Neural Network to Classify Withdrawn Drugs Using Basic Chemical Descriptors

Introduction

The drug development process is extremely expensive and time consuming. Despite rigorous clinical trials, certain drugs are withdrawn even after FDA approval for many reasons including unforeseen safety issues or more effective replacement drugs. Early identification of drugs with high potential for withdrawal using machine learning techniques could help reduce risks and costs associated with the arduous process of drug discovery and development.

My study focuses on predicting whether a drug is approved or withdrawn based on molecular features derived from its chemical structure. Using a structure-based dataset from DrugBank, which includes molecular formulas, SMILES representations, and approval status, we extracted key chemical descriptors, such as elemental counts and molecular weight. A neural network model was implemented to address this binary classification problem, as neural networks are well-suited for learning complex, non-linear relationships. The goal of this study is to evaluate the predictive power of molecular features and assess the performance of the neural network model in classifying drugs by approval status. I find limitations to this method and suggest further refinement needed.

Methods

The dataset was sourced from DrugBank and was filtered down to contain three main columns for feature extraction. These were SMILES representations, or Simplified Molecular Input Line Entry System, Molecular Formulas, and Drug approval status. To create a supervised binary classification problem, drugs labeled as "approved" were assigned 1, and those labeled as "withdrawn" were assigned 0. Rows with missing molecular formulas, SMILES representations, or approval labels were removed. Notably, there were far more drugs labeled as approved in this dataset, so I applied SMOTE (Synthetic Minority Over-sampling Technique) on the training set to address class imbalance and improve model learning

Key chemical descriptors were extracted from the molecular formulas and SMILES representations. These features included elemental counts of Carbon, Hydrogen, Nitrogen, Oxygen, Phosphorus, Sulfur, and halogens, Molecular weight, hydrogen bond acceptors, hydrogen bond donors, bond complexity: Ring counts, single, double, and triple bonds, as well as a derived complexity score. I initially planned to extract these features using the ‘rcdk’ library, but I ended up using ChatGPT to manually calculate these numbers due to environment issues.

After extracting features, the dataset was split into 80% training and 20% testing sets. The features had unique characteristics that needed to be treated differently to prep for use in the neural network. Log transformation was applied to count-based features to reduce skewness. Standardization was performed on count-based and continuous features using the mean and standard deviation of the training set. Binary features were set to 0 or 1.

Finally, a simple feedforward neural network was implemented using the Keras with the following architecture: an input layer, two hidden layers that had 16 neurons each with Leaky ReLU activation. Batch normalization was applied after each hidden layer and dropout layers with a rate of 0.2 to prevent overfitting. The output layer has a single neuron with a sigmoid activation function for binary classification.

The model was compiled using the Adam optimizer and binary cross-entropy as the loss function. Model performance was evaluated using accuracy and loss on both the training and test datasets. The neural network was trained for 30 epochs with a batch size of 32. The model was validated using 30% of the training data during training.

Results

A graph of different colored lines

Description automatically generated

As shown in Figure 1, both the training and validation accuracy improved over the 30 epochs, eventually plateauing at approximately 80% for the validation set. Similarly, the loss for both datasets decreased steadily but stabilized at 0.46 for the validation set, suggesting that the model reached its performance ceiling. While no significant overfitting occurred, the improvements in accuracy and loss became marginal after a certain point.

The model achieved an accuracy of 83.4%, with a loss of 0.46. The recall score of 97.1% indicates that the model performed well in identifying "approved" drugs (positive class). This came at the expense of a lower precision of 85.4% and an AUC of 0.62. The relatively low AUC suggests that the model struggled to reliably distinguish between withdrawn and approved drugs. Discussion

Many attempts were made to increase performance of the model, including improving class balance using SMOTE, but it became clear that the limited performance of the neural network can likely be attributed to the shallow nature of the feature set used for training. The features I use didn’t quite capture the reasons for a drug’s withdrawal. Biological activity, pharmacokinetic properties, or clinical outcomes, which are often key determinants of a drug's approval status, were not included in this analysis.

Future work should incorporate richer, domain-specific features, such as molecular fingerprints or biological properties, and explore alternative modeling techniques. By integrating more comprehensive datasets and advanced methods, it will be possible to develop more reliable tools for early-stage drug discovery. Success in this domain could potentially save time, money, and lives.

References

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