Predicting the Severity of Adverse Drug Reactions

Abstract

Clinicians use databases such as Lexi-Interact to determine the overall severity of side effects from prescribed drug combinations [1]. However, many drug combinations are not found within such databases, though adverse side effects of such combinations have been reported to the FDA's Adverse Event Reporting System. We used **multinomial classification methods**, SVM, Naive Bayes, Logistic Regression and Random Forests, to **predict drug-drug interaction severity values from the adverse drug reactions in the FDA's database.** SVM and Random Forests both had classification **accuracies of over 95%** though SVM had both higher overall accuracy and higher recall for the most severe severity labels.

Models

Logistic Regression

Maximize: $LL(\theta) = \sum_{i=1}^{n} y^{(i)} \log(\sigma(\theta^T \cdot x^{(i)})) + (1 - y^{(i)}) \log[1 - \sigma(\theta^T \cdot x^{(i)})]$

L2 regression, cross-entropy loss

Naive Bayes

Maximixe: $\prod p(x^i|y^i)p(y^i)$

Random Forest

Minimize: $\Sigma q_m \Sigma p_{mk}(1 - p_{mk})$

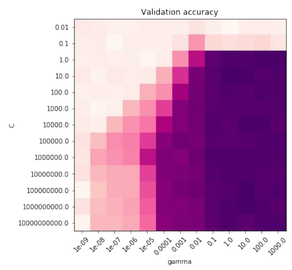
q represents the ratio of samples in region m and p represents the ratio of class k in region m

Hyperparameter: decision tree number

SVM

Optimize: $min_{w,b} \frac{1}{2}||w||^2 \text{ given } y^{(i)}(w^T x^{(i)} + b) \geq 1 \text{ for all } i$

RBF Kernel: tuned gamma, C



(Left) Figure 2. Hyperparameter tuning for SVM Optimal C value is 10 with a gamma of 10^{10}.

Gamma is a measure of how far a single example's influence can spread and C determines the relative weight of accuracy versus widening the decision boundary.

References

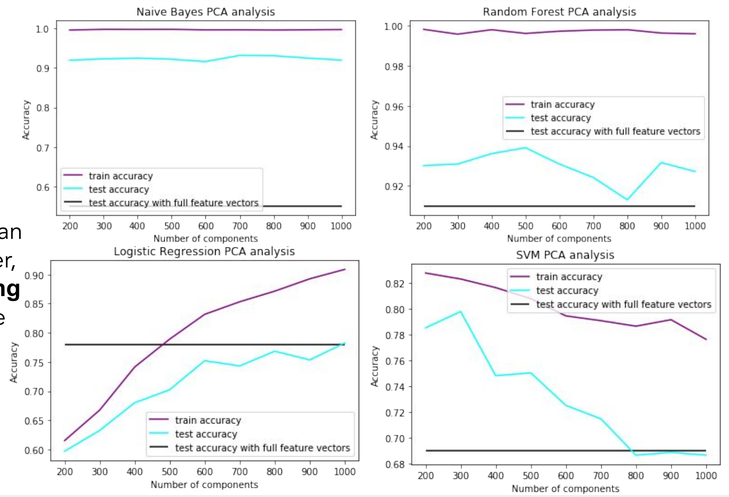
[1] Debruyne, P. R., Pottel, L., Lycke, M., Boterberg, T., Ketelaars, L., Pottel, H., ... & Rottey, S. (2012). Experience with Lexicomp® Online Drug Database for medication review and drug-drug interaction analysis within a comprehensive geriatric assessment in elderly cancer patients. Journal of Analytical Oncology, 1(1), 32-41.

[2] Tatonetti, N. P., Patrick, P. Y., Daneshjou, R., & Altman, R. B. (2012). Data-driven prediction of drug effects and interactions. *Science translational medicine*, *4*(125), 125ra31-125ra31.

[3] Up-to-date [online]. Lexi-interact online. www.uptodate.com/crlsql/ interact/frameset.jsp (accessed 3 June 2019).

Data/Features

The presence or absence of **1,317 potential adverse drug reactions** recorded in the FDA database will be a sparse vector **transformed via PCA** to represent each of the ~63,000 drug-drug interactions [2]. The true labels for these interactions are one of 5 classes from Lexi-Interact, which were combined by physician action to help combat class imbalance. Further, **minority class upsampling within the training set** was used to eliminate class imbalance. The intersection of drug-drug interaction records from the FDA database with the drug-drug severity scores from Lexi-Interact resulted in **3,646 drug pairs**.



(Left) Figure 1. Accuracy across varying number of PCA components with an 80/20 train/test split and 10-fold cross-validation to determine the optimal number of PCA components for the feature vectors.

Table 1. Frequency of Labels

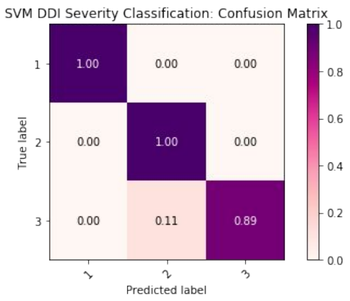
Label	Frequency
No Action	225
Consider Modification	2604
Action Required	817

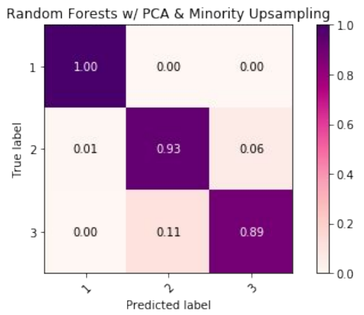
Evaluation

Table 2. Classification Results. Accuracy for each method with optimal hyperparameters and feature vectors with an 80/20 train/test split and 10-fold cross-validation.

Model	Train Accuracy	Test Accuracy
Logistic Regression	91.0%	79.7%
Naive Bayes	99.7%	93.1%
Random Forest	99.9%	95.2%
Multi-Class SVM	99.9%	96.5%

(Below) Figure 3. Normalized Confusion Matrix for the optimal SVM model. Represents 729 test examples. Labeled as:
(1) No Action
(2) Consider Modification
(3) Action Required





(Above) Figure 4. Normalized Confusion Matrix for the optimal Random Forest Model. Represents 729 test examples. Labeled as:
(1) No Action
(2) Consider Modification
(3) Action Required

Table 3. Recall/Precision by class for SVM and Random Forest Models.

	Random Forests (Precision/Recall)	SVM (Precision/Recall)
No Action	1.00/1.00	1.00/1.00
Consider Modification	0.91/0.97	0.91/1.00
Action Required	0.96/0.88	1.00/0.89

Discussion

- Logistic Regression seems to have a problem with **over-fitting**
- **PCA transformation** greatly improved Naive Bayes accuracy, probably as it eliminated sparsity
- SVM accuracy was greatly influenced by **hyperparameters**
- Low Recall for "Action Required" perhaps a function of **drug delivery method** as some drugs can be delivered multiple ways (orally, systemically, optically) which influences drug interaction severity

Future

Validate the predicted severity of a drug pair not in Lexi-Interact against a panel of clinical pharmacists, individuals familiar with clinical outcomes of drug interactions. This is a crucial step as there may be a **selection bias** when only training on drug pairs found within Lexi-Interact.