Data Mining and Modeling Methods for Site Inspection Selection

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Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent the United States Food and Drug Administration’s views or policies.

Outline

- Motivation
- Objectives and background
- Data sets and structures
- Challenges
- Methods and their performance
- Other considerations

Motivation

In a clinical trial setting, data reliability can be jeopardized by:

- Poorly Collected data
- Poorly Processed data
- Poorly Reported data
- Tampered or Fraudulent data

The number and complexity of clinical trials have risen dramatically making it difficult for regulators to choose clinical sites for inspection

Objectives

To determine whether

- supervised data mining methods can be used to predict site inspection results
- unsupervised statistical monitoring

can be used to identify ‘unusual’ clinical sites for inspection (*ongoing work*)

Objectives

Onsite inspections help ensure the integrity of the clinical trials via source data verification

Due to limited resources only less than 1% of the sites can be inspected annually. It is therefore crucial to select the appropriate clinical sites

Data sets

Site inspection results can be classified into:

- NAI (No Action Indicated)
- VAI (Voluntary Action Indicated)
- OAI (Official Action Indicated)

Data sets

Clinical trial data and the results from clinical site Inspections

Response

can be:

- Ordinal with three distinct classes (OAI, VAI, NAI)
- Binary: 2 of 3 ordinal classes are suppressed to 1 (VAI, OAI) vs. NAI

Challenges (ordinal response)

Missing data

Assumptions: missing values are MAR and can be predicted by observed values

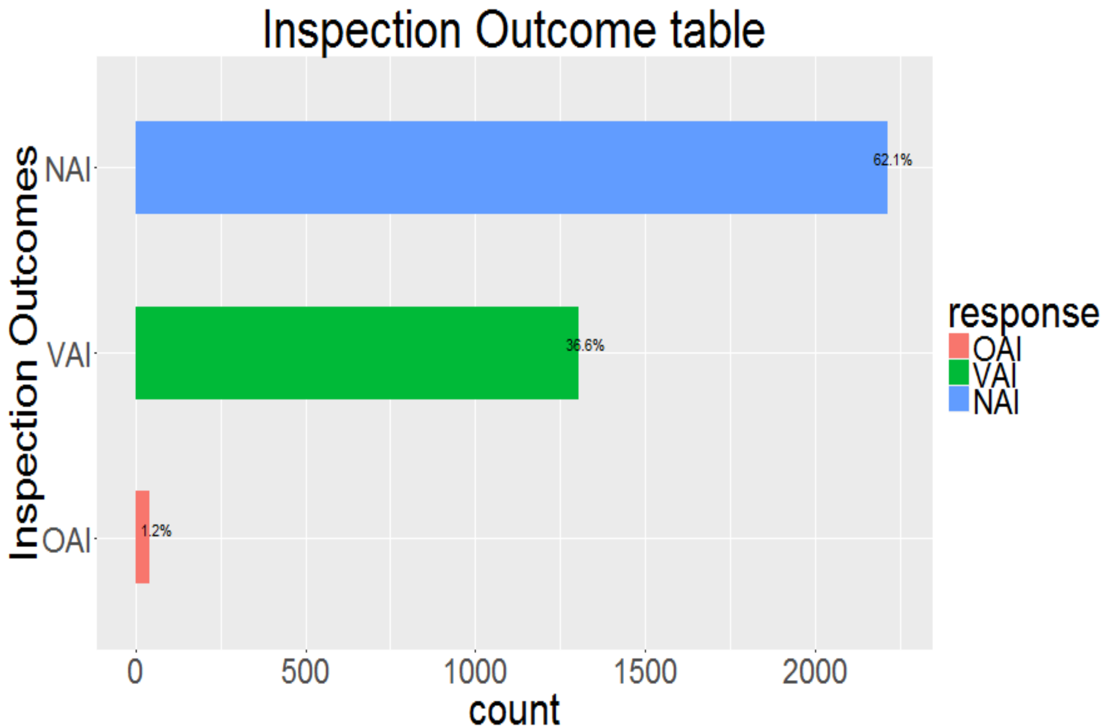
Random Forest (RF) imputation

- Replace missing values with sample median
- Use RF to compute proximity between missing and non-missing samples
- Repeat

Variable	Type	% missing
Enrollment	continuous	
Site Specific Efficacy	continuous	27.7%
Protocol deviation	continuous	
NS adverse event	continuous	
% subject death	continuous	
Enroll/Screen %	continuous	
Subject discontinuation	continuous	
Number of INDs	continuous	
Financial disclosure	continuous	29.9%
Complaint history	Binary	
Time since last inspection	continuous	4.32%
OAI history	Binary	

Challenges (ordinal response)

Imbalanced outcomes-OAI classification is a rare event with only 1% of sites being classified as OAI



Challenges (ordinal response)

Synthetic Minority Over-Sampling Technique-SMOTE

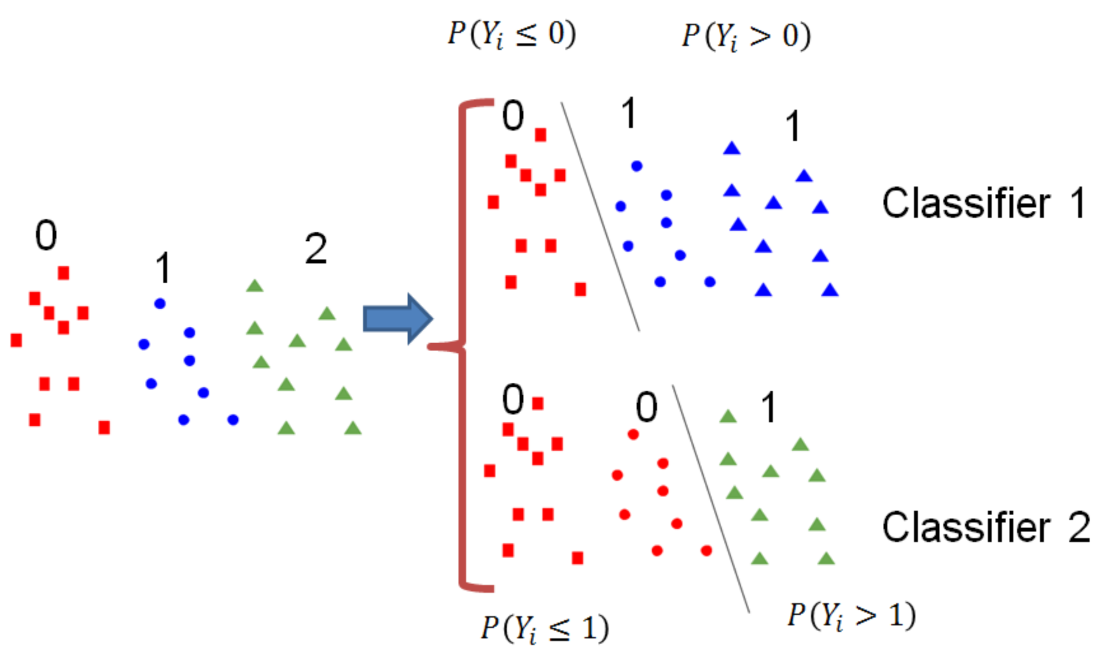
- Generate synthetic samples for the minority class
- Input the number of nearest neighbors, k, T minority class samples and size of SMOTE, N
- Output is the synthetic minority class samples

Statistical methods (ordinal response)

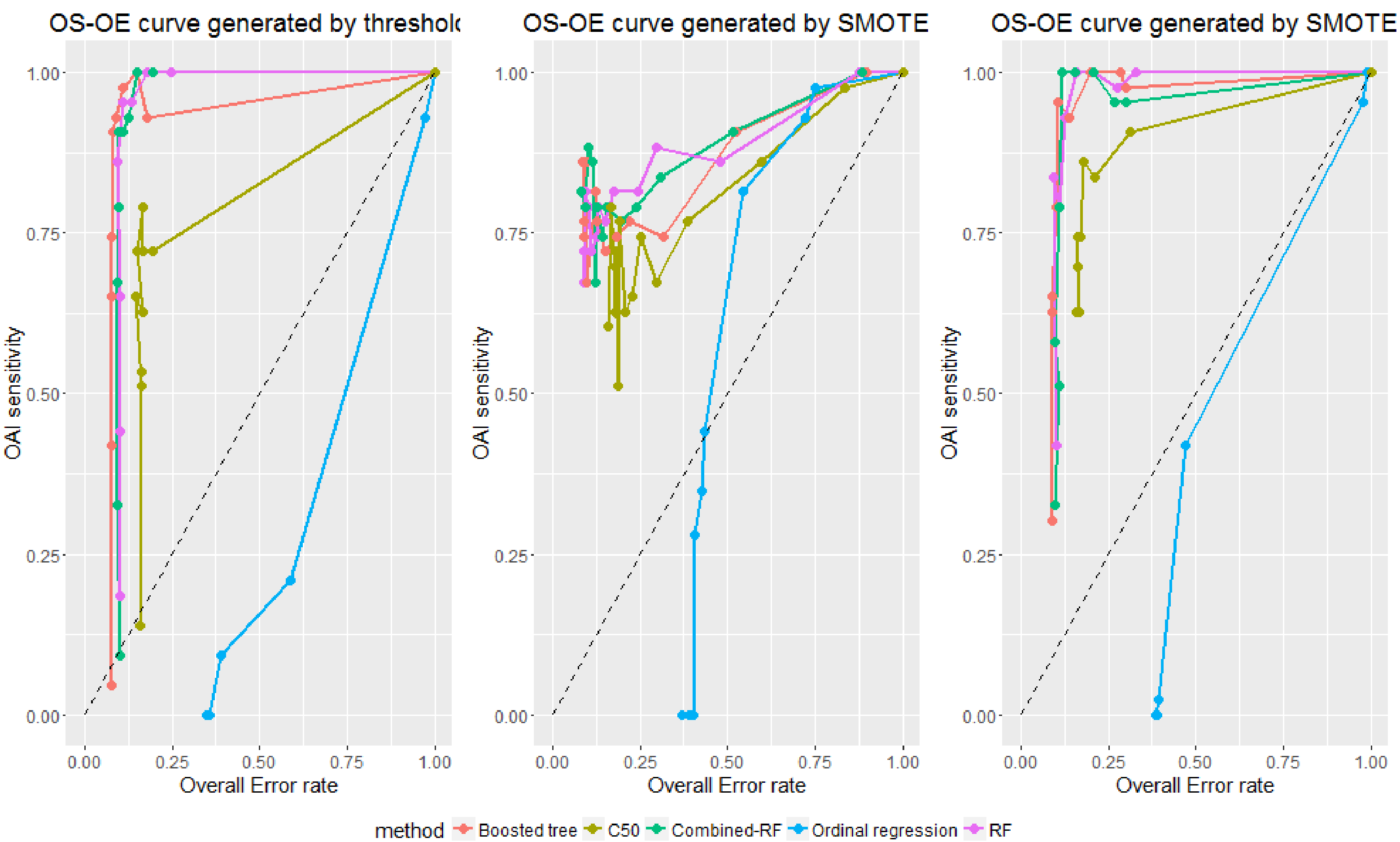
- Ordinal regression
- Combined binary classifiers
- Random forests
- Boosted trees

Combined binary classifier

Convert an ordinal regression problem into nested binary classification problems by splitting the data into groups $Y_i \leq j$ and $Y_i > j$ and a binary probability classifier to estimate the probabilities $P(Y_i \leq j)$ and $\mathrm{P}(Y_i > j)$



Classifier performance



Statistical methods (binary response)

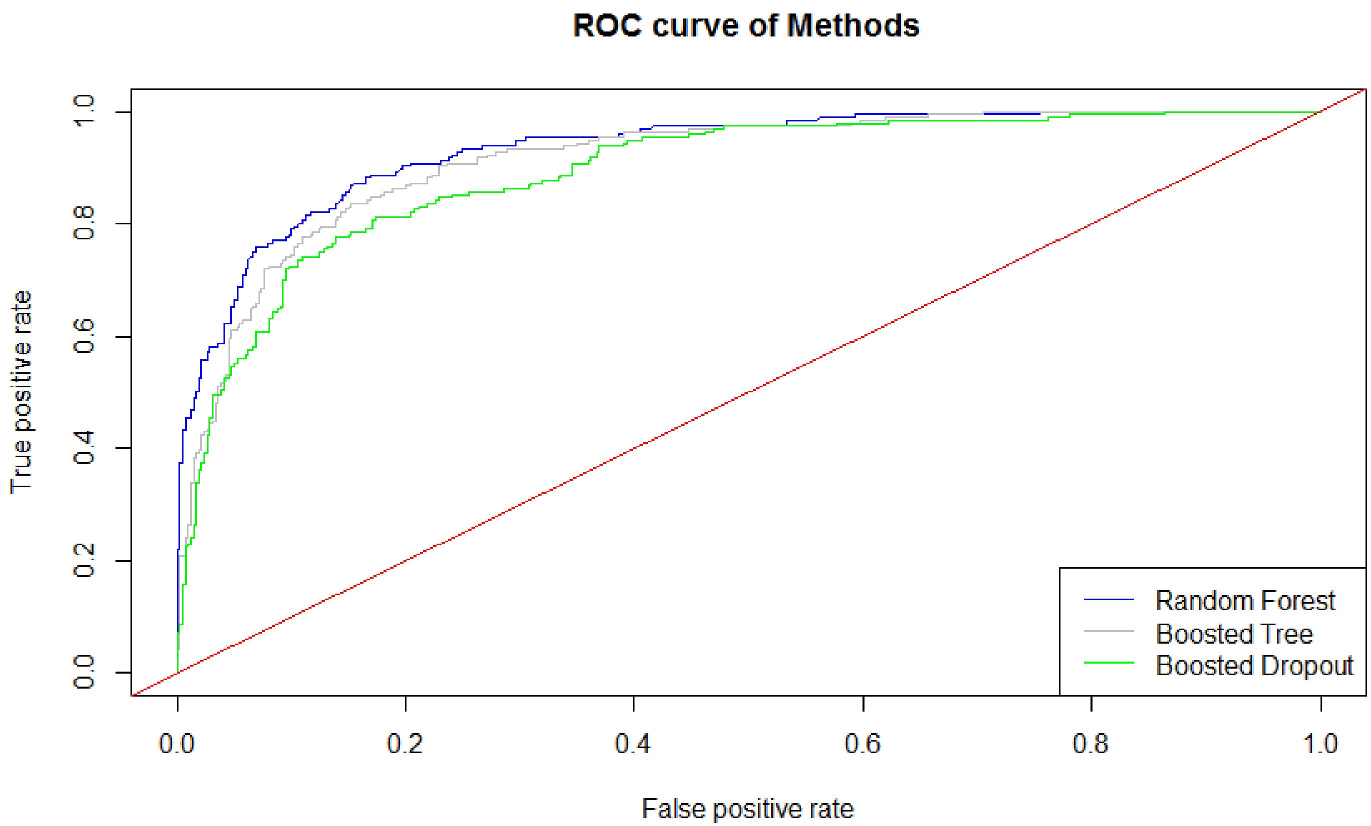
- Random Forest
- Boosted Tree
- Boosted Dropout

  (As boosting is susceptible to overfitting-high bias, low variance)

Challenges (binary response)

- Studying the sensitivity of each variable to predict the outcome
- Using the EM-algorithm to impute missing data
- Using 5-fold cross-validation to assess model performance

Classifier Performance



Model performance

Method	CV error	Misclassification
RF	13.5%	14.0%
Boosted Tree	15.9%	14.9%
Boosted Tree with Dropout	16.9%	16.4%

Outcome

R-Shiny application that uses the supervised learning methods and

- Predicts the potentially fraudulent cases from different clinical sites
- Validates the parameter that gives the best fit
- Detects the covariates that are most predictive of the outcomes

CRADA

Cooperative Research and Development Agreement with CluePoints

The main objective is to detect atypical sites in a multicenter study

Method tests the distribution of data in one center with data in other centers and produces a p-value demonstrating how unlikely the outcomes from one clinical center are (unsupervised approach)

Approaching the end of 2nd year is a 3 year agreement

References

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Thank you!

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