metrics where bigger is better -> order with decreasing = TRUE
sort_options_2 <- c("auc", "precision", "accuracy", "recall", "specificity")

for (sort_by_2 in sort_options_2) {

  grid <- h2o.getGrid("rf_grid", sort_by = sort_by_2, decreasing = TRUE)
```

```r
  model_ids <- grid@model_ids
  best_model <- h2o.getModel(model_ids[[1]])

  h2o.saveModel(best_model, path = "models", force = TRUE)

}
```

The ultimate performance test for our model will be it's prediction accuracy on the test set it hasn't seen before. Here, I will compare the AUC and mean squared error for each best model from before. You could of course look at any other quality metric that is most appropriate for your model.

```r
files <- list.files(path = "models")
rf_models <- files[grep("rf_grid_model", files)]

for (model_id in rf_models) {

  path <- paste0("U:\\Github_blog\\Webinar\\Webinar_ML_for_disease\\models\\", model_id)
  #path <- paste0("/Users/Shirin/Documents/Github/Webinar_ML_for_disease/models/", model_id)
  best_model <- h2o.loadModel(path)
  mse_auc_test <- data.frame(model_id = model_id,
                             mse = h2o.mse(h2o.performance(best_model, test)),
                             auc = h2o.auc(h2o.performance(best_model, test)))

  if (model_id == rf_models[[1]]) {

    mse_auc_test_comb <- mse_auc_test

  } else {

    mse_auc_test_comb <- rbind(mse_auc_test_comb, mse_auc_test)

  }
}

mse_auc_test_comb %>%
  gather(x, y, mse:auc) %>%
  ggplot(aes(x = model_id, y = y, fill = model_id)) +
    facet_grid(x ~ ., scales = "free") +
    geom_bar(stat = "identity", alpha = 0.8, position = "dodge") +
    scale_fill_brewer(palette = "Set1") +
    theme(axis.text.x = element_text(angle = 45, vjust = 1, hjust = 1),
          plot.margin = unit(c(0.5, 0, 0, 1.5), "cm")) +
    labs(x = "", y = "value", fill = "")
```

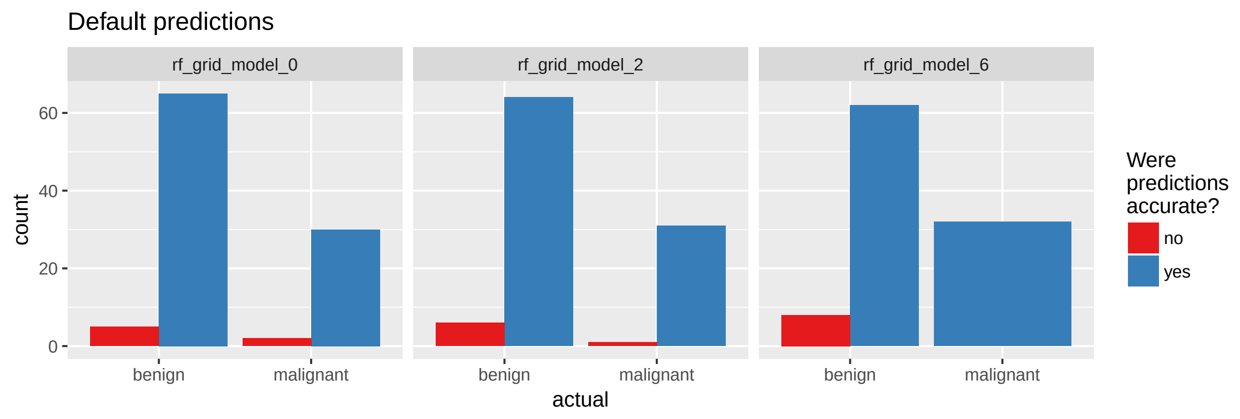


I will then create a dataframe with predictions for each test sample with all best models. As in last week's post, I want to compare the default predictions with stringent predictions.

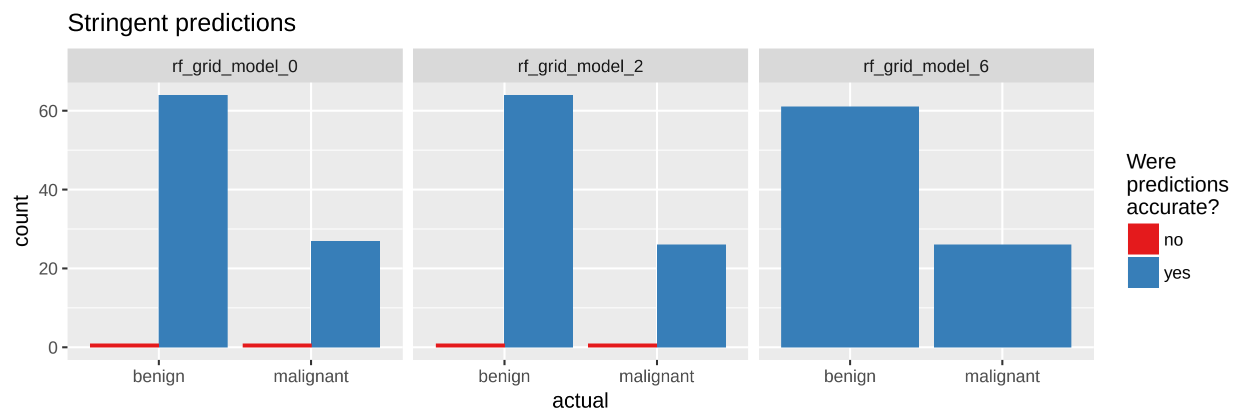
```
for (model_id in rf_models) {

  best_model <- h2o.getModel(model_id)

  finalRf_predictions <- data.frame(model_id = rep(best_model@model_id,
                                                 nrow(test)),
                                    actual = as.vector(test$classes),
                                    as.data.frame(h2o.predict(object = best_model,
                                                              newdata = test)))

  finalRf_predictions$accurate <- ifelse(finalRf_predictions$actual == finalRf_predictions$predict,
                                         "yes", "no")

  finalRf_predictions$predict_stringent <- ifelse(finalRf_predictions$benign > 0.8,
                                                  "benign",
                                                  ifelse(finalRf_predictions$malignant > 0.8,
                                                         "malignant", "uncertain"))

  finalRf_predictions$accurate_stringent <- ifelse(finalRf_predictions$actual == finalRf_predictions$pr
                                                   "yes",
                                         ifelse(finalRf_predictions$predict_stringent == "uncertain",
                                                "na", "no"))

  if (model_id == rf_models[[1]]) {

    finalRf_predictions_comb <- finalRf_predictions
  } else {

    finalRf_predictions_comb <- rbind(finalRf_predictions_comb, finalRf_predictions)

  }
}
```

```
##
  |
  |                                                                 |   0%
  |
  |=================================================================| 100%
##
  |
  |                                                                 |   0%
  |
  |=================================================================| 100%
##
  |
  |                                                                 |   0%
  |
  |=================================================================| 100%
```

```
finalRf_predictions_comb %>%
  ggplot(aes(x = actual, fill = accurate)) +
    geom_bar(position = "dodge") +
    scale_fill_brewer(palette = "Set1") +
    facet_wrap(~ model_id, ncol = 3) +
    labs(fill = "Were\npredictions\naccurate?",
         title = "Default predictions")
```



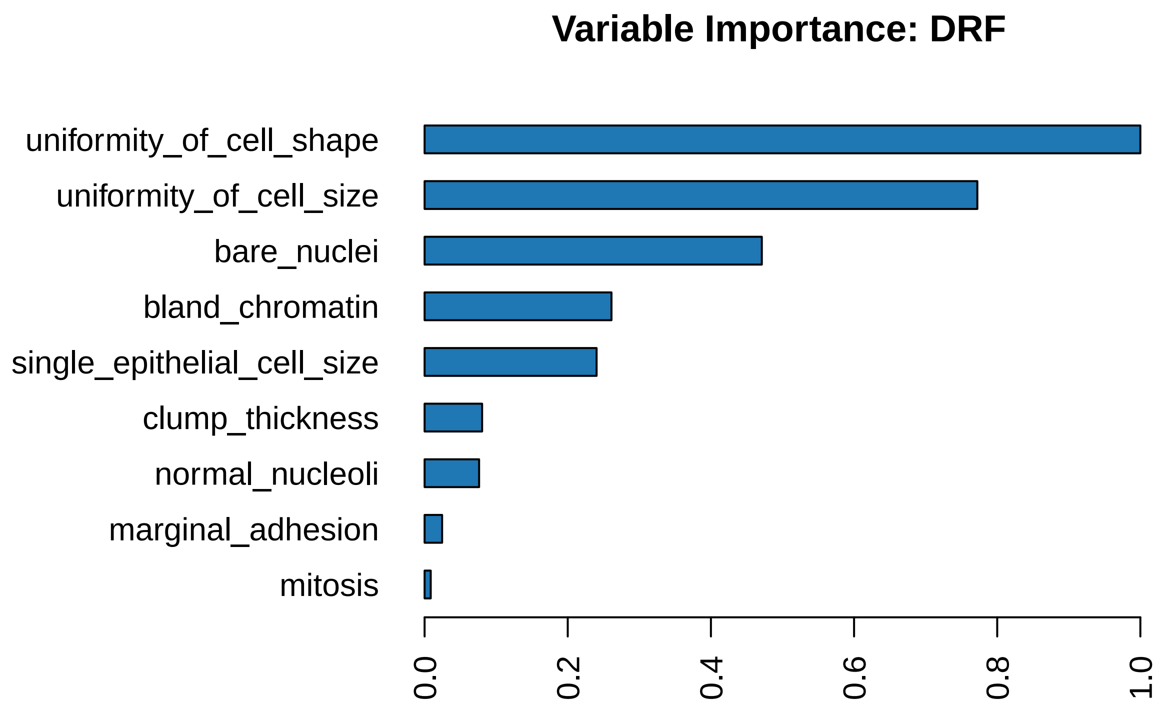
```
finalRf_predictions_comb %>%
  subset(accurate_stringent != "na") %>%
  ggplot(aes(x = actual, fill = accurate_stringent)) +
    geom_bar(position = "dodge") +
    scale_fill_brewer(palette = "Set1") +
    facet_wrap(~ model_id, ncol = 3) +
    labs(fill = "Were\npredictions\naccurate?",
         title = "Stringent predictions")
```



With predictions made by different models, we can see where each model performs best. This obviously corresponds with the quality metric we chose to define the best model. Stringent prediction thresholds reduced the number of false predictions but of course also the number of predictions made at all.

```
rf_model <- h2o.loadModel("U:\\Github_blog\\Webinar\\Webinar_ML_for_disease\\models\\rf_grid_model_6")
#rf_model <- h2o.loadModel("models/rf_grid_model_6")
#summary(rf_model)
#str(rf_model)
```

```
h2o.varimp_plot(rf_model)
```



```
#h2o.varimp(rf_model)
```

One performance metric we are interested in is the mean per class error for training and validation data.

```r
h2o.mean_per_class_error(rf_model, train = TRUE, valid = TRUE, xval = TRUE)
```

```
##       train       valid        xval 
## 0.024674571 0.007042254 0.023097284
```

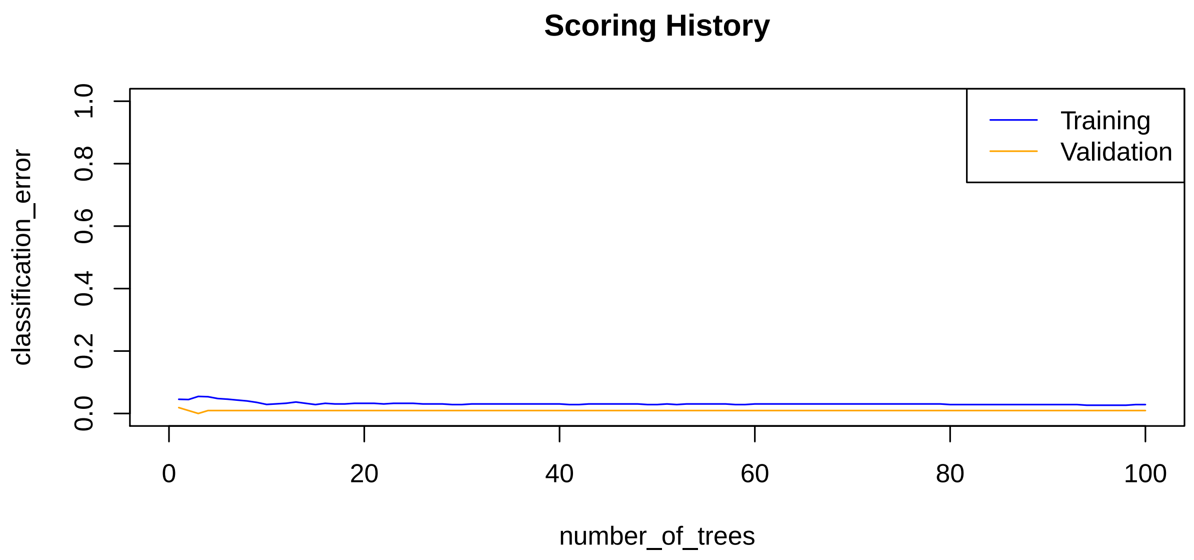
The confusion matrix tells us, how many classes have been predicted correctly and how many predictions were accurate. Here, we see the errors in predictions on validation data

```r
h2o.confusionMatrix(rf_model, valid = TRUE)
```

```
## Confusion Matrix (vertical: actual; across: predicted)  for max f1 @ threshold = 0.293125896751881:
##           benign malignant    Error     Rate
## benign        70         1 0.014085    =1/71
## malignant      0        35 0.000000    =0/35
## Totals        70        36 0.009434  =1/106
```

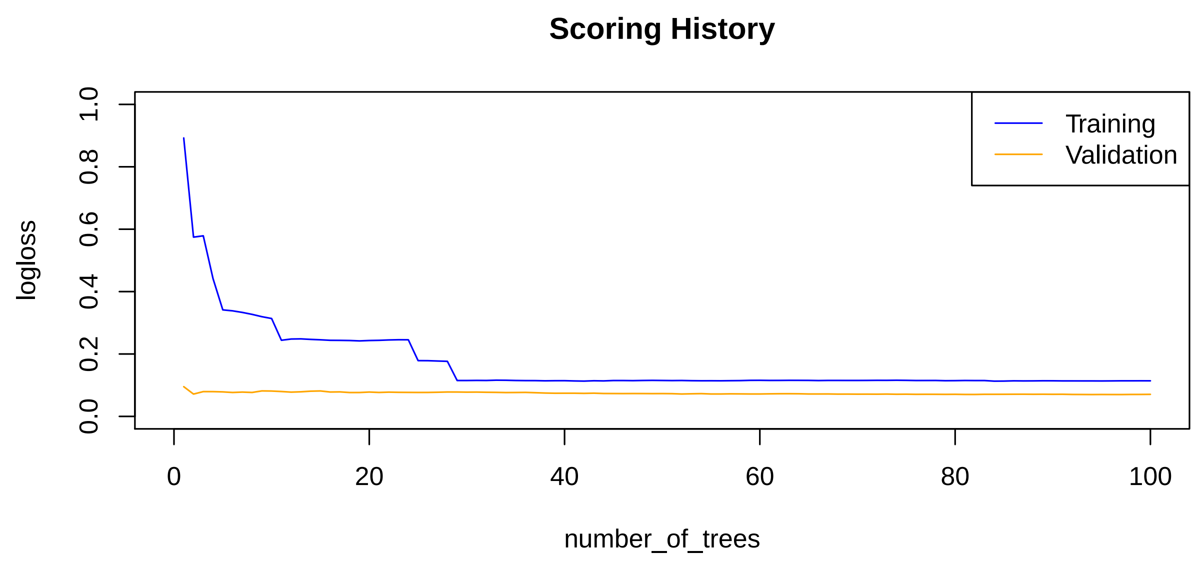
We can also plot the classification error.

```r
plot(rf_model,
     timestep = "number_of_trees",
     metric = "classification_error")
```

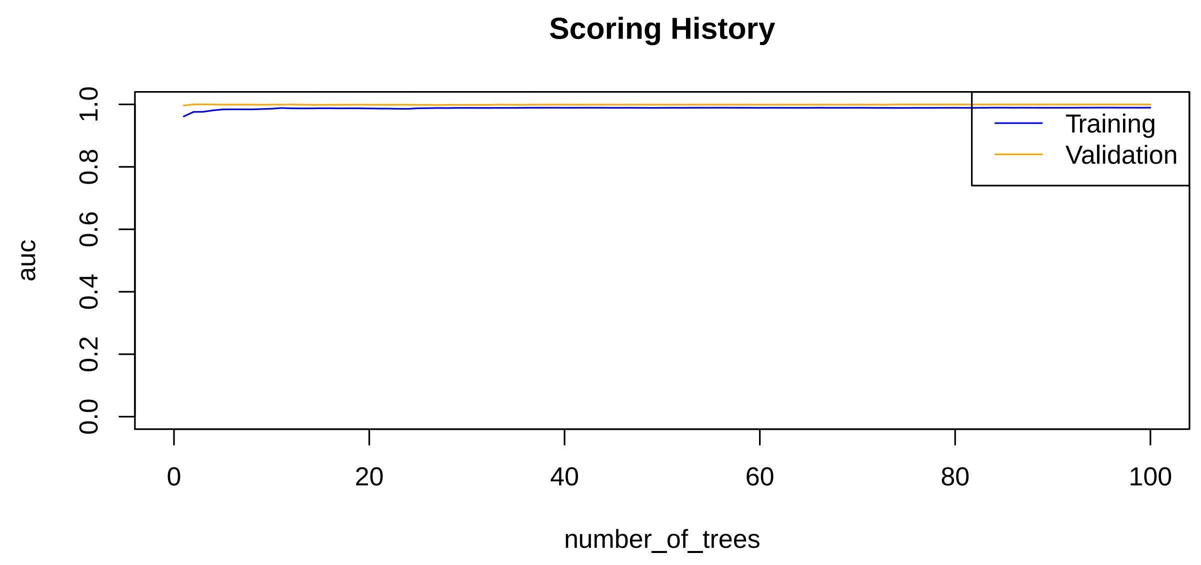


Next to the classification error, we are usually interested in the logistic loss (negative log-likelihood or log loss). It describes the sum of errors for each sample in the training or validation data or the negative logarithm of the likelihood of error for a given prediction/ classification. Simply put, the lower the loss, the better the model (if we ignore potential overfitting).

```r
plot(rf_model,
     timestep = "number_of_trees",
     metric = "logloss")
```

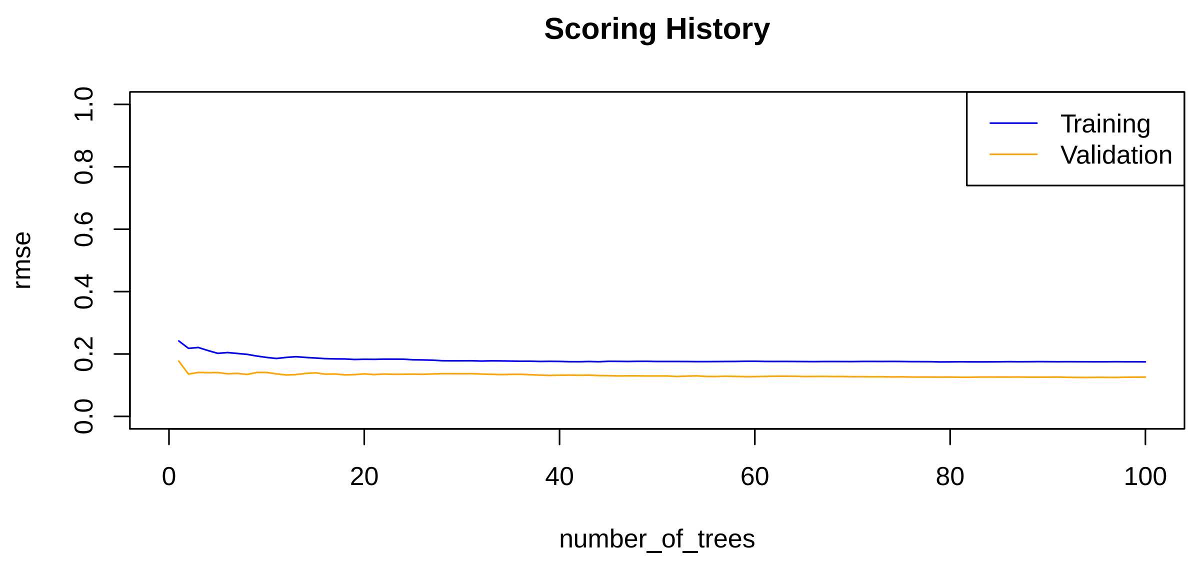


```r
plot(rf_model,
     timestep = "number_of_trees",
     metric = "AUC")
```



We can also plot the mean squared error (MSE). The MSE tells us the average of the prediction errors squared, i.e. the estimator's variance and bias. The closer to zero, the better a model.

```r
plot(rf_model,
     timestep = "number_of_trees",
     metric = "rmse")
```



Next, we want to know the area under the curve (AUC). AUC is an important metric for measuring binary classification model performances. It gives the area under the curve, i.e. the integral, of true positive vs false positive rates. The closer to 1, the better a model. AUC is especially useful, when we have unbalanced datasets (meaning datasets where one class is much more common than the other), because it is independent of class labels.

```
h2o.auc(rf_model, train = TRUE)
```

```
## [1] 0.989521
```

```
h2o.auc(rf_model, valid = TRUE)
```

```
## [1] 0.9995976
```

```
h2o.auc(rf_model, xval = TRUE)
```

```
## [1] 0.9890496
```

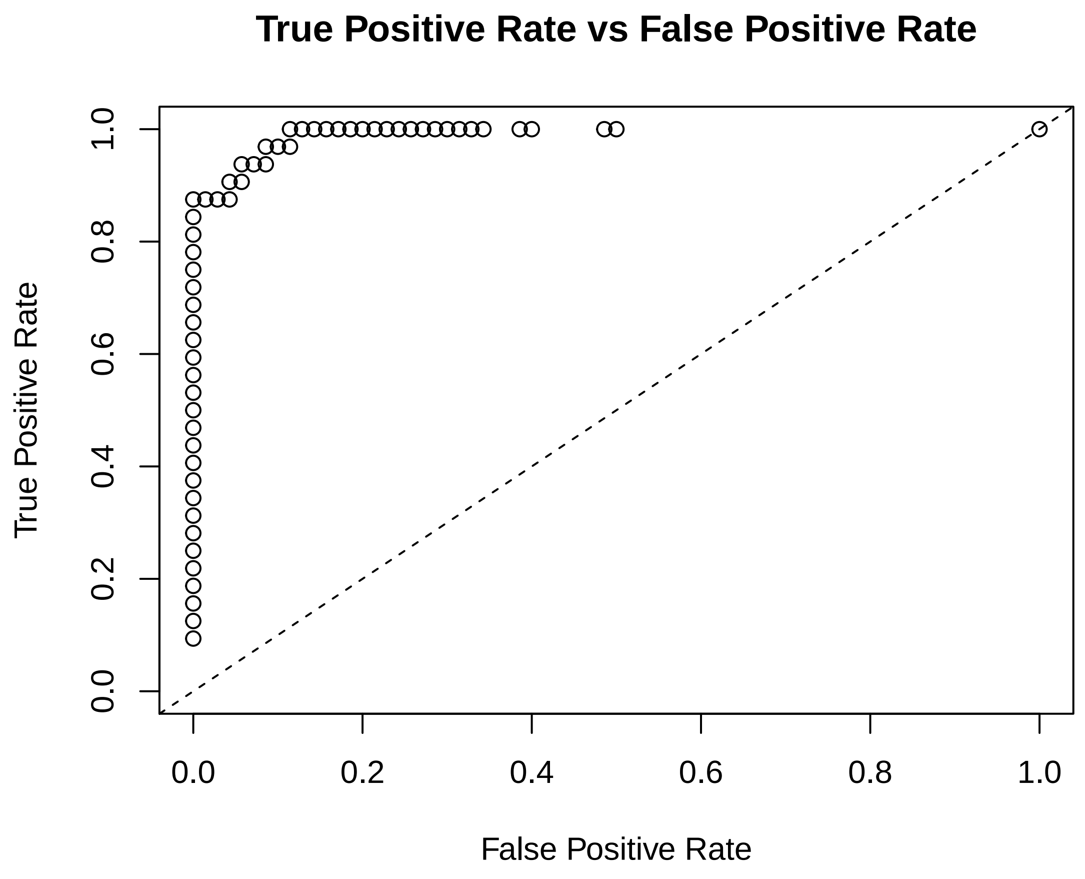
Now that we have a good idea about model performance on validation data, we want to know how it performed on unseen test data. A good model should find an optimal balance between accuracy on training and test data. A model that has 0% error on the training data but 40% error on the test data is in effect useless. It overfit on the training data and is thus not able to generalize to unknown data.

```
perf <- h2o.performance(rf_model, test)
perf
```

```
## H2OBinomialMetrics: drf
##
## MSE:  0.03673598
## RMSE:  0.1916663
## LogLoss:  0.1158835
## Mean Per-Class Error:  0.0625
## AUC:  0.990625
## Gini:  0.98125
##
## Confusion Matrix (vertical: actual; across: predicted) for F1-optimal threshold:
##           benign malignant    Error    Rate
## benign        70         0 0.000000   =0/70
## malignant      4        28 0.125000   =4/32
## Totals        74        28 0.039216  =4/102
##
## Maximum Metrics: Maximum metrics at their respective thresholds
##                         metric threshold    value idx
## 1                       max f1  0.735027 0.933333  25
## 2                       max f2  0.294222 0.952381  37
## 3                 max f0point5  0.735027 0.972222  25
## 4                 max accuracy  0.735027 0.960784  25
## 5                max precision  1.000000 1.000000   0
## 6                   max recall  0.294222 1.000000  37
## 7              max specificity  1.000000 1.000000   0
## 8             max absolute_mcc  0.735027 0.909782  25
## 9   max min_per_class_accuracy  0.424524 0.937500  31
## 10 max mean_per_class_accuracy  0.294222 0.942857  37
##
## Gains/Lift Table: Extract with `h2o.gainsLift(<model>, <data>)` or `h2o.gainsLift(<model>, valid=<T/
```

Plotting the test performance's AUC plot shows us approximately how good the predictions are.

```r
plot(perf)
```



We also want to know the log loss, MSE and AUC values, as well as other model metrics for the test data:

```r
h2o.logloss(perf)
```

```
## [1] 0.1158835
```

```r
h2o.mse(perf)
```

```
## [1] 0.03673598
```

```r
h2o.auc(perf)
```

```
## [1] 0.990625
```

```r
head(h2o.metric(perf))
```

```
## Metrics for Thresholds: Binomial metrics as a function of classification thresholds
##   threshold       f1       f2 f0point5 accuracy precision   recall
## 1  1.000000 0.171429 0.114504 0.340909 0.715686  1.000000 0.093750
## 2  0.998333 0.222222 0.151515 0.416667 0.725490  1.000000 0.125000
## 3  0.998000 0.270270 0.187970 0.480769 0.735294  1.000000 0.156250
## 4  0.997222 0.315789 0.223881 0.535714 0.745098  1.000000 0.187500
## 5  0.996210 0.358974 0.259259 0.583333 0.754902  1.000000 0.218750
## 6  0.994048 0.400000 0.294118 0.625000 0.764706  1.000000 0.250000
##   specificity absolute_mcc min_per_class_accuracy mean_per_class_accuracy
## 1    1.000000     0.257464               0.093750                0.546875
## 2    1.000000     0.298807               0.125000                0.562500
## 3    1.000000     0.335794               0.156250                0.578125
## 4    1.000000     0.369755               0.187500                0.593750
## 5    1.000000     0.401478               0.218750                0.609375
## 6    1.000000     0.431474               0.250000                0.625000
##   tns fns fps tps      tnr      fnr      fpr      tpr idx
## 1  70  29   0   3 1.000000 0.906250 0.000000 0.093750   0
## 2  70  28   0   4 1.000000 0.875000 0.000000 0.125000   1
## 3  70  27   0   5 1.000000 0.843750 0.000000 0.156250   2
## 4  70  26   0   6 1.000000 0.812500 0.000000 0.187500   3
## 5  70  25   0   7 1.000000 0.781250 0.000000 0.218750   4
## 6  70  24   0   8 1.000000 0.750000 0.000000 0.250000   5
```

The final predictions with probabilities can be extracted with the *h2o.predict()* function. Beware though, that the number of correct and wrong classifications can be slightly different from the confusion matrix above. Here, I combine the predictions with the actual test diagnoses and classes into a data frame. For plotting I also want to have a column, that tells me whether the predictions were correct. By default, a prediction probability above 0.5 will get scored as a prediction for the respective category. I find it often makes sense to be more stringent with this, though and set a higher threshold. Therefore, I am creating another column with stringent predictions, where I only count predictions that were made with more than 80% probability. Everything that does not fall within this range gets scored as "uncertain". For these stringent predictions, I am also creating a column that tells me whether they were accurate.

```r
finalRf_predictions <- data.frame(actual = as.vector(test$classes),
                                  as.data.frame(h2o.predict(object = rf_model, newdata = test)))
```

```
##
  |
  |                                                                 |   0%
  |
  |=================================================================| 100%
```

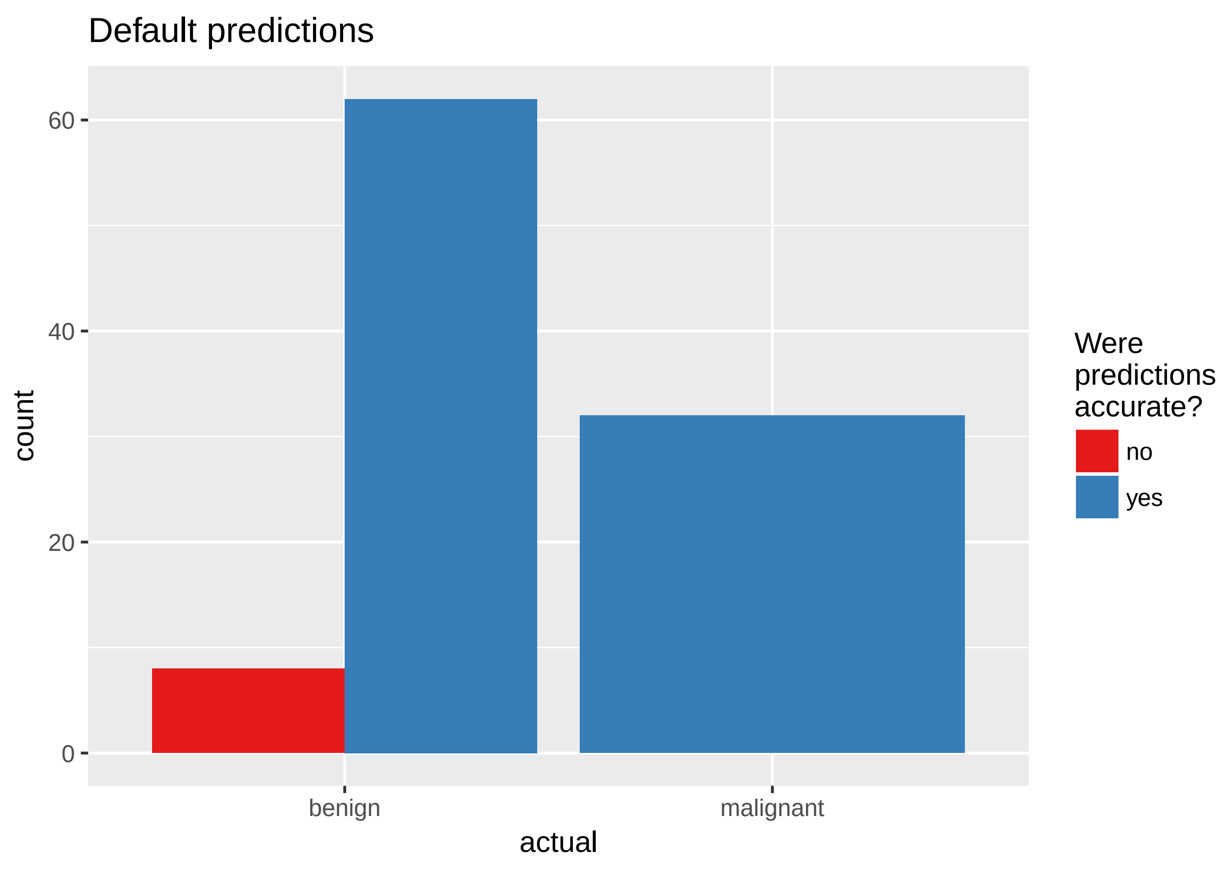
```
finalRf_predictions$accurate <- ifelse(finalRf_predictions$actual == finalRf_predictions$predict, "yes"

finalRf_predictions$predict_stringent <- ifelse(finalRf_predictions$benign > 0.8, "benign",
                                               ifelse(finalRf_predictions$malignant > 0.8, "malignant"
finalRf_predictions$accurate_stringent <- ifelse(finalRf_predictions$actual == finalRf_predictions$predi
                                           ifelse(finalRf_predictions$predict_stringent == "uncertain", "na

finalRf_predictions %>%
  group_by(actual, predict) %>%
  dplyr::summarise(n = n())
```

```
## Source: local data frame [3 x 3]
## Groups: actual [?]
##
##      actual   predict     n
##      <fctr>    <fctr> <int>
## 1    benign    benign    62
## 2    benign malignant     8
## 3 malignant malignant    32
```

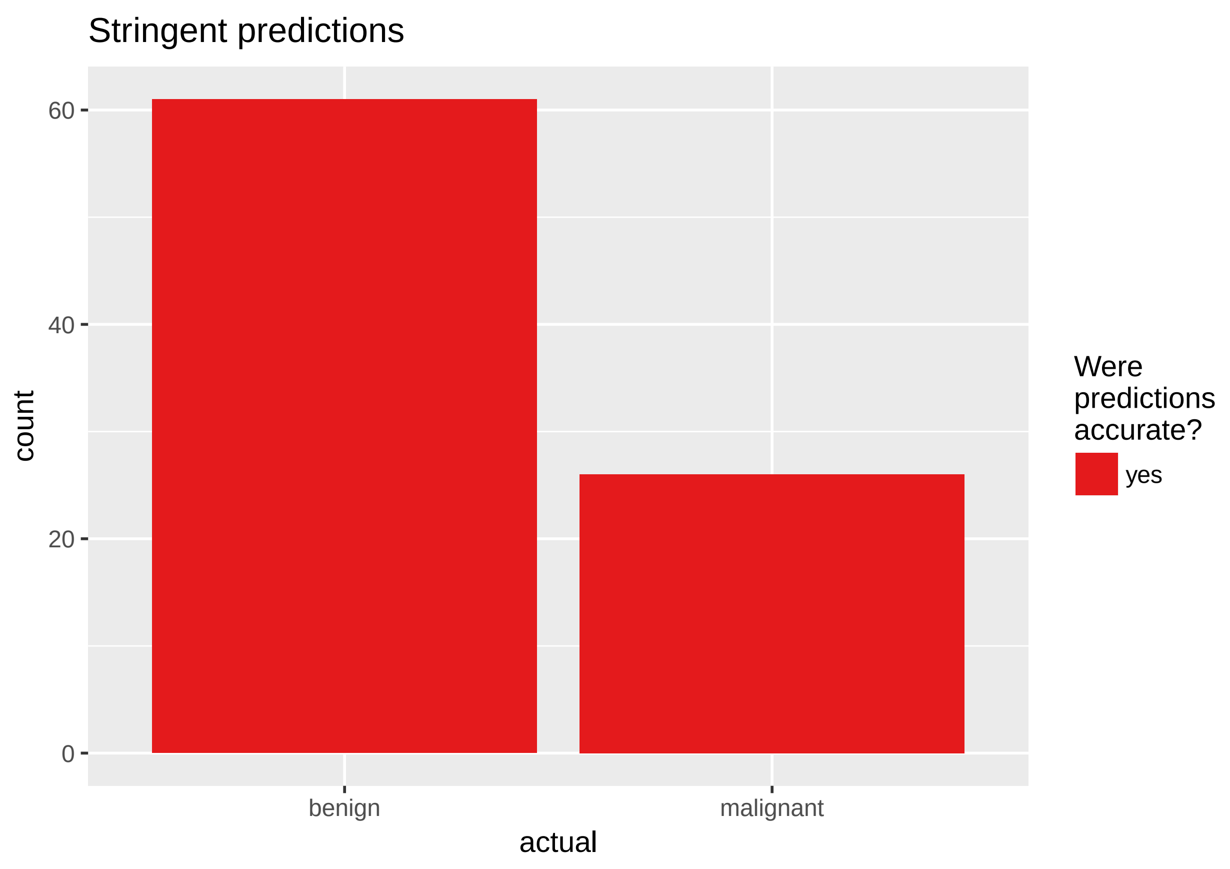
```
finalRf_predictions %>%
  group_by(actual, predict_stringent) %>%
  dplyr::summarise(n = n())
```

```
## Source: local data frame [4 x 3]
## Groups: actual [?]
##
##      actual predict_stringent     n
##      <fctr>             <chr> <int>
## 1    benign            benign    61
## 2    benign         uncertain     9
## 3 malignant         malignant    26
## 4 malignant         uncertain     6
```

```
finalRf_predictions %>%
  ggplot(aes(x = actual, fill = accurate)) +
    geom_bar(position = "dodge") +
    scale_fill_brewer(palette = "Set1") +
    labs(fill = "Were\npredictions\naccurate?",
         title = "Default predictions")
```



```r
finalRf_predictions %>%
  subset(accurate_stringent != "na") %>%
  ggplot(aes(x = actual, fill = accurate_stringent)) +
    geom_bar(position = "dodge") +
    scale_fill_brewer(palette = "Set1") +
    labs(fill = "Were\npredictions\naccurate?",
         title = "Stringent predictions")
```



Deep learning with neural networks

Deep learning with neural networks is arguably one of the most rapidly growing applications of machine learning and AI today. They allow building complex models that consist of multiple hidden layers within artifiical networks and are able to find non-linear patterns in unstructured data. Deep neural networks are usually feed-forward, which means that each layer feeds its output to subsequent layers, but recurrent or feed-back neural networks can also be built. Feed-forward neural networks are also called multilayer perceptrons (MLPs).

We can specify quite a few parameters, like

- **Cross-validation**: Cross validation can tell us the training and validation errors for each model. The final model will be overwritten with the best model, if we don't specify otherwise.
- **Adaptive learning rate**: For deep learning with h2o, we by default use stochastic gradient descent optimization with an an adaptive learning rate. The two corresponding parameters *rho* and *epsilon* help us find global (or near enough) optima.
- **Epochs**: Increasing the number of epochs (one full training cycle on all training samples) can increase model performance, but we also run the risk of overfitting. To determine the optimal number of epochs, we need to use early stopping.
- **Early stopping**: By default, early stopping is enabled. This means that training will be stopped when we reach a certain validation error to prevent overfitting. `stopping_metric`: metric that we want to use as stopping criterion. `stopping_tolerance` and `stopping_rounds`: training stops when the the stopping metric does not improve by the stopping tolerance proportion any more (e.g. by 0.05 or 5%) for the number of consecutive rounds defined by stopping rounds.

- **Activation Functions**: The activation function defines the node output relative to a given set of inputs. We want our activation function to be non-linear and continuously differentiable.

`Rectifier`: is the default activation function. It is the fastest and most versatile option. It can lead to instability though and tends to be lower in accuracy. `Tanh`: The hyperbolic tangent is a scaled and shifted variant of the sigmoid activation function. It can take on values from -1 to 1 and centers around 0. Tanh needs more computational power than e.g. the Rectifier function. `Maxout`: is an activation function that is the max of the inputs. It is computationally quite demanding but can produce high accuracy models.

`...WithDropout`: When we specify `with dropout`, a random subset of the network is trained and the weights of all sub-networks are averaged. It works together with the parameter `hidden_dropout_ratios`, which controls the amount of layer neurons that are randomly dropped for each hidden layer. Hidden dropout ratios are useful for preventing overfitting on learned features.

- **Hidden layers**: Defines the number of hidden layers and the number of nodes per layer and are the most important hyper-parameter to set for deep neural networks, as they specify how many hidden layers and how many nodes per hidden layer the model should learn
- **L1 and L2 penalties**: `L1`: lets only strong weights survive. `L2`: prevents any single weight from getting too big.
- **Rho and Epsilon**: `rho`: similar to prior weight updates. `epsilon`: prevents getting stuck in local optima

```
hyper_params <- list(
                     activation = c("Rectifier", "Maxout", "Tanh", "RectifierWithDropout",
                                    "MaxoutWithDropout", "TanhWithDropout"),
                     hidden = list(c(5, 5, 5, 5, 5), c(10, 10, 10, 10), c(50, 50, 50)),
                     epochs = c(50, 100, 200),
                     l1 = c(0, 0.00001, 0.0001),
                     l2 = c(0, 0.00001, 0.0001),
                     rate = c(0, 01, 0.005, 0.001),
                     rate_annealing = c(1e-8, 1e-7, 1e-6),
                     rho = c(0.9,0.95,0.99,0.999),
                     epsilon = c(1e-10,1e-8,1e-6,1e-4),
                     input_dropout_ratio = c(0, 0.1, 0.2),
                     max_w2 = c(10, 100, 1000, 3.4028235e+38)
                     )
```

Now, we can train the model with combinations of hyper-parameters from our specified stopping criteria and hyper-parameter grid.

```
dl_grid <- h2o.grid(algorithm = "deeplearning",
                    x = features,
                    y = response,
                    grid_id = "dl_grid",
                    training_frame = train,
                    validation_frame = valid,
                    nfolds = 25,
                    fold_assignment = "Stratified",
                    hyper_params = hyper_params,
                    search_criteria = search_criteria,
                    seed = 42
                    )
```

```
grid <- h2o.getGrid("dl_grid", sort_by = "auc", decreasing = TRUE)

model_ids <- grid@model_ids
```

```r
best_model <- h2o.getModel(model_ids[[1]])
```

Because training can take a while, depending on how many samples, features, nodes and hidden layers you are training on, it is a good idea to save your model.

```r
h2o.saveModel(best_model, path = "models", force = TRUE)
```

We can then re-load the model again any time to check the model quality and make predictions on new data.

```r
dl_model <- h2o.loadModel("models/dl_grid_model_8")
```

We now want to know how our model performed on the validation data. The *summary()* function will give us a detailed overview of our model. I am not showing the output here, because it is quite extensive.

```r
perf <- h2o.performance(dl_model, test)
plot(perf)

h2o.confusionMatrix(dl_model, test)
```

```r
h2o.shutdown()
```

If you are interested in more machine learning posts, check out the category listing for **machine_learning** on my blog.

```r
sessionInfo()
```

```
## R version 3.3.3 (2017-03-06)
## Platform: x86_64-w64-mingw32/x64 (64-bit)
## Running under: Windows 7 x64 (build 7601) Service Pack 1
##
## locale:
## [1] LC_COLLATE=English_United States.1252
## [2] LC_CTYPE=English_United States.1252
## [3] LC_MONETARY=English_United States.1252
## [4] LC_NUMERIC=C
## [5] LC_TIME=English_United States.1252
##
## attached base packages:
## [1] stats4    parallel  stats     graphics  grDevices utils     datasets
## [8] methods   base
##
## other attached packages:
##  [1] ggrepel_0.6.5        reshape2_1.4.2       h2o_3.10.3.6
##  [4] corrplot_0.77        plyr_1.8.4           xgboost_0.6-4
##  [7] randomForest_4.6-12  rpart.plot_2.1.1     rpart_4.1-10
## [10] dplyr_0.5.0          caret_6.0-73         lattice_0.20-34
## [13] tidyr_0.6.1          pcaGoPromoter_1.18.0 Biostrings_2.42.1
## [16] XVector_0.14.0       IRanges_2.8.1        S4Vectors_0.12.1
## [19] BiocGenerics_0.20.0  ellipse_0.3-8        ggplot2_2.2.1.9000
##
## loaded via a namespace (and not attached):
##  [1] Rcpp_0.12.9          class_7.3-14         assertthat_0.1
##  [4] rprojroot_1.2        digest_0.6.12        foreach_1.4.3
##  [7] R6_2.2.0             backports_1.0.5      MatrixModels_0.4-1
## [10] RSQLite_1.1-2       evaluate_0.10       e1071_1.6-8
## [13] zlibbioc_1.20.0     lazyeval_0.2.0      minqa_1.2.4
## [16] data.table_1.10.4   SparseM_1.76        car_2.1-4
## [19] nloptr_1.0.4        Matrix_1.2-8        rmarkdown_1.3
## [22] labeling_0.3        splines_3.3.3       lme4_1.1-12
## [25] stringr_1.2.0       RCurl_1.95-4.8      munsell_0.4.3
## [28] compiler_3.3.3      mgcv_1.8-17         htmltools_0.3.5
## [31] nnet_7.3-12         tibble_1.2          codetools_0.2-15
## [34] bitops_1.0-6        MASS_7.3-45         ModelMetrics_1.1.0
## [37] grid_3.3.3          jsonlite_1.3        nlme_3.1-131
## [40] gtable_0.2.0        DBI_0.6             magrittr_1.5
## [43] scales_0.4.1        stringi_1.1.2       RColorBrewer_1.1-2
## [46] iterators_1.0.8     tools_3.3.3         Biobase_2.34.0
## [49] pbkrtest_0.4-6      yaml_2.1.14         AnnotationDbi_1.36.2
## [52] colorspace_1.3-2    memoise_1.0.0       knitr_1.15.1
## [55] quantreg_5.29
```