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: \( L(\theta) = -\sum \frac{1}{n} \log(p(\theta \cdot x_i)) + (1 - p(\theta \cdot x_i)) \)
L2 regression, cross-entropy loss

Naive Bayes
Maximize: \( \prod \frac{p(x_i | y_j)}{p(x_i)} \)

Random Forest
Minimize: \( \sum_{i=1}^{n} \log(\sum_{j=1}^{K} \frac{e^{x_i}}{K}) \)

SVM
Optimize: \( \frac{1}{2} \|w\|^2 + C \sum_{i=1}^{n} \max(0, 1 - y_i (w \cdot x_i + b)) \)
RBF Kernel, tuned gamma, C

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.

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.

<table>
<thead>
<tr>
<th>Model</th>
<th>Train Accuracy</th>
<th>Test Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic Regression</td>
<td>91.0%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Naive Bayes</td>
<td>99.7%</td>
<td>93.1%</td>
</tr>
<tr>
<td>Random Forest</td>
<td>99.9%</td>
<td>95.2%</td>
</tr>
<tr>
<td>Multi-Class SVM</td>
<td>99.9%</td>
<td>96.5%</td>
</tr>
</tbody>
</table>

(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.

(Left) Figure 2. Hyperparameter tuning for SVM Optimal C value is 10 with a gamma of 10^{-7}.

(Left) Table 1. Frequency of Labels

<table>
<thead>
<tr>
<th>Label</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Action</td>
<td>225</td>
</tr>
<tr>
<td>Consider Modification</td>
<td>2604</td>
</tr>
<tr>
<td>Action Required</td>
<td>817</td>
</tr>
</tbody>
</table>

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

Validation of 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.

Future

References