Lee Xiong An

Holmusk Take home Test
15-22 Dec 2021

Qualifications

- 2020, M. Sc. (Statistics), National University of Singapore (NUS)
- 2015, B. Sc. (Second Upper, Life Science Major, Biophysics Minor), NUS

Job Experience

- (2020-present) JTC Corporation, Data Scientist, Business Analytics/Analytics Solution Dept
  - Building of predictive models (team member)
  - Tableau team lead (user-facing)
  - Data analytics training
- (2018-2020) A*STAR Bioinformatics Institute, Senior Research Officer, Image Analytics Division
  - Plant analytics project (co-principal investigator)
  - Computer vision pipeline for MERFISH images (team lead)
- (2015-2018) A*STAR Bioinformatics Institute, Research Officer, Biomolecular Modelling Division
  - Predicting Toxicity for institutes' internal molecular library using graph convolutional networks
  - Molecular Dynamics

Problem Statement

I. Compare the real world efficacy of Drug A vs Drug B using survival analysis

II. Take into account confounding factors affecting treatment as data is EHR and imbalanced

Dataset

- Patient_characteristics.csv – contains the information about socio-demographics of patients, diagnosis, lab values, and other existing therapies patients are on
- Event_duration.csv – Contains information about if the event happened to a patient or if patient was censored and the durations for each case from the start of therapy

patient_id	0
Bleeding_event (1=event, 0=censored)	0
duration_in_years	0.019178
treatment_variable	Drug_A
sex	1
age	86
other_drugs_1	0
other_drugs_2	0
other_drugs_3	0
other_drugs_4	0
other_drugs_5	0
other_drugs_6	0
other_drugs_7	0
other_drugs_8	1
diagnosis_1	0
diagnosis_2	0
diagnosis_3	0
diagnosis_4	0
diagnosis_5	0
diagnosis_6	0
diagnosis_7	0
diagnosis_8	1
diagnosis_9	0
diagnosis_10	1
diagnosis_11	0
diagnosis_12	0
diagnosis_13	1
diagnosis_14	0
diagnosis_15	0
lab_1	0.974967
lab_2	358.572186
lab_3	NaN
lab_4	NaN
lab_5	5.49857
lab_6	17.060713
lab_7	1.077035
lab_8	67.781782
Diag_Score_1	5
Diag_Score_2	5

Approach for Problem

I. Method to detect confounding using decision tree

II. Obtaining balanced dataset using (I)

III. Validating that balanced dataset has reduced confounding

IV. Compare efficiency of Drug A & B using univariate KM on balanced dataset

V. Limitations of method

Confounding factors 101 (for the unfamiliar)

- For EHR data, results may be confounded unlike that of a clinical trial where everything is controlled and balanced
- If sicker patients were given treatment with drug A, drug A would be associated with poorer outcomes and vice versa
  - Drug A is confounded with “sick”, hence analysis is likely invalid
- A remedy is to rebalance the dataset such that both drugs have similar profiles of people

Method to Detecting confounding

- A balanced dataset such that both drugs have similar profiles of people
  - You will not be able to predict drug type from person’s profile effectively
- Building a machine learning model with patient profile and predict drug type administered
  - If confounding is strong, the model will predict drug type well
  - If confounding is small, the model will predict poorly, I.e. patient profile not associated with drug type
  - Model evaluated by ROC AUC

ROC AUC (for unfamiliar)

- ROC AUC is a simple metric that is easy to understand, $P(X_1 > X_0)$ proof below
- 0.5 means model is random, 1 mean model is perfect, 0 means model is perfectly wrong

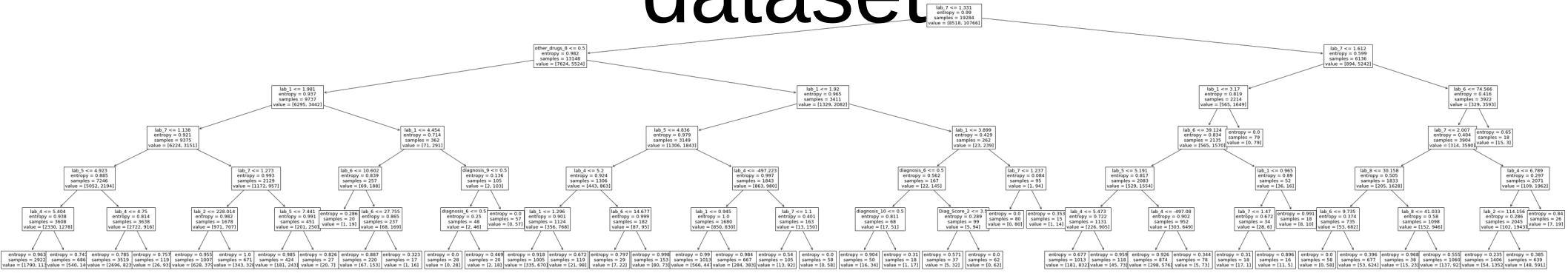
$$\mathrm{TPR}(T) : T \mapsto y(x)$$
$$\mathrm{FPR}(T) : T \mapsto x$$
$$A = \int_{x=0}^{1} \mathrm{TPR}(\mathrm{FPR}^{-1}(x))\,dx = \int_{\infty}^{-\infty} \mathrm{TPR}(T)\mathrm{FPR}'(T)\,dT = \int_{-\infty}^{\infty}\int_{-\infty}^{\infty} I(T' > T) f_1(T') f_0(T)\,dT'\,dT = P(X_1 > X_0)$$

where X_1 is the score for a positive instance and X_0 is the score for a negative instance, and f_0 and f_1 are probability densities as defined in previous section.

Results : Confounding Model

- DecisionTreeClassifier model used,
  - Decision Tree is simple model to split population into subgroups
  - Explanatory variable : patient characteristic
  - Dependent Variable : Drug Type
  - 10 fold CV used
  - maximum_ depth = 6 and min_samples in final nodes = 15 gave good trade-offs between accuracy and complexity
  - ROC AUC = 0.79
- Data is definitely confounded
  - Even the presence of null values give ROC AUC 0.65

Tree used to generate balanced dataset



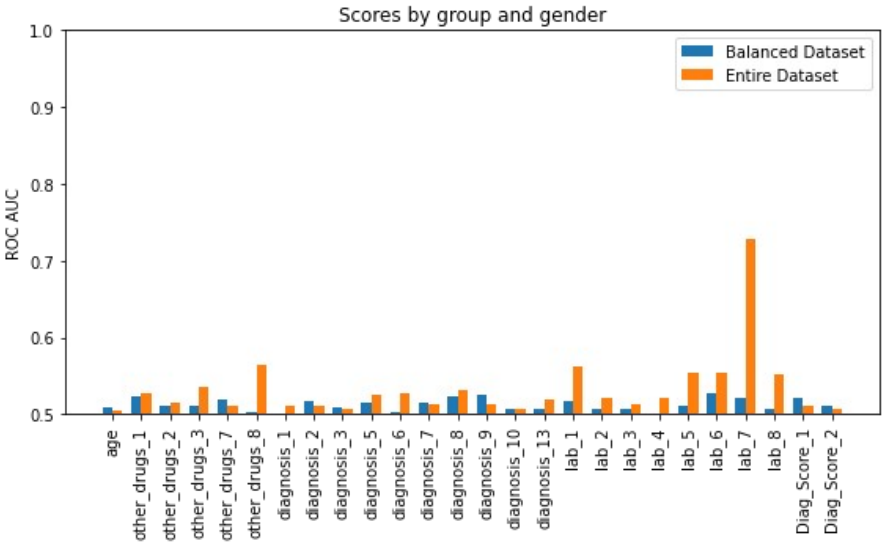
- DecisionTreeClassifier model used, maximum_ depth = 6 and min samples in final nodes = 15
  - 10 fold CV ROC AUC = 0.79
- This tree is generated with 100% of data

Characteristics of balanced dataset

- Decision tree has profiled patients into 44 nodes of which 37 nodes have both patients with drug A and B
  - These 37 nodes make up 98% of the dataset
  - The other 7 nodes only have treatment=Drug B and dropped from balanced dataset
- A balanced dataset of 10K (53%) is sampled from these 37 nodes

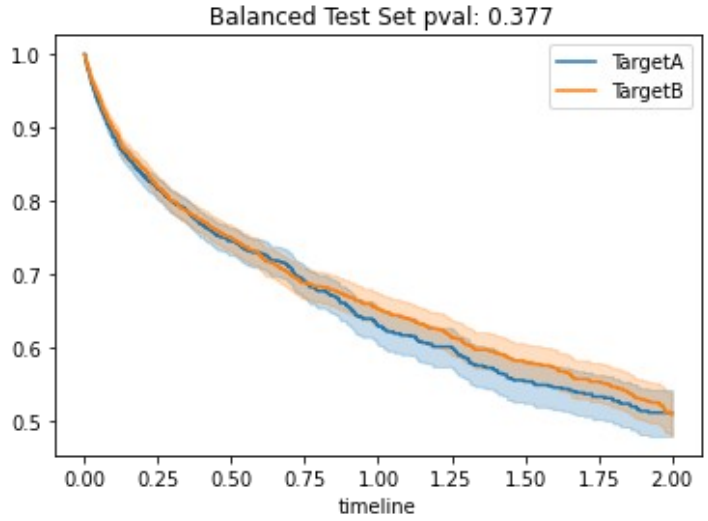
Metrics for Balanced Dataset

- Trained *univariate* decision tree with depth=3, min_leaf=30
  - Explanatory variable: X axis
  - Target variable: Drug A/B
  - 10 fold ROC AUC Score plotted
- Balanced dataset cannot be predicted by individual or overall patient characteristics
  - Even using all patient information, model performs 0.55 ROC AUC



Compare Real World Efficacy of Drug A vs B

- Plot shows KM curve and pval for Log Rank test
- No difference in efficacy for drug A vs B
- Dataset is balanced wrt to drug type hence KM results approximately hold even without explicitly modelling patient characteristics
  - Covariance between drug_type and patient characteristics ~ 0



Limitations

- The balanced dataset may not be a true representative of the main population
  - Reweighing could be done to account for that
- Our balancing method removes the strongest confounders, there are also many weak confounders not accounted for
  - Drug type can still be predicted from patient characteristics in balanced dataset at ROC AUC = 0.55
  - Take account of weak confounders

Approach

I. Method to detect confounding using decision tree

II. Obtaining balanced dataset using (I)

III. Validating that balanced dataset has reduced confounding

IV. Compare efficiency of Drug A & B using univariate KM on balanced dataset

V. Limitations of method