Statistical Consulting Project

Addressing Class Imbalance in Random Forest Classifier Used to Identify Potential Pancreatic Cancer Cases

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Project Context

- Completed for a consulting course (Statistics, MS program)
- Client is fictional
- Students imagined client problems to address with a real analysis

Topic Selection

Elements desired:

- Has application in the oncology field
- Makes use of machine learning methods for classification learned in the previous semester
- Requires handling class imbalance

Dataset Selection

From the following study publication:

Debernardi S, O'Brien H, Algahmdi AS, Malats N, Stewart GD, Plješa-Ercegovac M, et al. (2020) A combination of urinary biomarker panel and PancRISK score for earlier detection of pancreatic cancer: A case–control study. PLoS Med 17(12): e1003489. https://doi.org/10.1371/journal.pmed.1003489

Focus of the above study:

Development of a non-invasive diagnostic test for more proactive pancreatic cancer detection, which uses several urinary biomarkers as predictors in classifying patients as high or low risk for the cancer.

Some Background

Pancreatic ductal adenocarcinoma (PDAC)

- The type of pancreatic cancer examined in the Debernardi, et al. study
- Most common, most aggressive, form of pancreatic cancer
- Across all cancers, one of the most lethal
- Very poor survival rate (~ 9% beyond 5 years)
- Silent killer: once symptoms of PDAC develop, it is far less treatable

Impact?

Early detection could increase 5 year survival rate to 70%.
Early detection requires frequent diagnostic screening for PDAC indicators, before symptoms develop.

Historical Biomarkers	Debernardi, et al. Biomarkers
• Invasive collection (e.g., plasma) • Lower biomarker concentration • Infrequent screening	• Completely non-invasive urine sample collection • Much higher biomarker concentration • Frequent screening is practical

The Data & Modifications

Debernardi, et al. Dataset	Modified Dataset
• Response: diagnosis 1: healthy control (n=183) 2: benign pancreas condition (n=208) 3: PDAC (n=199) • Predictors: age (years) creatinine (mmol/L) LYVE1 (pg/ml) REG1B (pg/ml) TFF1 (pg/ml)	• Response: diagnosis “no”: no PDAC (n=391) “yes”: PDAC (n=44) • Predictors: sex (M/F) age (years) creatinine (mmol/L) LYVE1 (pg/ml) REG1B (pg/ml) TFF1 (pg/ml)

Urine Panel Predictors

Why do these indicate higher risk of PDAC?

creatinine - High levels are associated with acute pancreatitis, a known risk factor for PDAC
LYVE1 - (lymphatic vessel endothelial hyaluronan receptor 1) is a protein present in lymphatic vessels when pancreatic cancer is invading
REG1B - (regenerating family member 1 beta) is a glycoprotein seen in patients with pancreatitis
TFF1 - (trefoil factor 1) is a gastrointestinal secretory peptide which is more highly expressed during development of a variety of cancer types

Setting: Client Study & Goals

The client seeks to

- develop a random forest classifier as the procedure for a simple non-invasive urine test for early detection of PDAC
- use the data from the Debernardi, et al. study to validate the model
- use predictors age, sex, creatinine, and urinary biomarkers LYVE1, REG1B, and TFF1 to classify samples as “no” = low risk, or “yes” = high risk for PDAC

Performance Requirements

True positive rate
≥ 0.90

False positive rate
≤ 0.25

Setting: Client Problems

The test accuracy shows 0.90, yet the true positive rate is only 4/13 ...?

The classifier is classifying true cancer cases as low risk for the cancer almost 70% of the time. But our priority is detecting cancer (or risk) when it is there!

Not sure how to see which predictors are the strongest.

```
## Confusion Matrix and Statistics
##
##           Reference
## Prediction yes  no
##        yes   4   3
##        no    9 115
##
##               Accuracy : 0.9084
##                 95% CI : (0.8455, 0.9518)
##    No Information Rate : 0.9008
##    P-Value [Acc > NIR] : 0.4573
##
##                  Kappa : 0.3552
##
```

Setting: Client Questions

Q1 Why is the model output showing high accuracy, when it has such a high misclassification rate for cancer cases?

Q2 What is causing the classifier to perform poorly with respect to identifying cancer as cancer, and how do you recommend this problem be addressed in order to meet the goals of the study?

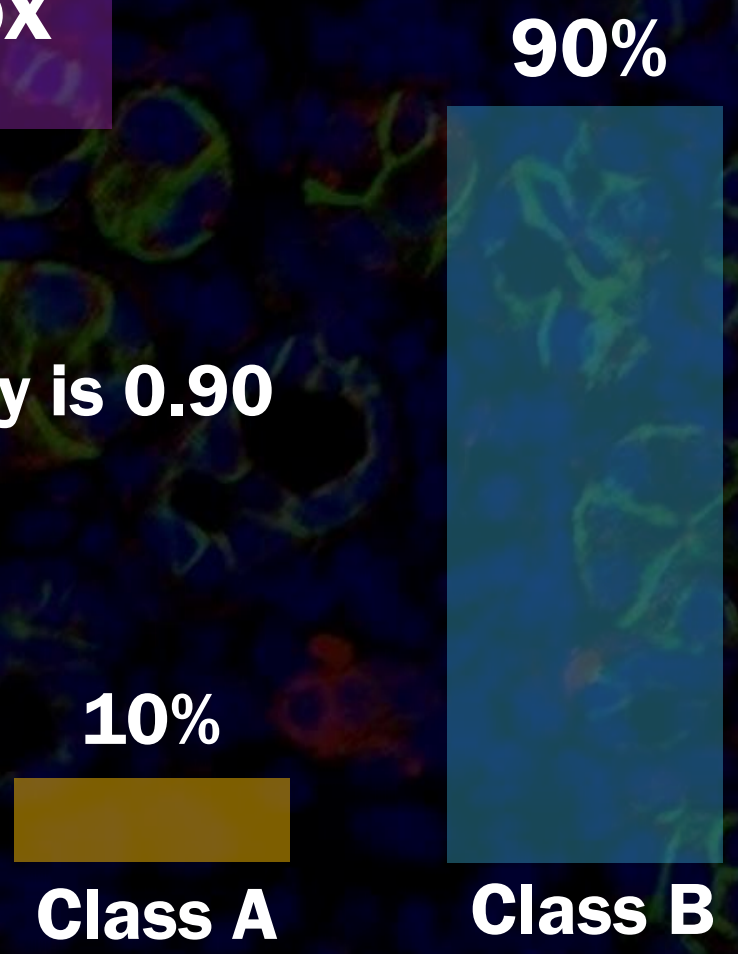
Q3 How can one get a sense of which variables are most important in predicting PDAC risk?

Accuracy Paradox

Class B is classified correctly 100% of the time

Class A is classified correctly 0% of the time

Accuracy is 0.90



Accuracy: Not the performance metric for these goals.

```
##                Accuracy : 0.9084
##                  95% CI : (0.8455, 0.9518)
##     No Information Rate : 0.9008
##     P-Value [Acc > NIR] : 0.4573
##
##                   Kappa : 0.3552
##
##  Mcnemar's Test P-Value : 0.1489
##
##             Sensitivity : 0.30769
##             Specificity : 0.97458
##          Pos Pred Value : 0.57143
```

True positive rate ≥ 0.90

False positive rate ≤ 0.25

→ **Sensitivity ≥ 0.90**

→ **1 - Specificity ≤ 0.25**

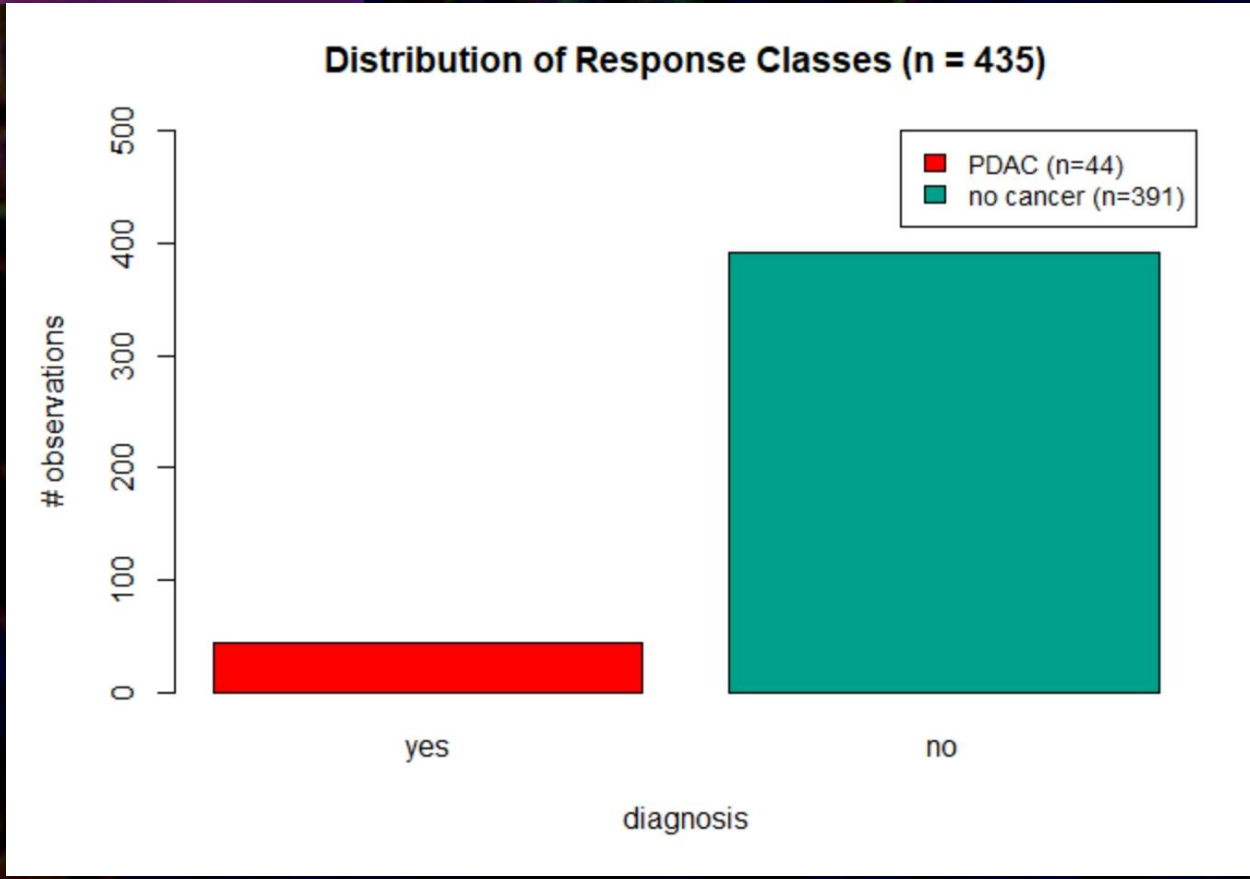
OR

Specificity ≥ 0.75

The reason: class imbalance

Typical classification algorithms work to minimize error rate, without accounting for the class distribution.

They are heavily biased towards the majority class.



What to do about it?

- Collect more PDAC samples!

  But this study won't allow for it, so instead try the following:

- Create train and test sets using random sampling, stratified by class
- Integrate a method for balancing the classes into the model training and validation process. Try different balancing methods and compare performances
- Try different classification algorithms appropriate for the study

Analysis: Objective

- Build a set of candidate models which include various combinations of modifications (algorithms and balancing methods) to enhance performance
- Compare them and tune probability cutoff (tau) of best performing models to reach or further optimize metrics for client performance goals

Analysis: Tools

Software:

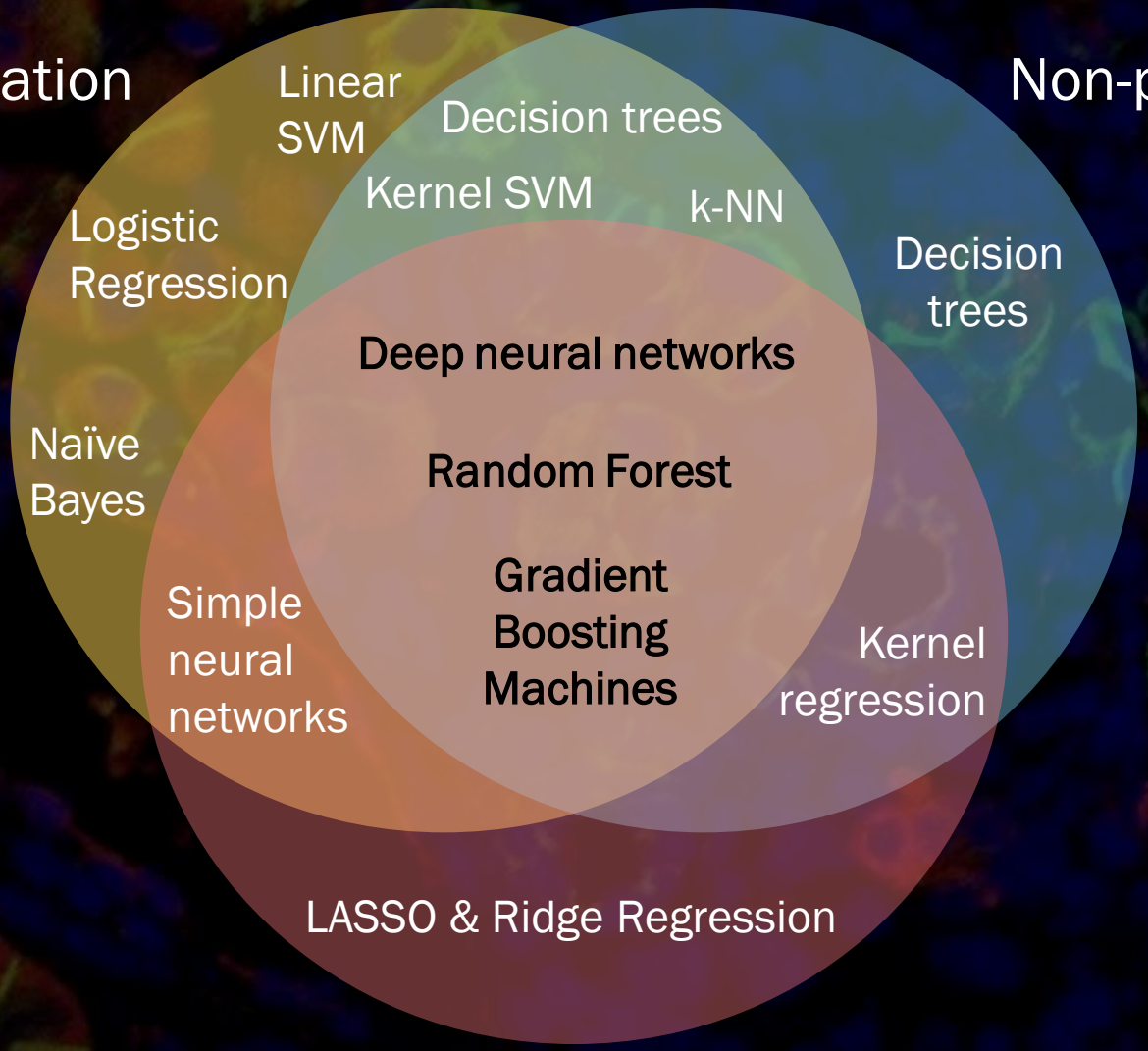
R (version 4.0.5 for Windows)

Packages:

caret – machine learning models
DMwR – SMOTE balancing
ROSE – ROSE balancing
pROC – ROC plots

dplyr – data manipulation
ggplot2 – some plots

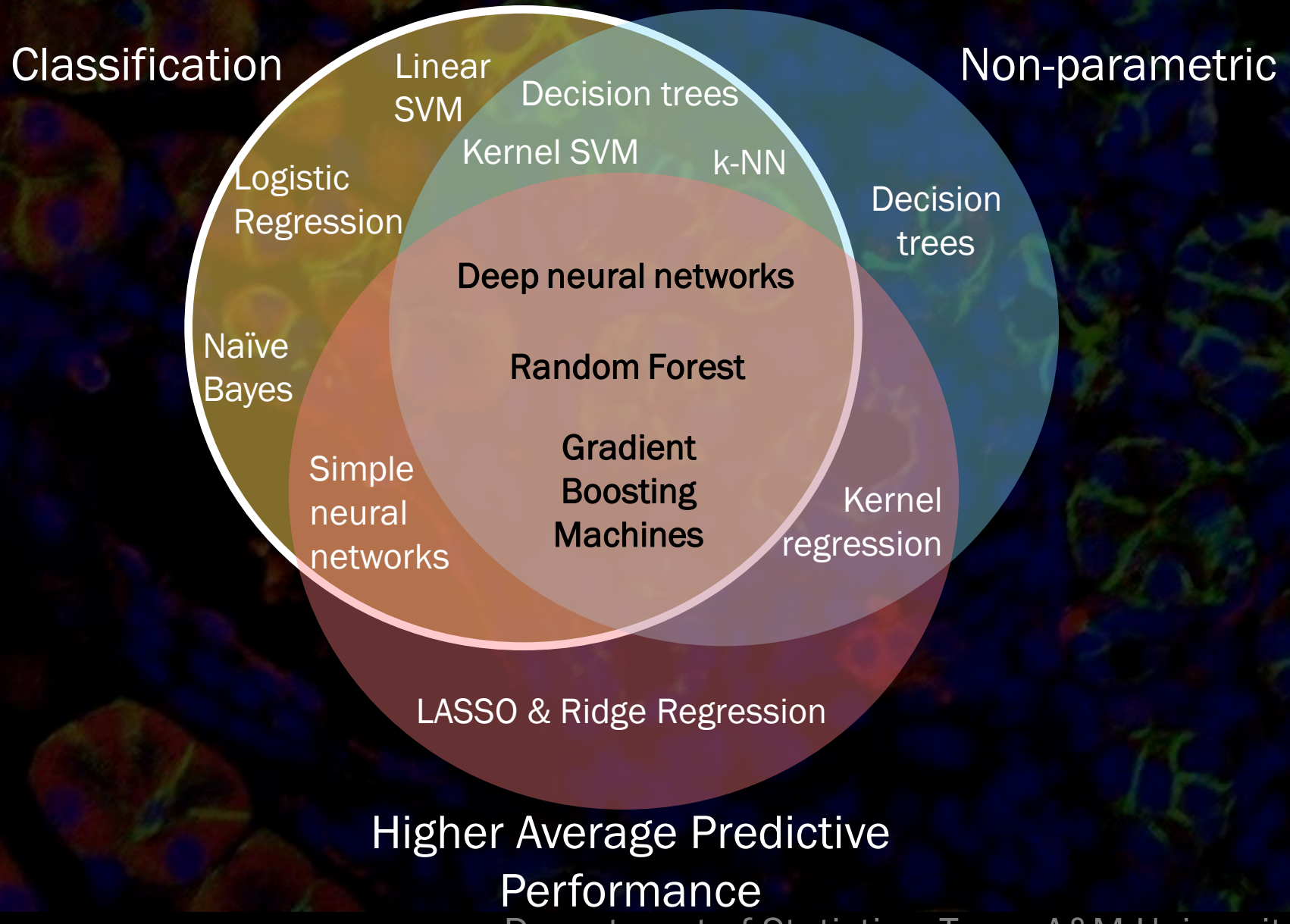
Analysis: Choice of algorithms



Higher Average Predictive Performance

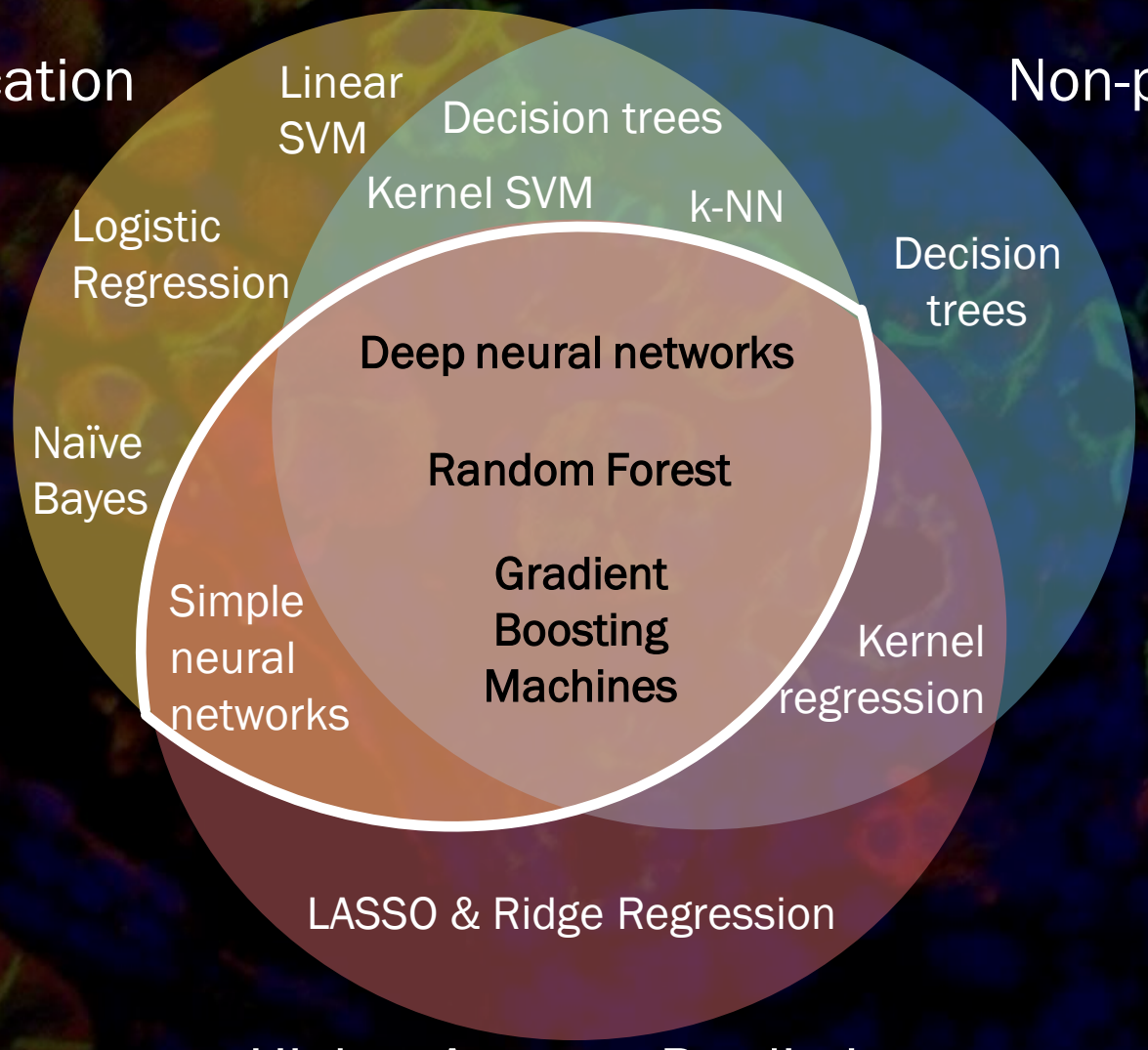
Analysis: Choice of algorithms

- Classification problem



Analysis: Choice of algorithms

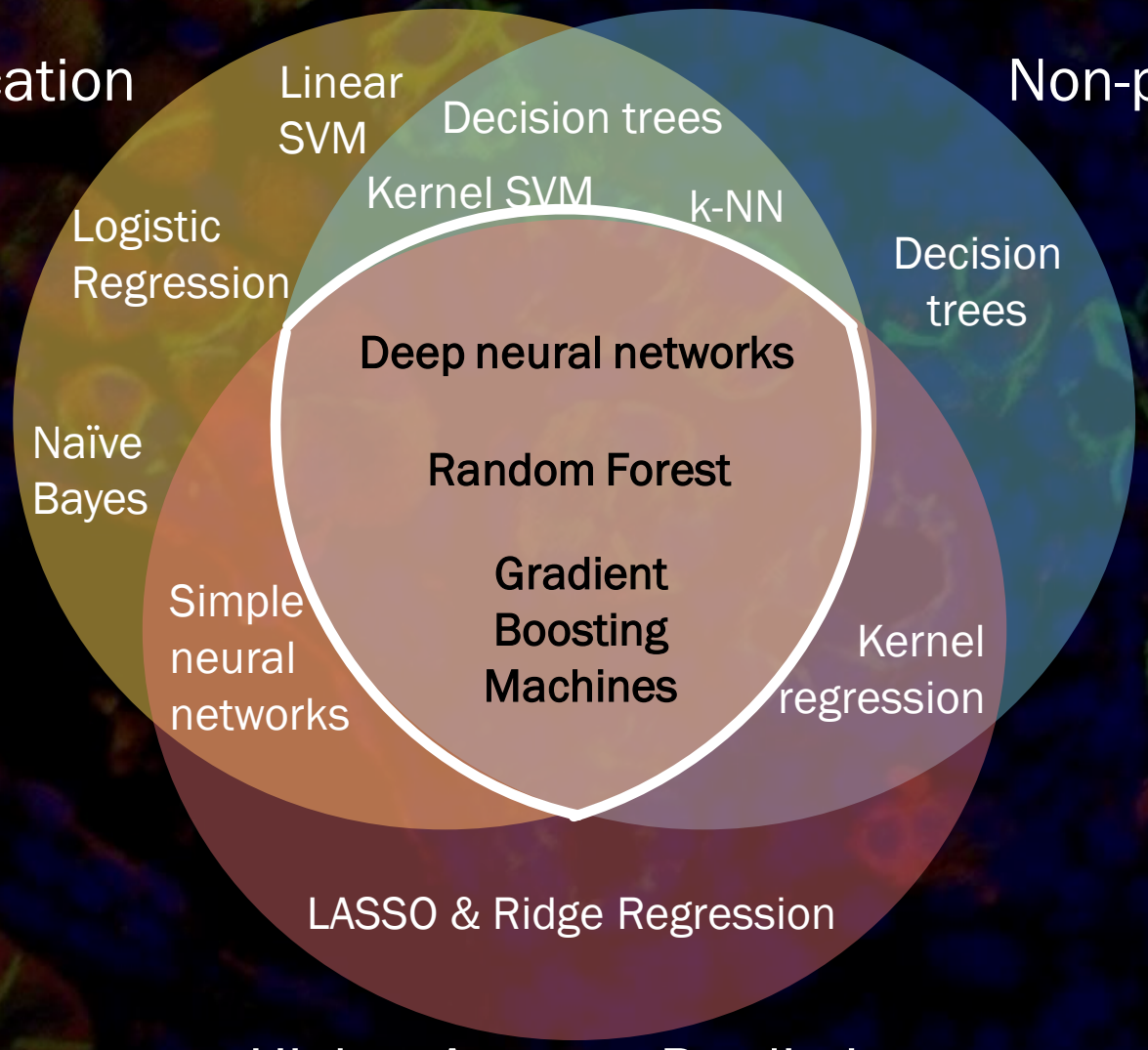
- Classification problem
- Prediction focused



Higher Average Predictive Performance

Analysis: Choice of algorithms

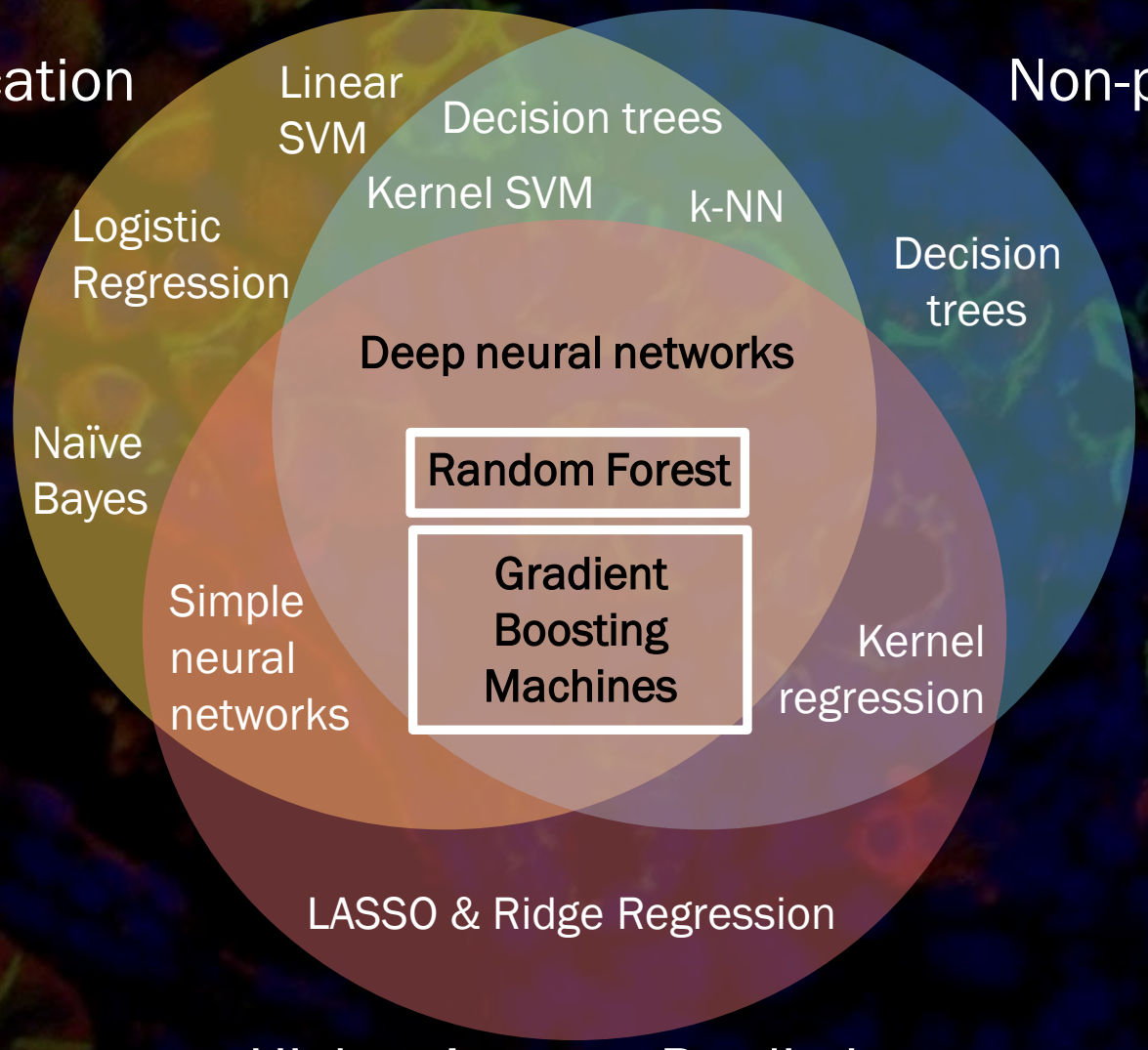
- Classification problem
- Prediction focused
- Non-parametric does not carry heavy assumptions



Higher Average Predictive Performance

Analysis: Choice of algorithms

- Classification problem
- Prediction focused
- Non-parametric does not carry heavy assumptions
- Stick with tree-based



Higher Average Predictive Performance

Analysis: Choice of balancing methods

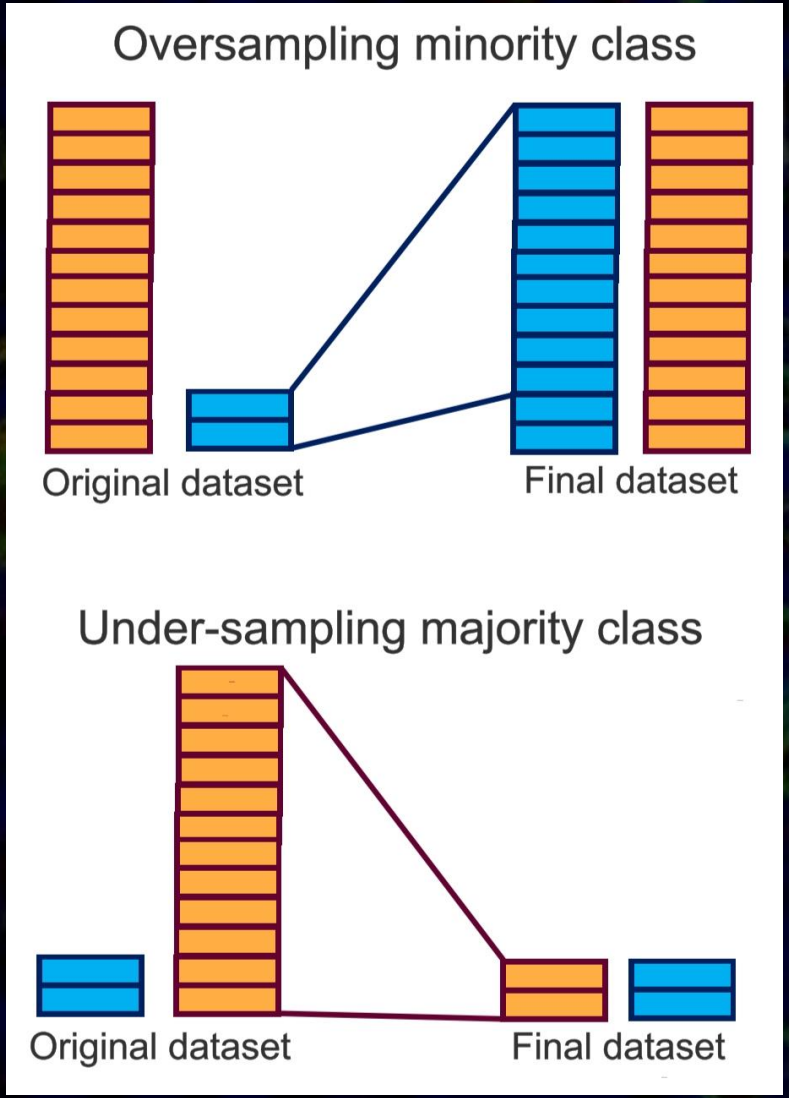
Chosen:

Under-sampling

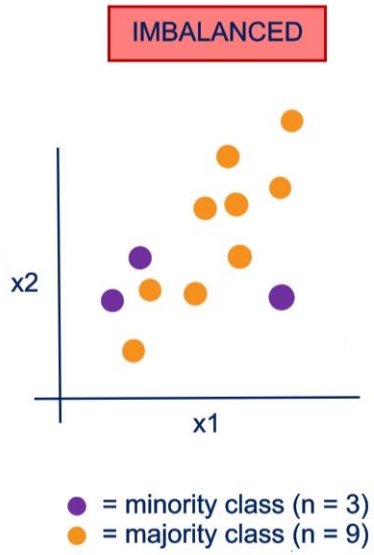
Oversampling via resampling

SMOTE (Synthetic Minority Oversampling TEchnique)

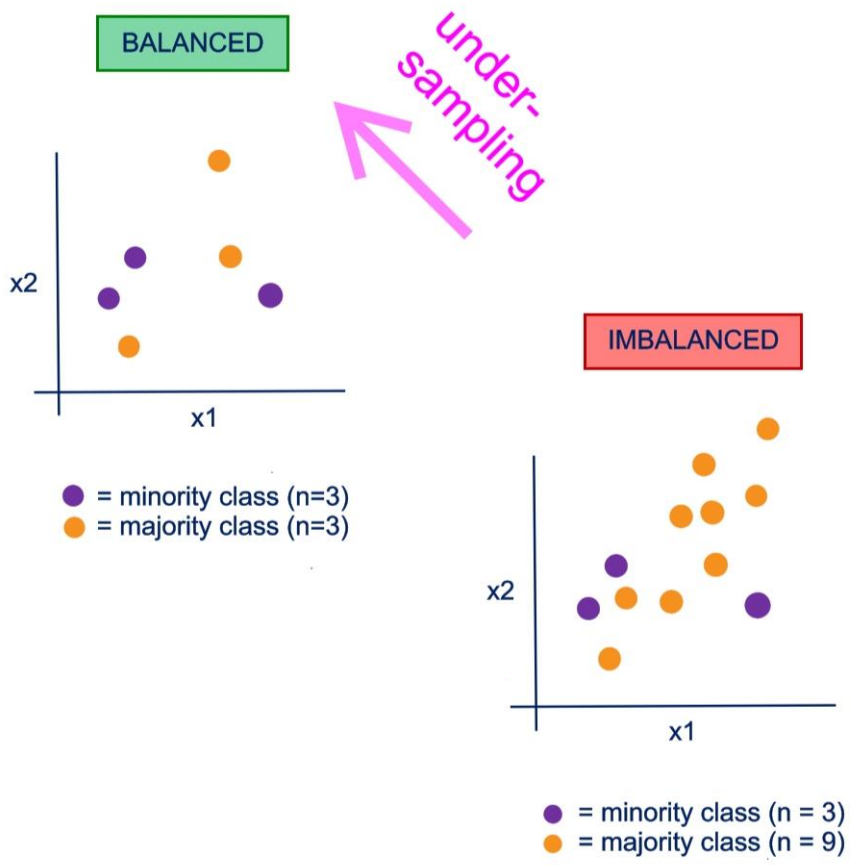
ROSE (Random Over-Sampling Examples)



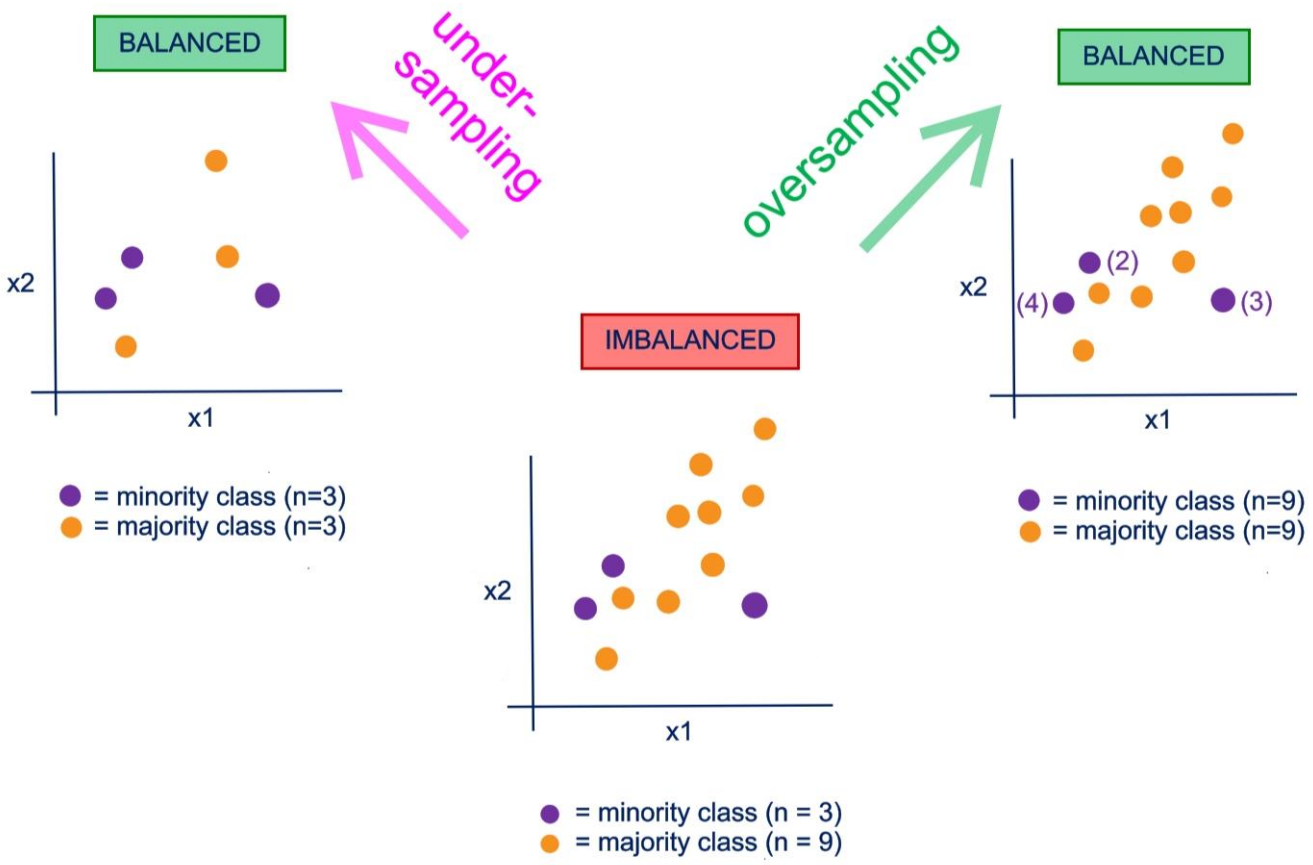
Balancing methods explained



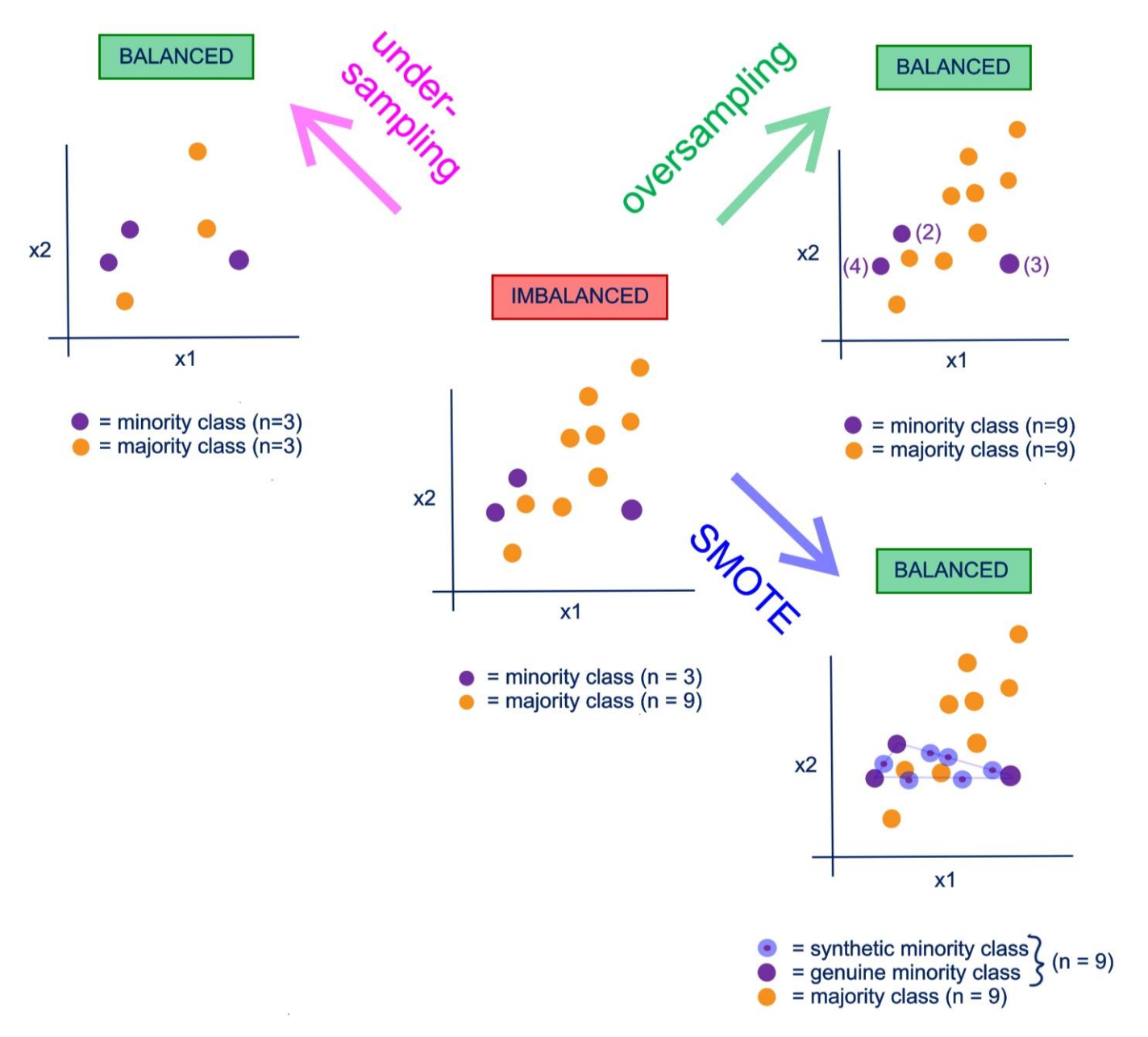
Balancing methods explained



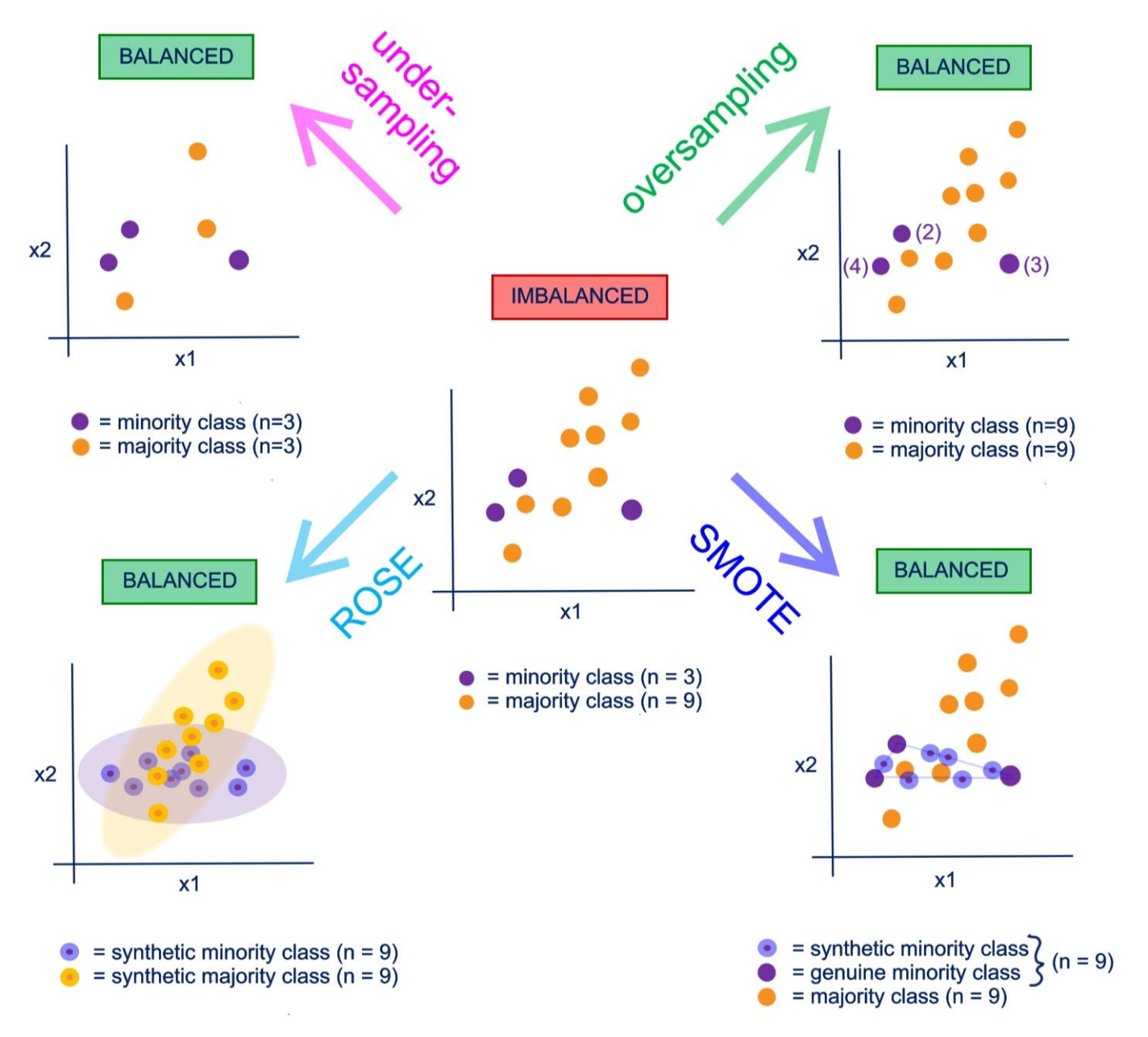
Balancing methods explained



Balancing methods explained



Balancing methods explained



Analysis: Models

Performance of these 10 models were compared:

Algorithms:

RF = random forest

GBM = gradient boosting machines

RF/imbalanced (client model)	GBM/imbalanced
RF/balanced (under-sampling)	GBM/balanced (under-sampling)
RF/balanced (oversampling)	GBM/balanced (oversampling)
RF/balanced (SMOTE)	GBM/balanced (SMOTE)
RF/balanced (ROSE)	GBM/balanced (ROSE)

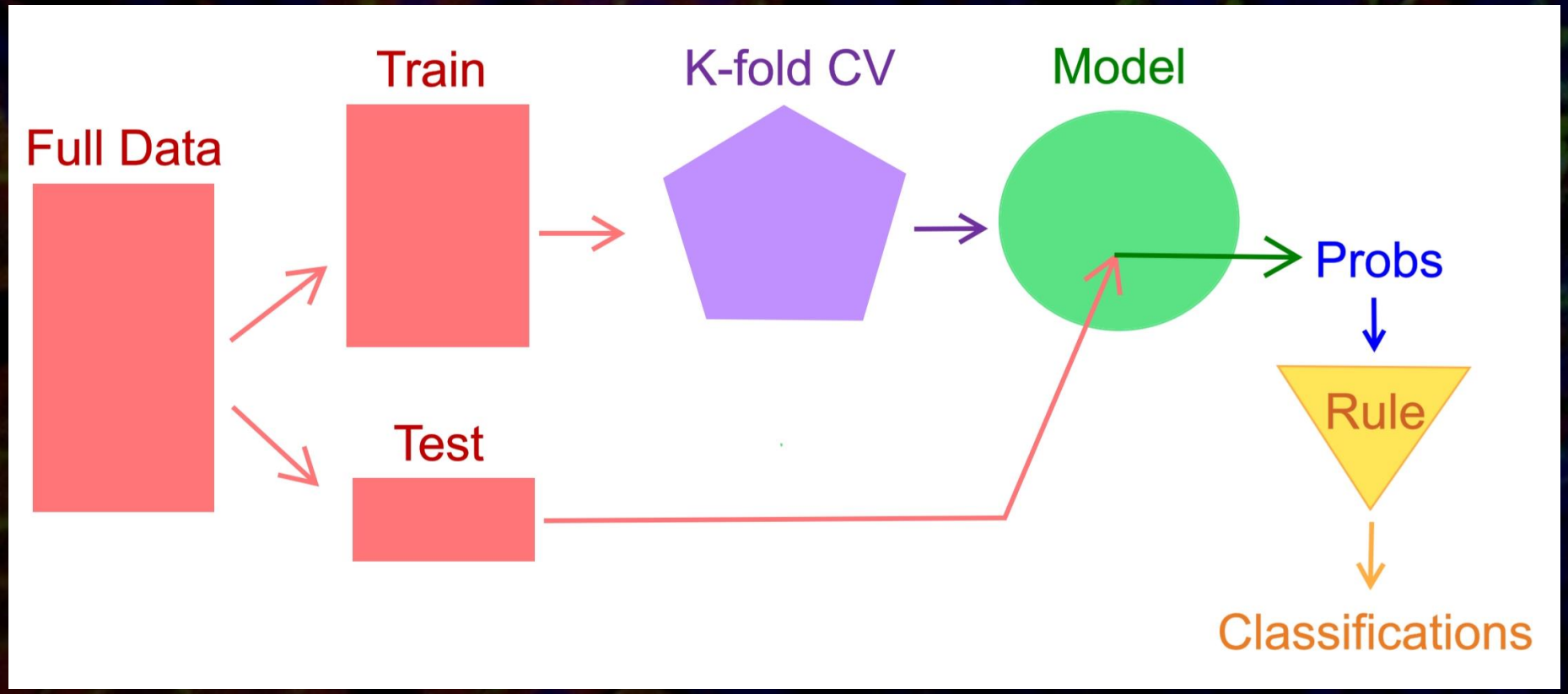
Analysis: Things Kept Consistent With Client Model

- Used the caret package in R for modeling
- Set the same seed as client model, across all models, to ensure the same randomization
- Used a train/test split (70/30) of the original dataset
- Used cross-validation (CV) with 5 folds and 10 repeats
- Allowed the caret package to choose the search grid for all model hyperparameters in CV
- Specified “ROC” as the metric for caret’s cross-validation model selection (Uses AUC)
- Used a probability threshold (tau) = 0.5, for initial model comparison

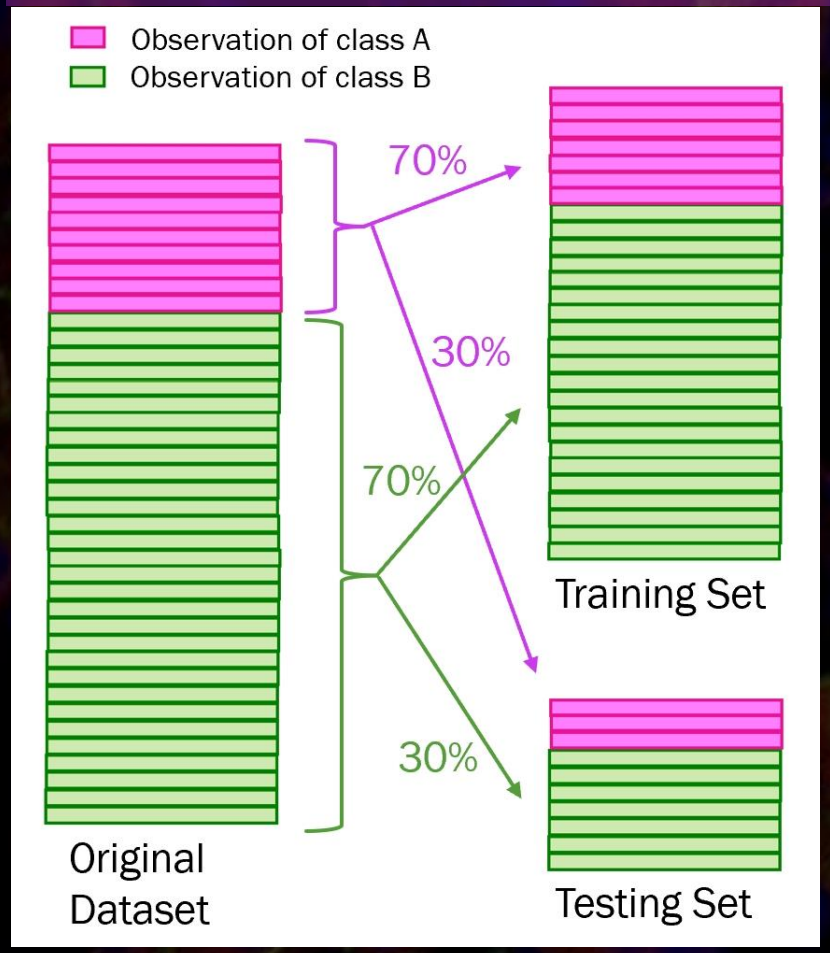
Next slides:
Modifications to data splitting and cross-validation, and where exactly balancing occurs in the modeling process

Analysis: Modeling Overview

This entire process is carried out for each of the 10 models previously mentioned.



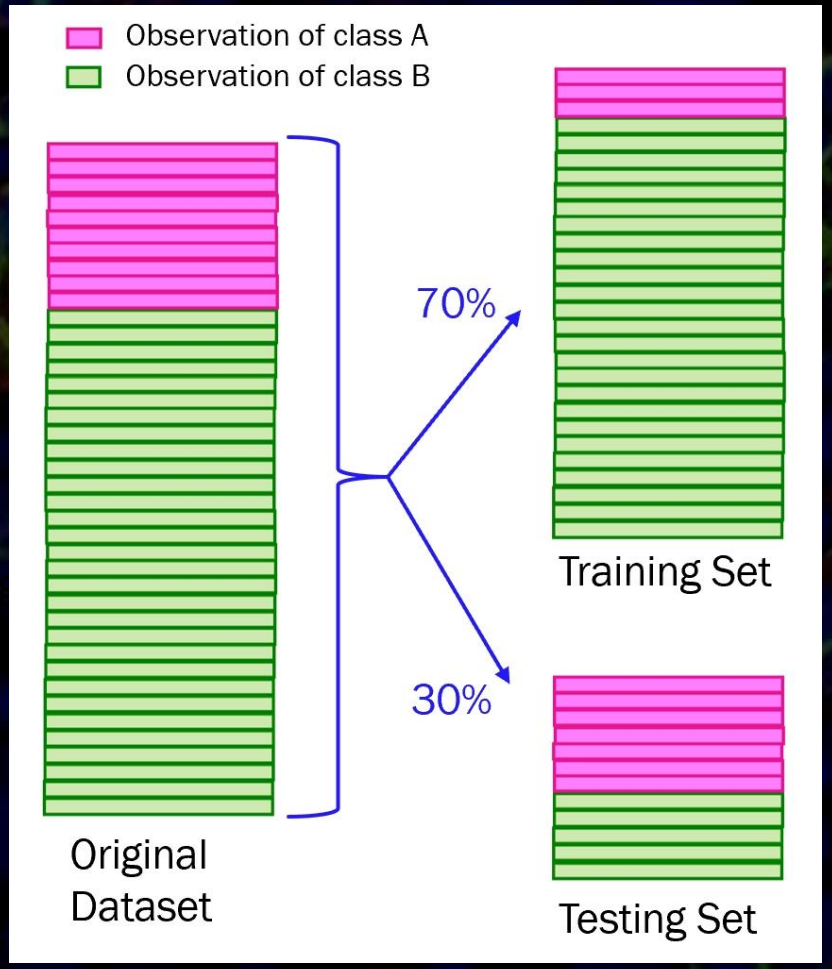
Analysis: Train/Test Split



Stratified

vs.

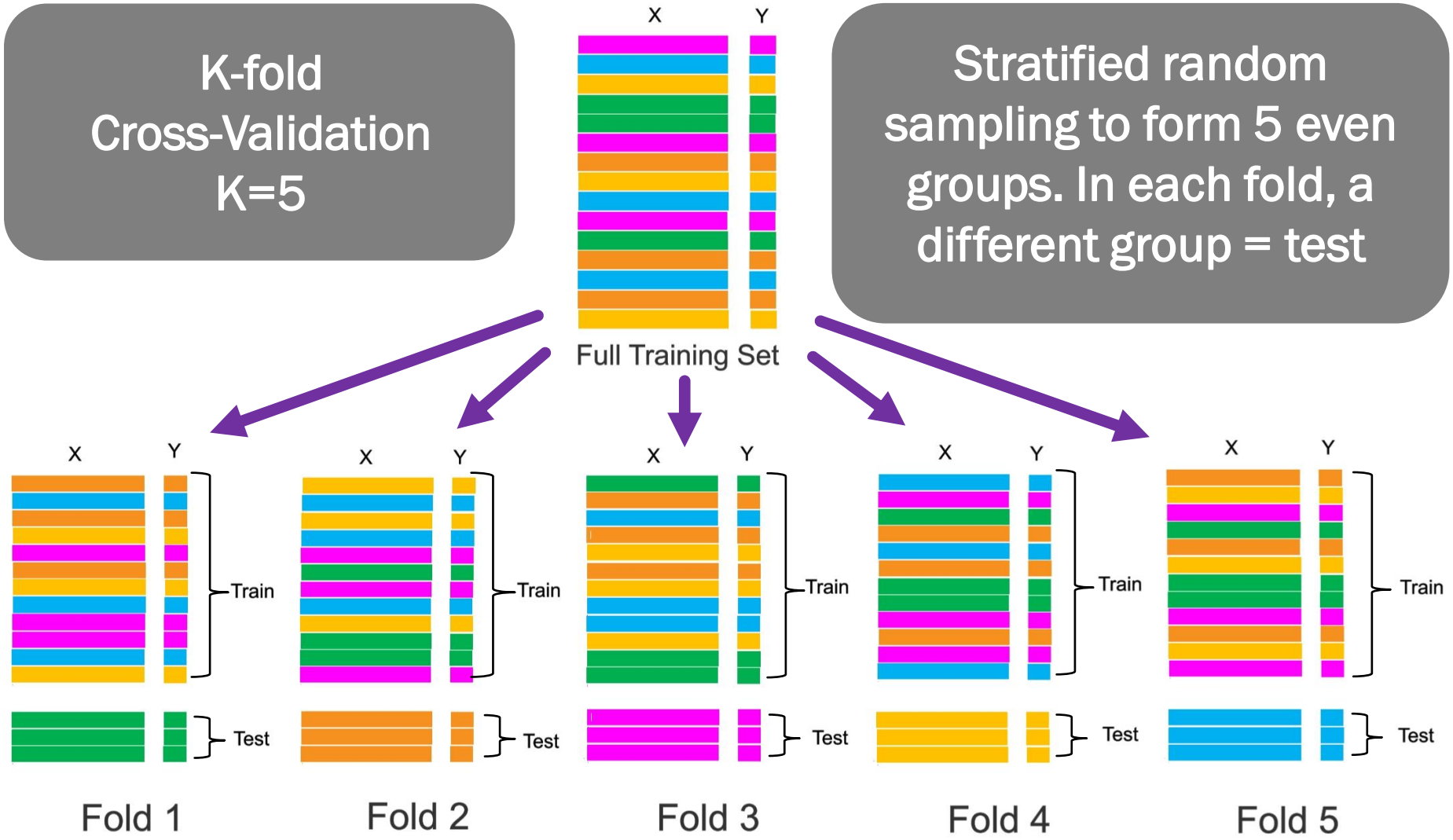
Unstratified



Analysis: Model Validation

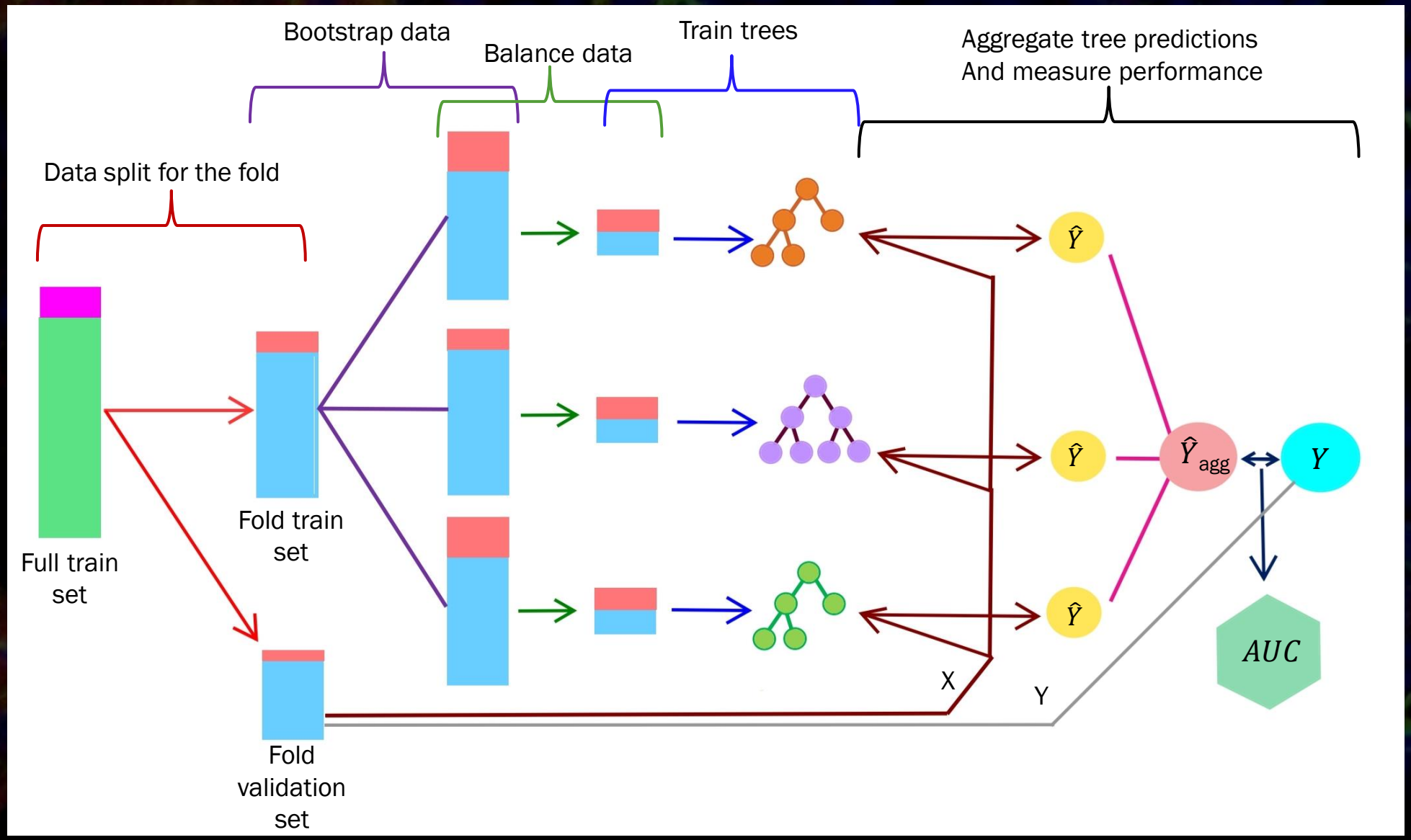
K-fold
Cross-Validation
K=5

Stratified random sampling to form 5 even groups. In each fold, a different group = test



Analysis: Model Validation

Process within each of the 5 folds for cross-validation



Analysis: Model Testing

After Stratified K-fold cross-validation chooses the parameters which yield the most robust model:

1) Test dataset (just X) is fed to this model and probabilities are generated:

The probability that each observation belongs to the "no" (low risk) class.

2) These probabilities are converted to class predictions using this rule:

If probability > τ → class prediction = "no"

(otherwise, class prediction = "yes")

Initially, τ = 0.5

3) The predicted classes are then compared to the true classes (Y of test set), and the output gives:

The true positive rate (sensitivity)
The true negative rate (specificity)

(1 – specificity gives the false positive rate)

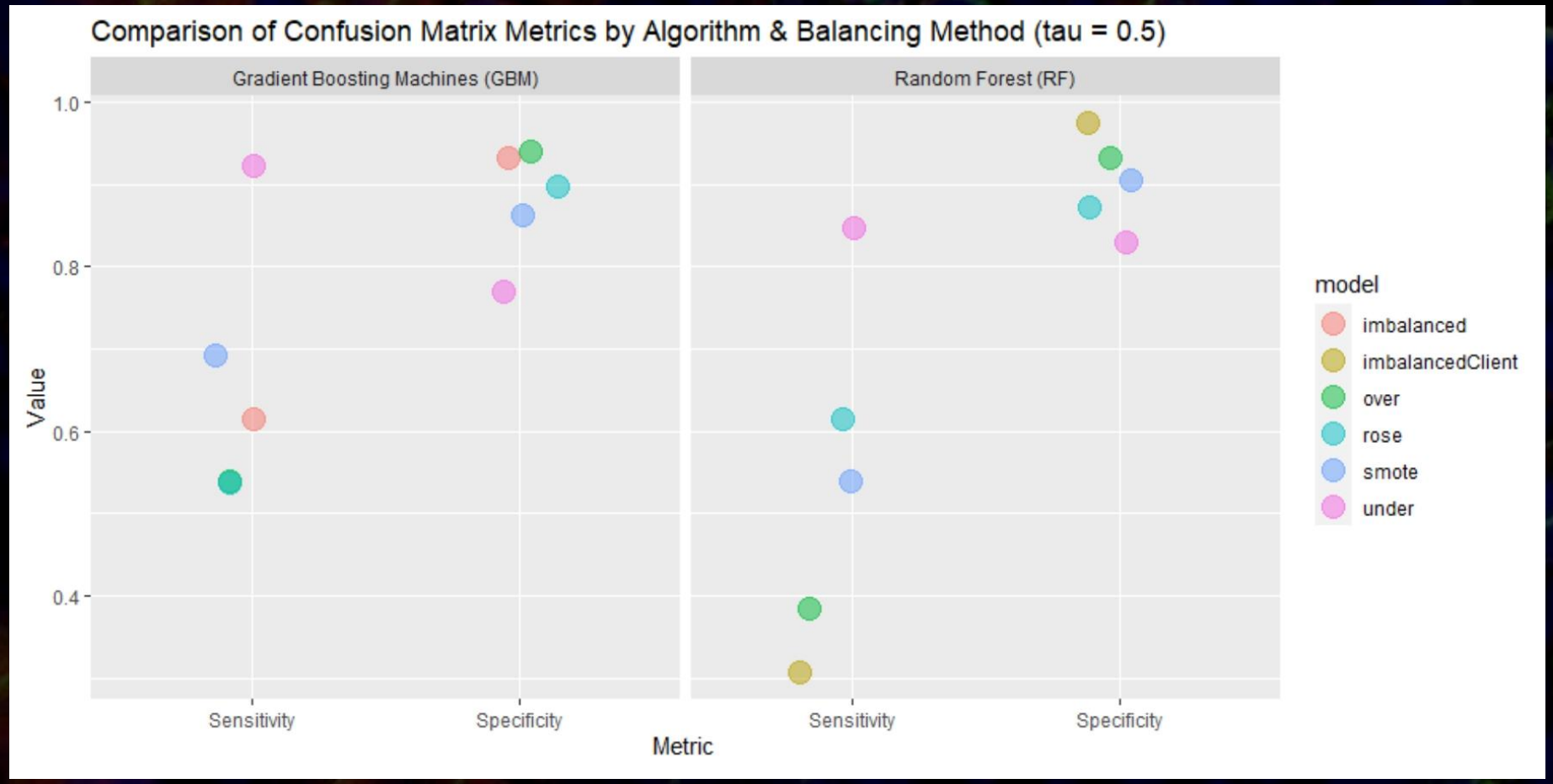
Analysis: Results

Goals: **Sensitivity ≥ 0.90** **Specificity ≥ 0.75**

GBM/under appears to make both goals.

RF/under might with tuning.

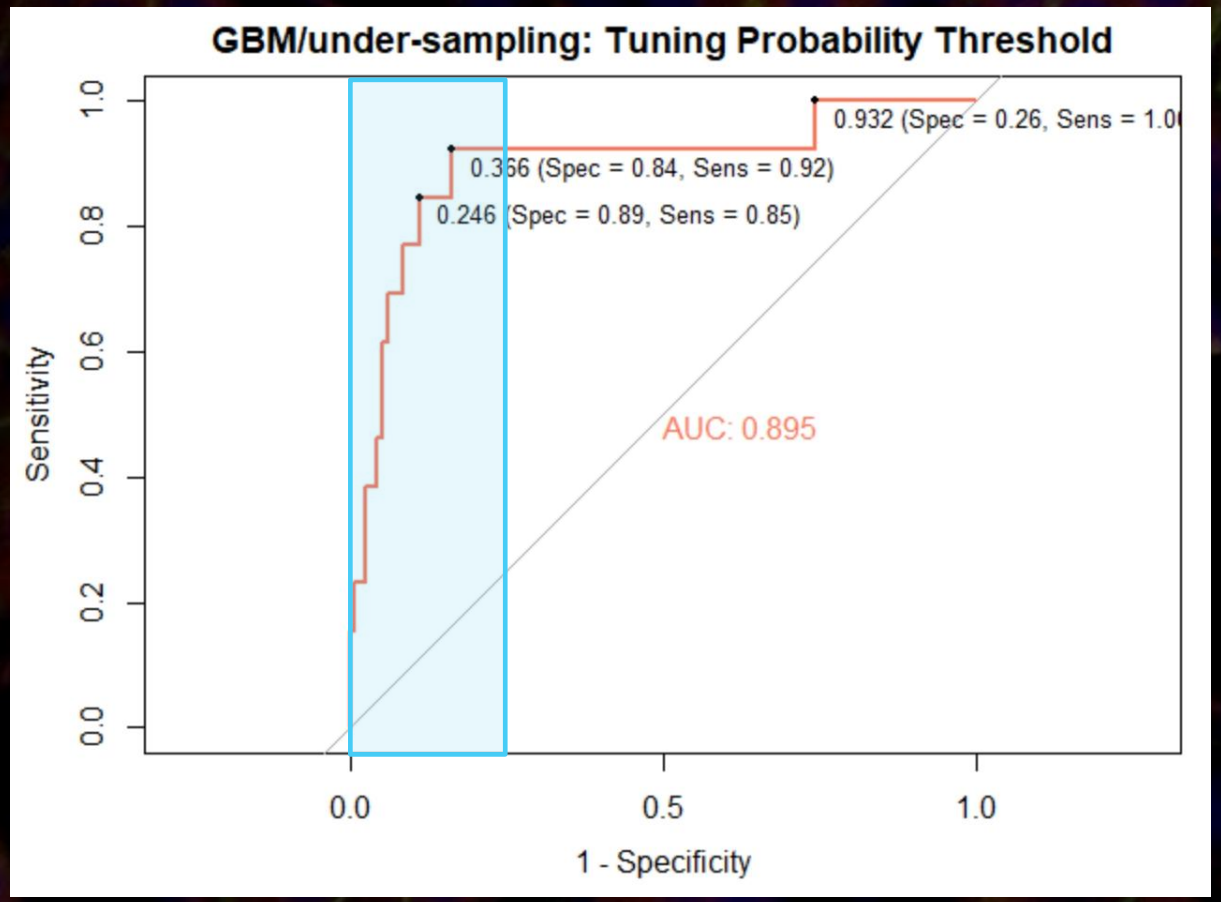
Let's tune both.

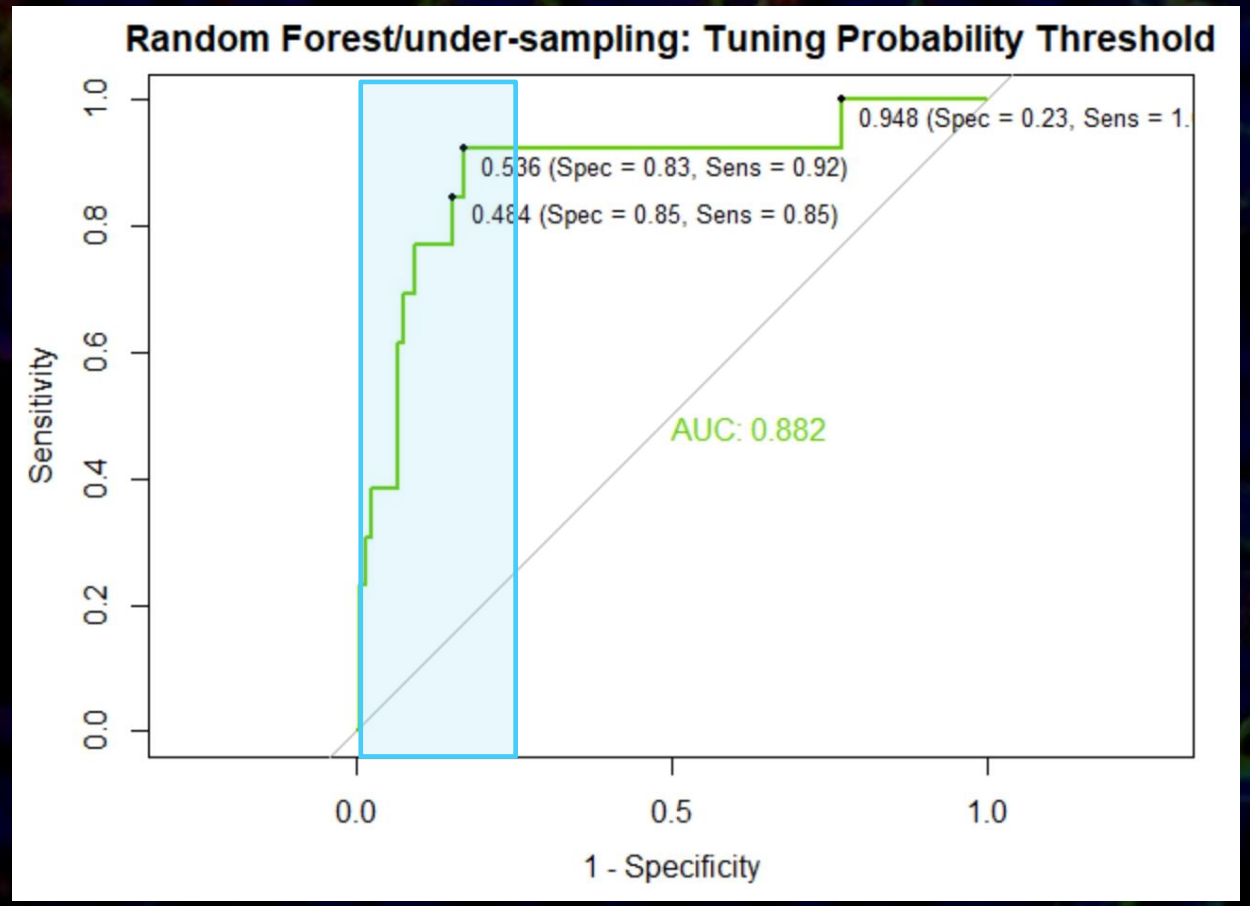


Analysis: Results

Tuning: How do they compare at various thresholds (τ)?

Goal range for 1 – specificity (<= 0.25)





Analysis: Results

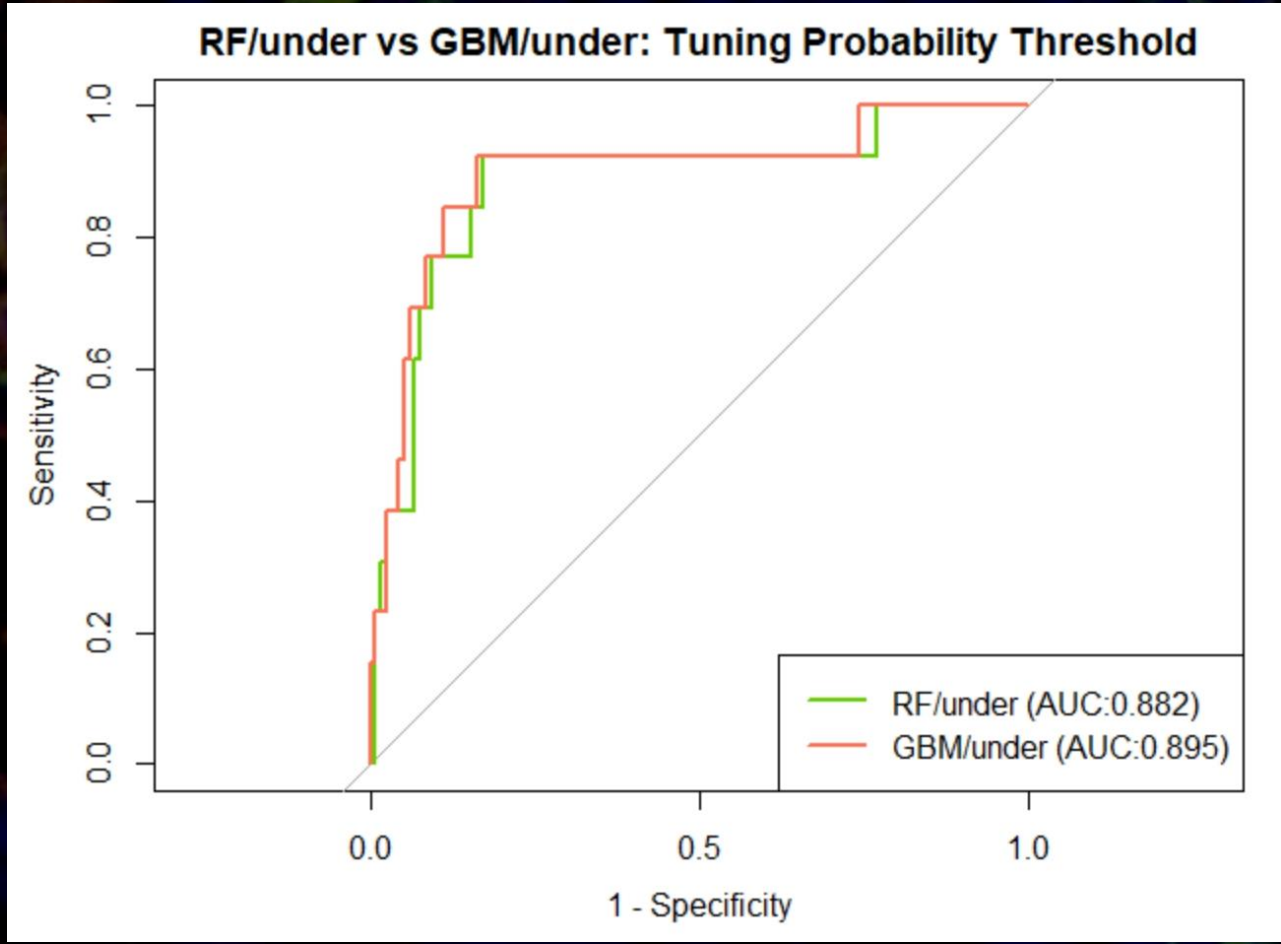
RF/under:

Optimal at tau = 0.536
Sensitivity: 0.923
1 - specificity: 0.171

GBM/under:

Optimal at tau = 0.366
Sensitivity: 0.923
1 - specificity: 0.162

GBM/under has slightly better performance.



Recommendation

Procedure:

GBM algorithm
(n.trees = 50, interaction.depth = 3, shrinkage = 0.1, n.minobsinnode = 10)
using stratified data splitting and under-sampling with classification cutoff

τ = 0.366

Performance:

Sensitivity
(true positive rate)
= 0.923

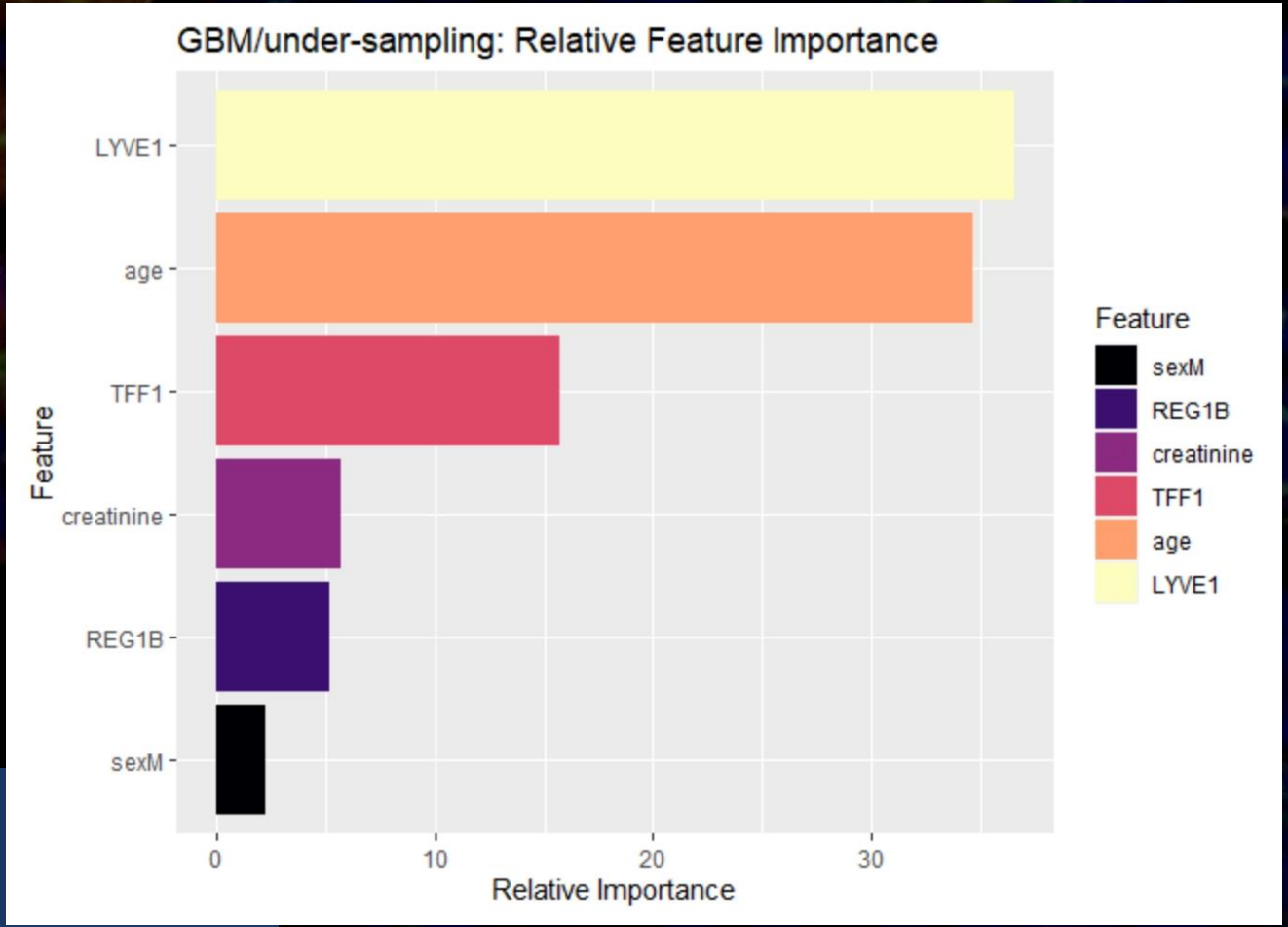
1 – Specificity
(false positive rate)
= 0.162

Variable Importance

GBM: The caret package in R can output the strength of each variable in predicting the response by inserting your model into the function summary().

R Code for the plot:

```
# GBM/Under
RI <- summary(modelgbm_us, plot = FALSE)
RI <- transform(RI, var = reorder(var, rel.inf))
ggplot2::ggplot(RI, aes(rel.inf, var, fill = var)) +
  geom_col(aes()) +
  labs(title="GBM/under-sampling: Relative Feature Importance") +
  labs(x="Relative Importance",y="Feature") +
    scale_fill_viridis_d(option="magma", name = "Feature")
```

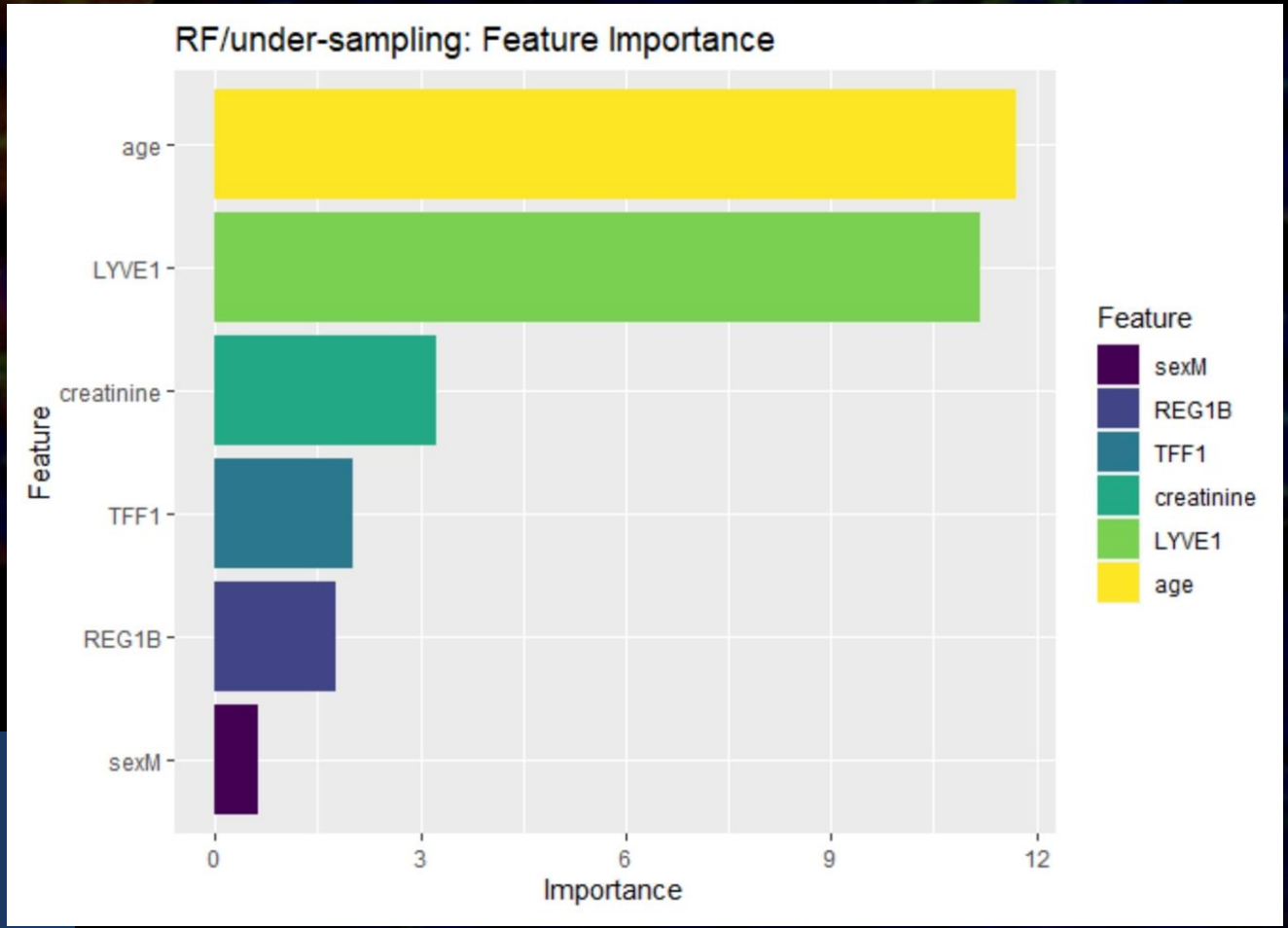


Variable Importance

Random Forest: The caret package in R can output the strength of each variable in predicting the response by inserting your model into the function varImp().

R Code for the plot:

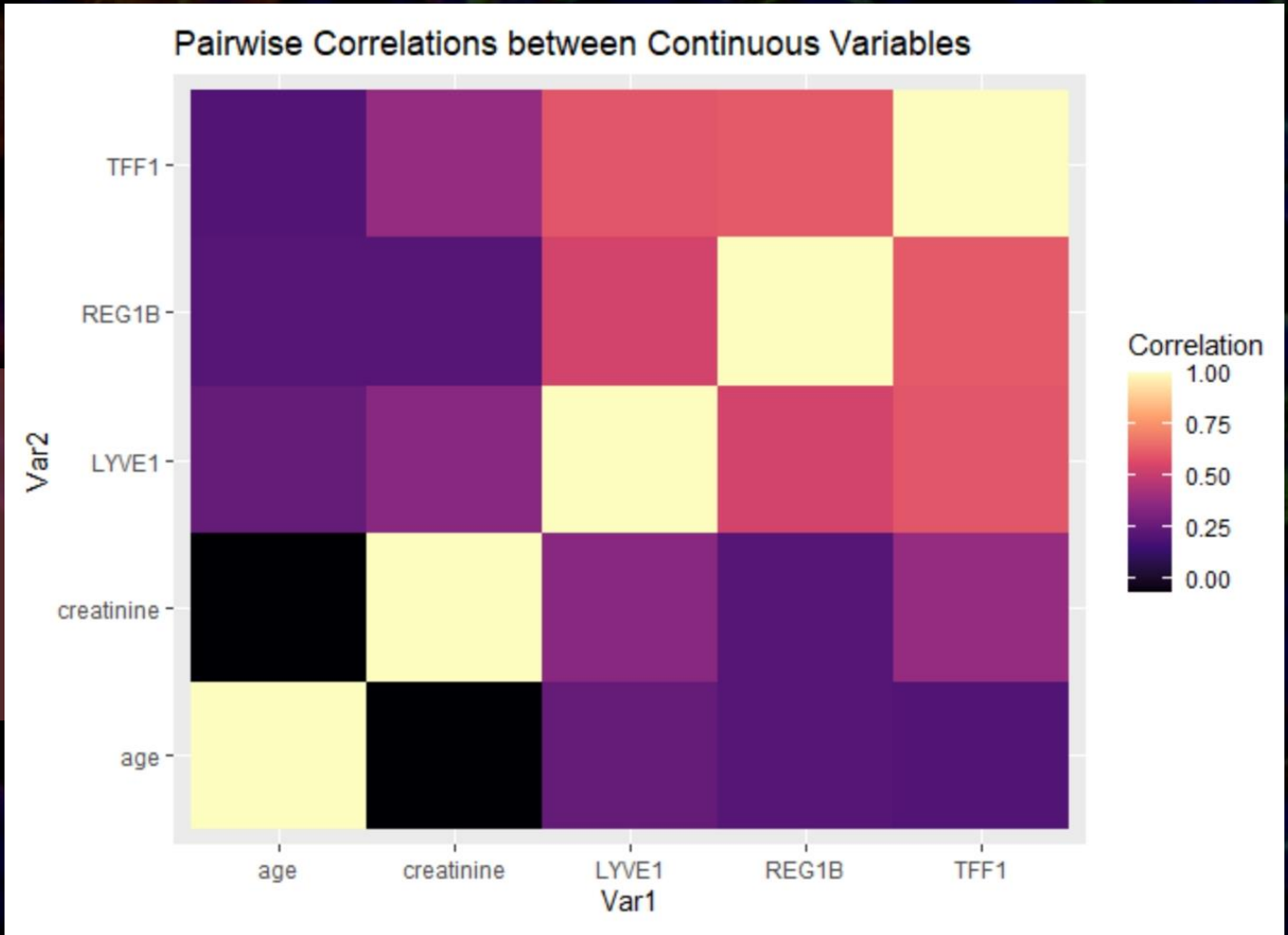
```
# RF/Under
VI <- varImp(modelrf_us, scale=FALSE)
VI <- VI$importance
VI$feat <- row.names(VI)
VI <- transform(VI, feat = reorder(feat, Overall))
ggplot2::ggplot(VI, aes(Overall, feat, fill = feat)) +
  geom_col(aes()) +
  labs(title="RF/under-sampling: Feature Importance") +
  labs(x="Importance",y="Feature") +
    scale_fill_viridis_d(option="viridis", name = "Feature")
```



Variable Importance

Warning:
Can be misleading if correlation between any 2 variables exceeds about 0.7

Highest correlation between any two predictors is 0.61, so we can trust the variable importance plots.



Takeaways for the Client

Q1

Performance discrepancy: accuracy paradox
Don't look at accuracy. Find the metrics for your goals.
True positive rate = Sensitivity False positive rate = 1 - Specificity

Q2

Poor classification cause: class imbalance
This recommended procedure corrects for this and meets study goals:

GBM algorithm using under-sampling with probability cutoff $\tau = 0.366$

Q3

Use varImp() or summary() on your model and plot with ggplot2 in R to see variable importance.

Conclusion

It can be done! Even with imbalanced data, this less invasive screening test for PDAC risk can perform as needed, given the right procedure.

It is clinically practical enough to be put to use in the real world, increasing frequency of screening and increasing survival rates of those with PDAC.

Sources

1. Debernardi S, O'Brien H, Algahmdi AS, Malats N, Stewart GD, Plješa-Ercegovac M, et al. (2020) A combination of urinary biomarker panel and PancRISK score for earlier detection of pancreatic cancer: A case–control study. PLoS Med 17(12): e1003489. https://doi.org/10.1371/journal.pmed.1003489
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7. Kohavi, R. (1995). A study of cross-validation and bootstrap for accuracy estimation and model selection. In Proceedings of the 14th International Joint Conference on Artificial Intelligence - Volume 2, pp. 1137–1143.
8. Slide background image: credit to Michael Feigin, Tuveson Lab, CSHL

Thank you!