A Study on Drug Similarity Measures for Predicting Drug-Drug Interactions and Severity Using Machine Learning Techniques

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Abstract: Drug-Drug interaction (DDI) can lead to adverse reactions by decreasing the absorption rate in a patient body. The existing literature has limited focus on the impact of various similarity measures on DDI effects. This paper analyzes seven drug features (chemical substructures, targets, transporters, enzymes, side-effects, offsides, and carriers) obtained from Drugbank, Sider, TWOSIDES, and OFFSIDE databases to analyze DDI. This research examines five Machine Learning models (Logistic Regression, Random Forest, Decision Tree, KNN, ANN) on 16 different similarity measures to observe the performance of predicting samples through accuracy and AUC-curve analysis. The Jaccard similarity is chosen for further DDI prediction as it gives the best similarity score. The feature selection process (using Chi-Square) further reduces the time and space complexity. It compares combinations of every selected feature (chemical substructures, side-effects, offsides, enzymes) on Logistic Regression, Random Forest, and XGB classifiers. The results show that the Random Forest Classifier predicts DDI with the best accuracy of 72%. It also uniquely categorizes the severity level of side effects (minor, moderate, and major) due to DDI events through multi-class classification. Thus, it gives a better clinical significance to fast-track the clinical trials.

1 INTRODUCTION

Drugs are critical in treating diseases and sustaining healthy lifestyles (Huang et al., 2021). But drugs can interfere with other drugs (called *Drug-Drug Interaction (DDIs)*) during treatment and cause serious health complications (Seo et al., 2020). The occurrence of DDIs may lead to various *Adverse Drug Reactions (ADRs)* that cause unavoidable detrimental consequences and high costs for health service providers and hospitals (Liu et al., 2012) (Galeano et al., 2020). However, the processes involved in drug-drug interaction detection are costlier and time-consuming but crucial for drug research and development (Han et al., 2022) (Ferdousi et al., 2017). The complex nature of DDIs makes them extremely difficult to predict, while ADRs are expensive to diagnose and practically hard to treat. In drug development and identification of DDIs, several computational approaches have successfully been used (Wu et al., 2022).

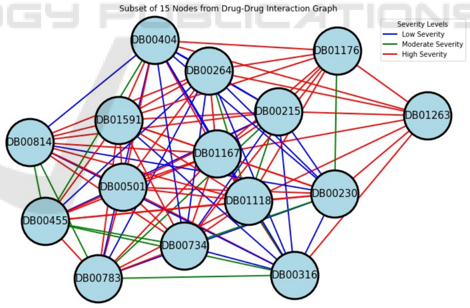

Figure 1: Drug -Drug Interaction with its severity levels graph.

The proposed approach is framed as a Drug-Drug Interaction (DDI) prediction problem, where DDI refers to the featured matrix network, $M = \{D, E, F\}$. Here, $D = \{d_l\}_{l=1}^{N}$ is the set of drugs, where l is the number of N nodes. $E \in \{0,1\}^{NXN}$ is the existence of drug interactions, where a_{mn} is an entry of matrix E at the m^{th} row and n^{th} column, and shows an interaction between drugs d_m and d_n. So, $a_{mn} = 1$ indicates the existence of interaction, and $a_{mn} = 0$ denotes the absence of interaction. $F \in R^{NXP}$ represents the drug features matrix, where P is the dimension of the features. $f_i \in R^{1XP}$ corresponds to the m_{th} row of matrix

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E which is the feature vector of drug d_m. With the node feature matrix F and adjacency matrix E, this research aims to study the following DDI prediction problems.

- *Binary DDI Prediction*: The binary DDI prediction is crucial to quickly ascertain whether an interaction between a pair of drugs (d_m, d_n) exists or not. It is useful in terms of computational resources and time, especially when dealing with a large number of drug pairs. Formally, it is to learn a mapping from $f_{in}(d_m, d_n)$ to $Interact_{ij} \in [0, 1]$. Here, $Interact_{ij}$ indicates the interaction probability of (d_m, d_n).
- *Multi-class DDI side-effects Prediction*: It is to predict the specific interaction type of drug-pair (d_m, d_n) based on drug interactions. Computationally, it is to learn a mapping $F : DXD \iff S_D$, where S_D represents the degree of severity of side effects.

For a more transparent visual representation, Figure 1 presents a subset of 15 drugs depicted as nodes, along with their corresponding interactions showcased as edges. Their interaction severity is shown in 3 colors: Blue for low, Green for moderate, and red for high severity levels. For example, Figure 1 shows that Drug ID DB00783 and DB00316 interact with moderate severity, whereas Drug ID DB00361 and DB01263 interact with high severity risks. Thus, this paper offers valuable insights into potential risks and their implications.

The organization of the remaining paper is as follows: Section 2 presents the Methodology. Section 3 explains the comparative analysis. Section 4 concludes the work along with the future work.

2 METHODOLOGY AND RESULTS

The proposed framework is implemented on a server with 64 GB of RAM and Intel(R) Core(TM) i9-7980XE CPU @ 2.60 GHz (18 Cores, 36 Threads). The code is deployed on PyCharm version 3.5 and uses Power BI packages. Figure 2 shows the workflow of the proposed framework.

2.1 Dataset

The proposed framework uses drug datasets from DRUGBANK (version 5.1.9) (Wu et al., 2022), SIDER (Seo et al., 2020), OFFSIDES, & TWOSIDES (Tatonetti et al., 2012). It uses only approved drugs containing *biological*, *chemical*, and *phenotypic* data.

Table 1: Performance of similarity measures.

Similarity Measures	LR	DT	RF	KNN	NN
Bray	0.62	0.63	0.63	0.64	0.62
Dice	0.64	0.63	0.63	0.64	0.64
Jaccard	0.64	0.64	0.63	0.64	0.64
Hamming	0.56	0.60	0.61	0.58	0.55
Russel Rao	0.63	0.64	0.64	0.64	0.64
Faith	0.55	0.60	0.61	0.59	0.52
Gower	0.56	0.60	0.61	0.59	0.53
Sokal_Michener	0.56	0.60	0.61	0.59	0.52
Ample	0.58	0.60	0.60	0.61	0.60
Anderberg	0.60	0.61	0.60	0.61	0.61
Baroni	0.63	0.63	0.63	0.64	0.63
Kulczynski	0.64	0.63	0.64	0.64	0.64
Goodman	0.61	0.61	0.61	0.61	0.61
Rogers Tanimoto	0.64	0.63	0.63	0.64	0.64
Yule	0.58	0.63	0.64	0.64	0.58
Inner_Product	0.54	0.60	0.61	0.58	0.52

Biological data includes lists of *drug-carrier pairs*, *drug-target pairs*, *drug-enzyme pairs*, and *drug-transporter pairs*. These lists are the base to construct a feature space corresponding to the four types of binary fingerprints of the biological elements: *carrier*, *target*, *enzyme* and *transporter* (Liu et al., 2012). The length of the bit vectors for carrier, target, enzyme, and transporter features is 78, 2856, 434, and 273, respectively.

Chemical data consists of 2D chemical structures of the same drug list considered the drug feature. Chemical substructure information is retrieved from the PubChem database in SMILES (Simplified Molecular Input Line Entry System) format using MOE 2010.10 software. Then, MACCS (Molecular ACCess System) substructures are calculated with 166 key descriptor bits. This work used MACCS because of its availability in cheminformatics software libraries or databases, and promising performance in capturing relevant substructure information required for predicting DDI (Ibrahim et al., 2021).

The phenotypic data of drugs are also essential in predicting DDIs. Drug indications, side effects, and offside effects construct the phenotypic data of drugs. It extracts drug indications and side effects from SIDER and offside effects from OFFSIDES. The framework creates a comprehensive drug dataset by merging and intersecting these diverse datasets.

2.2 Similarity Measures

Similarity measures are numerical quantities that quantify the degree of association between pairs of drugs and are considered a measure of similarity sim_{ij} if, for every $d_i \in D$ satisfies the following properties: $0 \leq sim_{ij} \leq 1$ if $i \neq j$, $sim_{ij} = 1$, then $sim_{ij} = sim_{ji}$. Even though numerous binary similarity measures exist in the literature, only a few similarity measures are in use (Ibrahim et al., 2021) (Huang et al., 2021). Different similarity-based ML methods help predict DDI through binary classification (Wu et al., 2022) (Vilar

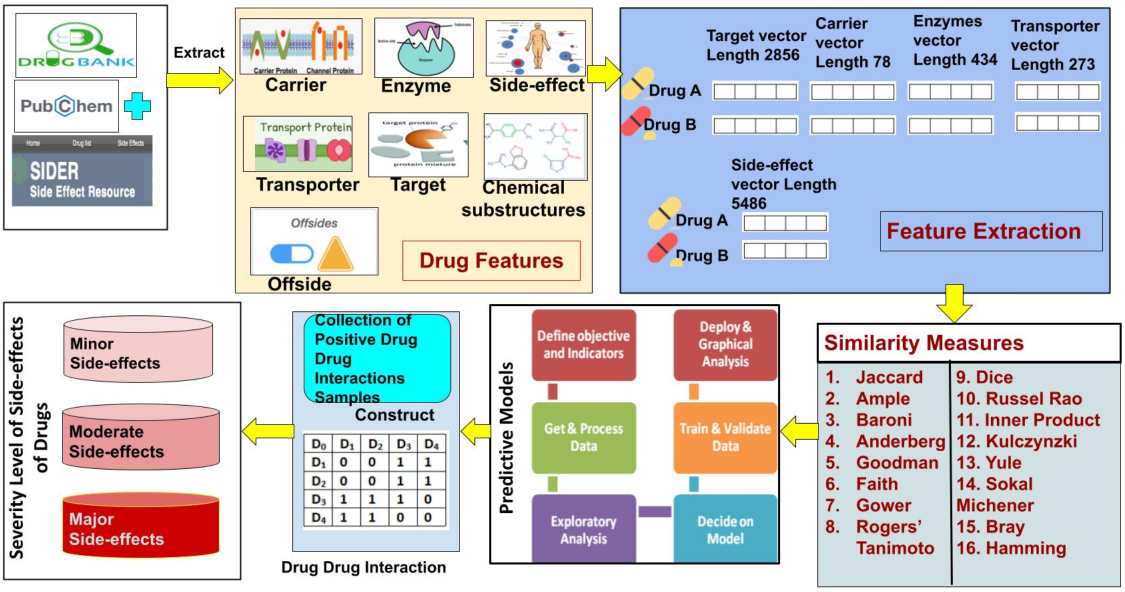


Figure 2: Workflow of Proposed Approach.

et al., 2014).

This paper implements 16 binary similarity measures for analyzing their performance on different classifiers, as shown in Table 2. Where v_i and $v_j \leftarrow$ are two row-vectors, each comprised of i and j variables with a value of 1 (present) or 0 (absent).

p $\leftarrow$ number of features where values for $v_i = 1$ and $v_j = 1$

q $\leftarrow$ number of features where values for $v_i = 0$ and $v_j = 1$

r $\leftarrow$ number of features where values for $v_i = 1$ and $v_j = 0$

s $\leftarrow$ number of features where values for $v_i = 0$ and $v_j = 0$

$\sigma \leftarrow$ observed agreement or similarity between two sets of drug interactions

$\sigma' \leftarrow$ expected agreement to occur randomly between two sets of drug interactions.

p+s $\leftarrow$ total number of matches between v_i and v_j

q+r $\leftarrow$ total number of mismatches between v_i and v_j

M $\leftarrow$ Similarity values

The binary similarity determines the analysis properties of the similarity and dissimilarity coefficients (de Albuquerque et al., 2022). The choice of the correct coefficients and the variables depends on the best performance of similarity measures on different classifiers, as shown in Table 1. Out of these, the classifier that results in the highest performance is chosen to predict the candidate side effects of drugs as shown in Table 3.

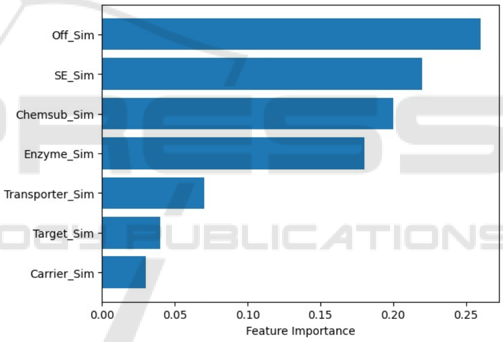


Figure 3: Chi-square test on Features.

2.3 Drug-Drug Interactions (DDI)

This paper uses the *Chi-square test*, a simple tool for univariate feature selection for classification. The threshold calculation is based on the mean of the summed chi-squared values for feature selection (i.e. $(\frac{sum\ of\ chi-squared\ values}{Total\ number\ of\ features} = \frac{1}{7} = 0.14)$). Figure 3 shows that only four binary similarities values such as *offside (Off_Sim)*, *side effect (SE_Sim)*, *chemical substructure (Chemsub_Sim)*, and *enzyme (Enzyme_Sim)* are above the threshold.

Each Drug is coded into binary vectors by considering every bit as the association between two drugs or not. If a drug is associated with another drug, the corresponding bit becomes 1; otherwise, it is 0. Drug similarities are evaluated based on DDI information from DrugBank and the interaction information with standard similarity calculation methods. Figure 4 in-

Table 2: Definitions of different Similarity Measures.

S.no.	Similarity Measures	Formulae	Descriptions
1	Bray (Huang et al., 2021)	$M = \frac{q+r}{2p+q+r}$	Computes the compositional dissimilarity between the two sites based on counts at each site.
2	Dice (de Albuquerque et al., 2022)	$M = \frac{p}{2p+q+r}$	Measures the similarity between two sets of data
3	Jaccard (de Albuquerque et al., 2022)	M=$\frac{p}{p+q+r}$	Check similarity of members for two sets to see which members are shared and which are distinct. Computes similarity for the two sets of data, with a range from 0% to 100%.
4	Hamming (Huang et al., 2021)	$Distance = q + r$	Measures the number of equals components, divided by the length of vectors. Defines the minimum number of substitutions needed to modify one string into the other, or the minimum number of errors that could have converted one string into the other.
5	Russel Rao (de Albuquerque et al., 2022)	M=$\frac{p}{p+q+r+s}$	Dot-product-based similarity measure in a range between 0 (minimum similarity) and 1 (maximum similarity). Measures the similarity between drug interactions as it is a specific and appropriate similarity measure with a 0 to 1 similarity range.
6	Faith (Huang et al., 2021)	M=$\frac{p+0.5s}{p+q+r+s}$	Feature and Information Theoretic measures parameterized ratio model of similarity.
7	Gower (Huang et al., 2021)	M= $\frac{p+s}{\sqrt{(p+q)(p+r)(q+s)(r+s)}}$	Measures how different two records (including logical, categorical, numerical or text data) are. The distance is always a number between 0 (identical) and 1 (maximally dissimilar).
8	Sokal_Michener (de Albuquerque et al., 2022)	M= $\frac{p+q}{p+q+r+s}$	Measures the negative matches that do not mean necessarily any similarity between two objects.
9	Ample (Huang et al., 2021)	M=$\frac{\lvert p(r+s)\rvert}{\lvert r(p+q)\rvert}$	Similar to absolute value of the Tarantula that has high correlation with chi-square based measures
10	Anderberg (Huang et al., 2021)	M=$\frac{p}{p+2(q+r)}$	Measures handle similarity between categorical attributes. Assigns higher similarity to rare matches, and lower similarity to rare mismatches
11	Baroni (Huang et al., 2021)	M=$\frac{\sqrt{ps}+p}{\sqrt{ps}+p+q+r}$	Selects compounds which exhibit a similar size distribution to the database. suitable for compound selection to identify a wide structural variety of compounds but with a similar distribution to the full database.
12	Kulczynski (de Albuquerque et al., 2022)	M=$\frac{p}{q+r}$	Measures the correlation between occurrences of two items, which is a fundamental concept in the analysis of presence-absence data. Solves many pattern recognition problems such as classification, clustering, and retrieval problems.
13	Goodman (Huang et al., 2021)	M=$\frac{\sigma-\sigma'}{2k-\sigma'}$	Measures the similarity of the orderings of the data when ranked by each of the quantities and strength of association of the cross tabulated data.
14	Roger_ Tanimoto (de Albuquerque et al., 2022)	M=$\frac{p+s}{p+2(q+r)+s}$	Emphasize on the weight of the count of four states
15	Yule (Huang et al., 2021)	M= $\frac{ps-qr}{ps+qr}$	Defined as the coefficient of colligation. Measures association between two binary variables
16	Cosine of Inner product (Huang et al., 2021)	M=$p + s$	Measures the cosine of the angle between two vectors and determines whether two vectors are pointing in roughly the same direction.

Table 3: Performance analysis of different similarity measures on different classifiers.

Similarity Measures	Classifiers	Accuracy	Precision	Recall	F1-score	AUC
Jaccard	LR	0.64	0.64	0.65	0.64	0.68
	DT	0.64	0.66	0.64	0.63	0.69
	RF	0.63	0.65	0.64	0.64	0.70
	KNN	0.64	0.65	0.65	0.64	0.69
	NN	0.64	0.65	0.65	0.64	0.65
Russel Rao	LR	0.63	0.62	0.62	0.62	0.68
	DT	0.64	0.66	0.65	0.64	0.69
	RF	0.64	0.65	0.65	0.64	0.69
	KNN	0.64	0.65	0.65	0.64	0.69
	NN	0.64	0.65	0.65	0.64	0.64
Kulczynski	LR	0.64	0.66	0.65	0.64	0.69
	DT	0.63	0.65	0.64	0.63	0.69
	RF	0.64	0.65	0.65	0.64	0.69
	KNN	0.64	0.65	0.65	0.64	0.69
	NN	0.64	0.66	0.65	0.64	0.65
Rogers Tanimoto	LR	0.64	0.65	0.64	0.63	0.68
	DT	0.63	0.65	0.64	0.63	0.69
	RF	0.63	0.65	0.64	0.64	0.65
	KNN	0.64	0.65	0.65	0.64	0.69
	NN	0.64	0.65	0.64	0.64	0.51

fers that Jaccard gives better accuracy with Random Forest than other similarity measures. Drugbanks give 13910 extracted drugs with a total of 2682157 interactions. Of these, there are only 4107 approved drugs, resulting in the total interactions dropping to 1889983. After filtering for duplicate interactions (such as d_{ij} and d_{ji}), the total number of interactions becomes 1341086. The common drugs with all four features (Off_Sim, SE_Sim, Chemsub_Sim, Enzyme_Sim) come down to 816 drugs, and the total number of interactions becomes 260301.

The positive samples for 816 drugs are calculated using the Jaccard similarity measure, where positive interactions are 144282 and unlabeled interactions are 116019. Unlabeled drug interactions are labeled by mapping drugs from the SIDER database. Thus, unlabeled interactions are converted into negative and positive interactions. Here, 89835 interactions are considered negative samples, and 26184 are considered positive. Hence, the total number of positive interactions increased to 170466.

2.4 Predictive Models

Predictive models require little computation time and supervision (Wu et al., 2022) (Kumari et al., 2023). The performance of the models is compared using metrics such as accuracy, precision, recall, F1 score, AUC score and Mathews Correlation Coefficient (MCC). The proposed experiment follows 5-fold cross-validation for a robust evaluation of the model's performance compared to a single train-test split. Each fold contains an equal number of samples. In each iteration, one fold is held out as the test set, while the remaining four folds are combined to form the training set. It mitigates the impact of the data's initial distribution and provides a more representative estimate of the model's ability to generalize unseen data. Then, aggregated similarity matrices (Off_Sim, SE_Sim, Chemsub_Sim, Enzyme_Sim) are applied to train the machine learning (ML) models. ML models such as Logistic Regression, Random Forest, and XGB are tuned with their hyperparameter values to achieve maximum learning process as shown in Table 4. Here, the optimal parameter makes the learning process faster, and the learning rate helps achieve minimum loss function and avoid underfitting scenarios. It continues till the model reaches its convergence. Thus, ML models achieve their best accuracy by tuning their hyperparameters to the best set of parameter values (Rajita et al., 2023). Random forest outperforms other models with an accuracy of 0.72 and an AUC score of 0.78 with a minimal set of four features: offside, side-effect, chemical substructure, and enzyme, as shown in Table 5.

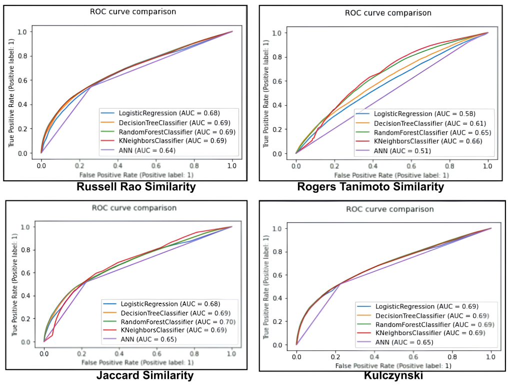
2.5 Severity Level of Drugs Side-Effects

The multi-class classification process classifies the severity of drug-drug interactions (DDIs) into three classes – *minor*, *moderate*, and *major*. By focusing on severity, healthcare professionals can prioritize their actions and interventions, leading to improved patient outcomes and better management of potential drug interactions. There are two approaches for multi-class classification: One-vs-Rest and One-vs-One techniques. This paper chooses the One-vs-Rest strategy because it classifies data more efficiently and faster. It splits a multi-class classification into one binary classification problem per class using heuristic methods where each classification model predicts a class membership probability or a probability-like score.

The frequency values and their corresponding probability-like scores are collected from the TWOSIDES database. The argmax (probability) of these scores (class index with the largest score) is then used to predict a class. Thus, each frequency class fits a mean reporting frequency in three percentage classes [33%, 66%, 100%] to the predicted scores and obtains a probability density function (pdf) for each class. The pdfs built for each frequency class are the defined boundaries for the classification decision with maximum likelihood. The thresholds obtained are 0.00315, 0.0128, and 1. Thus, given a predicted score x, a frequency class is chosen using the thresholds given in Equation1:

$$pdf(x) = \begin{cases} \text{minor} & \text{if } 0 \leq x \leq 0.00315 \\ \text{moderate} & \text{if } 0.00315 \leq x \leq 0.0128 \\ \text{major} & \text{if } 0.0128 \leq x \leq 1 \end{cases} \quad (1)$$

Table 6 infers that Drugid: DB00231 and DB00203 have an interaction frequency of 1 (minor) for three symptoms (Arthralgia, diarrhea, and Headache). Similarly, there are 170466 positive drug-drug interactions and a total of 11676 symptoms due to different interactions in the TWOSIDES database. The DDI events obtained from the constructed dataset are mapped with the TWOSIDES database. So, there are 18263659 drug-drug interactions for all provided symptoms in the constructed dataset. Table 7 presents the total number of drug interactions in three classes: minor, moderate, and major side-effect (symptom) frequencies.



Russell Rao Similarity

Rogers Tanimoto Similarity

Jaccard Similarity

Kulczynski

Figure 4: AUC for similarity measures on different classifiers.

2.6 Result Analysis

This section presents a comparison of Logistic Regression, Random Forest, and XGB (Extreme Gradient Boosting) classifiers to assess the impact of algorithmic diversity on the predictive performance for DDI. Where, Logistic Regression is a commonly used baseline model due to its simplicity, but Random Forest and XGB are more complex models known for their ability to capture intricate patterns and relationships. The comparison helps benchmark the performance of more sophisticated models against a simpler one to evaluate the trade-off between model complexity and predictive accuracy. In this work, the experiments are conducted up to three times, and the reported values for each classifier are based on the average of these repetitions. This approach ensures a more accurate representation of the classifiers' performance by minimizing the impact of random fluctuations.

Thus, the paper presents the performance of different Machine Learning Binary Classifiers employing four similarity measures using the AUC curve. A higher AUC score indicates better discriminative power and overall classifier performance. Figure 4 illustrates that the Random Forest model using the

Table 4: Hyperparameters tuned with their initial and final values for different classifiers.

Classifier	Hyperparameters		Epochs	Descriptions
	Initial values	Final Values		
LR	C=[0.1,1,10]	C=0.1	100	C is the regularization parameter. For a given value of C, the regularization strength decreases.
	Penalty=[l1, l2]	Penalty= l2		Penalty determines the type of regularization applied to the logistic regression model. Regularization helps prevent overfitting by adding a penalty term to the loss function.
	Solver=[newton-cg, lbfgs, liblinear]	Solver= liblinear		Solver determines the algorithm to use for optimizing LR model.
RF	max_depth=[30,50]	max_depth = 30	50	max_depth controls the maximum depth of each decision tree in the Random Fores
	max_features = [1,2,3,4]	max_features = [1]		max_features determines the maximum number of features to consider when looking for the best split at each node of the decision tree.
	n_estimators = [100,250,500]	n_estimators = 500		n_estimators represents the number of decision trees to be included in the RF ensemble.
XGB	booster = [gbtree, dart]	booster = gbtree	100	booster as gbtree provides strong predictive power and handles non-linear relationships well.
	max_depth=[30,50]	max_depth=50		max_depth determines the maximum depth of each decision tree in the boosting process

Table 5: Performance analysis of combinational features for different classifiers.

Classifier	features	Accuracy	Precision	Recall	F1-score	AUC	MCC
LR	off_sim	0.66	0.61	0.56	0.55	0.66	0.37
	SE_sim	0.67	0.64	0.55	0.52	0.65	0.36
	Chemsub_sim	0.65	0.65	0.50	0.51	0.56	0.36
	Enzyme_sim	0.65	0.65	0.51	0.51	0.63	0.35
	[off_sim, SE_sim]	0.67	0.63	0.59	0.58	0.69	0.40
	[off_sim, SE_sim, Chemsub_sim]	0.68	0.63	0.59	0.59	0.69	0.41
	[off_sim, SE_sim, Chemsub_sim, Enzyme_sim]	0.68	0.65	0.63	0.64	0.72	0.44
RF	off_sim	0.65	0.58	0.54	0.52	0.63	0.34
	SE_sim	0.64	0.57	0.54	0.52	0.58	0.34
	Chemsub_sim	0.62	0.52	0.51	0.48	0.52	0.33
	Enzyme_sim	0.65	0.50	0.50	0.49	0.63	0.32
	[off_sim, SE_sim]	0.67	0.62	0.58	0.57	0.68	0.40
	[off_sim, SE_sim, Chemsub_sim]	0.70	0.67	0.61	0.61	0.73	0.46
	[off_sim, SE_sim, Chemsub_sim, Enzyme_sim]	**0.72**	**0.69**	**0.66**	**0.66**	**0.78**	**0.52**
XGBoost	off_sim	0.64	0.56	0.54	0.53	0.63	0.36
	SE_sim	0.66	0.60	0.54	0.52	0.60	0.35
	Chemsub_sim	0.64	0.53	0.51	45.5	0.52	0.33
	Enzyme_sim	0.65	0.50	0.50	0.46	0.63	0.32
	[off_sim, SE_sim]	0.66	0.60	0.58	0.58	0.67	0.37
	[off_sim, SE_sim, Chemsub_sim]	0.68	0.64	0.62	0.63	0.70	0.43
	[off_sim, SE_sim, Chemsub_sim, Enzyme_sim]	0.70	0.66	0.65	0.66	0.75	0.50

Table 6: Frequency of Side-Effects (symptoms) Induced by Drug-Drug Interaction (DDI) Events.

Symptoms	mean_reporting frequency	drug_id1	drug_id2	Predicted frequency & severity levels
Arthralgia	0.044872	DB00231	DB00203	1 (minor)
Arthralgia	0.071429	DB00887	DB00107	1 (minor)
Diarrhea	0.012821	DB00231	DB00203	1 (minor)
Diarrhoea	0.214286	DB00887	DB00107	1 (minor)
Headache	0.102564	DB00231	DB00203	1 (minor)

Table 7: Number of drug-drug interaction for different side-effects based frequencies.

Severity Levels	Number of interactions
Major (High Frequent=3)	5965100
Moderate (Moderately Frequent=2)	6053430
Minor (Less Frequent=1)	6245129

Jaccard similarity measure achieves a higher AUC score than other similarity measures such as Kulczynski, Rogers Tanimoto, and Russell Rao. This superiority is attributed to Jaccard's capability to handle binary data and capture the presence or absence of shared features between instances. Consequently, it effectively captures the similarities and differences, improving classification performance. Moreover, the ensemble nature of Random Forest and its ability to mitigate overfitting contribute to its superior performance when employing the Jaccard Similarity measure. Based on the overall performance in the given machine learning models, the Jaccard coefficient is taken to calculate the scoring function for drug similarity. Consequently, datasets comprising positive samples labeled as 1 and negative samples labeled as 0 are constructed using the Jaccard similarity matrix as discussed in Section 2.3.

Random forest gives better accuracy of 72% with selected 4 features (offside, side-effect, chemical substructure, and enzyme) as shown in Table 5. This combination of relevant features makes the model more efficient than individual features alone. These findings highlight the importance of feature selection and its impact on model performance and resource utilization. Figure 5 also shows an increase in the performance of predictive models after feature selection.

The proposed framework also predicts the severity levels for the given DDI events. The approach collects probability-like scores for frequency classes from the TWOSIDES database, fits probability density functions to the scores, and uses thresholds to pre-

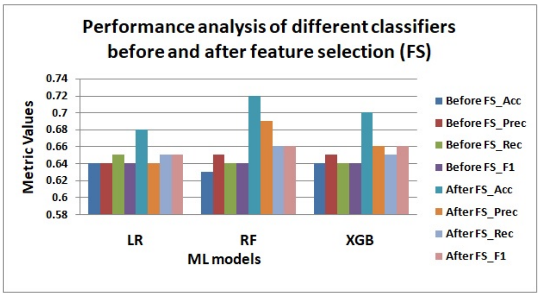


Figure 5: Performance analysis of different classifiers before and after feature selection.

dict the severity level for given DDI events based on the highest scoring class. The severity levels are categorized into different classes, and the predictions for these classes are summarized in Table 6. Additionally, Table 7 presents the total number of drug interactions for each of the three frequency classes, providing further insights into the drug data.

3 COMPARATIVE ANALYSIS

This section presents the comparison between the proposed framework and other existing methods. Table 8 provides the details of the different types of techniques along with the repositories for Biological (protein) data, Chemical data, and phenotypic (side effect) data. It is observed that different methods use different datasets for the prediction process. No standard data set is available to compare the results of various techniques. Thus, this paper compares the overall efficiency of different methods, the issues addressed by them, and their limitations. The docking-based approach predicts the side effects based on the analysis of the alignment of the drugs with the protein structures (Luo et al., 2011) (LaBute et al., 2014). However, these methods do not depend on experimental data that help identify novel and unexpected interactions. But, network-based and machine learning-based approaches overcome the limitations of docking-based approaches. The network-based approach visualizes the drug features and their interactions in a network and helps identify more interactions and their side effects (Huang et al., 2013) (Zhang et al., 2016). Also, the Machine learning approach (Liu et al., 2012) employs different classifiers to address the prediction problem as in this work. It is an automated intelligent approach that requires little supervision and comparatively less comprehensive data (Chen and Li, 2018). There is significance in examining different similarity measures on machine learning (ML) models instead of deep learning models. ML model lies in exploring and understanding the effectiveness and applicability of other techniques in solving the specific problem of drug-drug interaction (DDI) analysis (Liu et al., 2012). ML models, notably simpler algorithms such as decision trees or random forests, often exhibit good generalization performance and are easier to implement and deploy in real-world applications. This practical applicability makes them suitable for DDI analysis tasks where interpretability and efficiency are crucial. They can handle high-dimensional data efficiently, essential when dealing with multiple similarity measures and features.

4 CONCLUSIONS

This paper proposed an effective and robust framework to predict the potential DDIs by utilizing the drug properties (i.e., chemical, biological, and phenotype properties). This research compared 16 different similarity measures on various machine learning models, and the results show that the Jaccard similarity measure performed better. Feature selection further aided in DDI prediction with minimal features. Jaccard similarity measure helped analyze positive and negative interactions for training the models. Thus, it detected unexpected side effects and guided drug combinations. The proposed approach is at relatively early stage to showcase the need for

Table 8: Comparative analysis of Existing methods with the Proposed approach.

References	Type of technique	Phenotypic	Protein	Drug	Limitations
(Luo et al., 2011)	Docking based	FDA and AERS information	UniPort	Drugbank	Complex Task as it involves the iterative molecular simulation of 3D structures of drugs proteins drugs .
(LaBute et al., 2014)	Docking based	SIDER	PDB	Drugbank	No sufficient validation to infer the binding strength based on the docking affinity score.
(Huang et al., 2013)	Network based	SIDER	PubChem	Drugbank	Pathway-based models dependent on gene expression information
(Zhang et al., 2016)	Network based	SIDER	PubChem	KEGG and Drugbank	Dependence on experimental data prevents the identification of unexpected drug target bindings
(Liu et al., 2012)	Machine learning based	SIDER	KEGG and Drugbank	PubChem	The performance of the methods is limited to the diversity of compounds in dataset, quality of descriptors etc.
(Zheng et al., 2019)	Miscellaneous	SIDER	Gene ontology	Drugbank	The various parameters need to be specified every time.
Proposed approach	Machine learning based	SIDER, TWOSIDES and OFFSIDES	MACCS and Drugbank	Drugbank	The frequency of side-effects are constrained to the constructed dataset.

additional refinement in similarity measures. This paper also proposed predicting the severity levels of side effects through a multi-class classification approach. It classified drug interactions into minor (low-frequency), moderate (medium-frequency), and major (high-frequency) levels.

The authors aspire to develop more effective predictive models using Deep Learning methods, Recurrent Neural Network (RNNs) and their variations which could significantly contribute to the evolution of the reasearch work. Future work could also explore the other existing research to perform comparison on the same dataset for a more comprehensive evaluation of model performance.

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