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Synergizing Convolutional Neural Networks and Drug Similarity Estimation for Improved Drug-Drug Interaction Prediction

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ABSTRACT

Drug-drug interactions can cause adverse effects and impact patient safety. Traditionally, the prediction of DDIs has been labor intensive. However, these approaches have certain limitations in terms of scalability, convergence of different drug combinations, and capturing complex interactions. The potential combinations increase as the number of approved drugs increases; this results in the need for efficient methods. This research aims to utilize artificial intelligence and machine learning techniques to develop a method that accurately detects potential DDIs. The proposed idea allows for greater accuracy and automation in predicting DDI, reducing the time and cost required. The proposed method takes two drug formulas as input and employs a Drug Feature Extractor to extract their features. These features are then represented in feature maps, which are used when calculating a similarity score between input drugs and other drugs in the data set, and to predict potential DDIs. The model combines a drug similarity calculator and DDI predictor, enabling the system to process data in a "human-like" method; aiding in predicting interactions for newly developed drugs. The proposed model achieved state-of-art performance with an accuracy of 88.9%. The results demonstrate the efficacy of the proposed method in predicting potential drug interactions.

Introduction

Drug-drug interaction (DDI) is the reaction that occurs between two or more drugs when taken together; due to the presence of one drug, the effects or the toxicity of one drug can be altered. In some cases, it may be life threatening. Hence, identifying potential DDIs and managing them appropriately is crucial. The Diagnosis of DDIs is significant in the context of drug discovery and polypharmacy as it helps to ensure the safety and effectiveness of medications. With the growing numbers of drugs in the market, identifying potential DDIs are essential. By discovering DDIs in the early drug development process, pharmaceutical companies can prevent drug withdrawals and avoid financial losses. Furthermore, polypharmacy is on rise. This increases a risk for drug interactions. Drug interactions can lead to adverse effects such as drug toxicity and drug ineffectiveness. Early identification of DDIs can help prevent the risk of adverse outcomes. Therefore, it is significant to diagnose and discover DDIs to prioritize patient safety.

The prediction of DDIs has been dependent on labor-intensive experimental studies and empirical observations. However, these approaches have certain limitations. As the number of approved drugs and potential drug combinations continue to grow exponentially, there is an increasing need for more efficient and accurate methods to predict DDIs. Therefore, there is a significant need for accurate and efficient methods to anticipate potential drug interactions. The use of machine learning in discovering DDIs can optimize the research process, making it more quicker, efficient, cost-effective, and atomized.

Background Knowledge

Drug-Drug Interaction

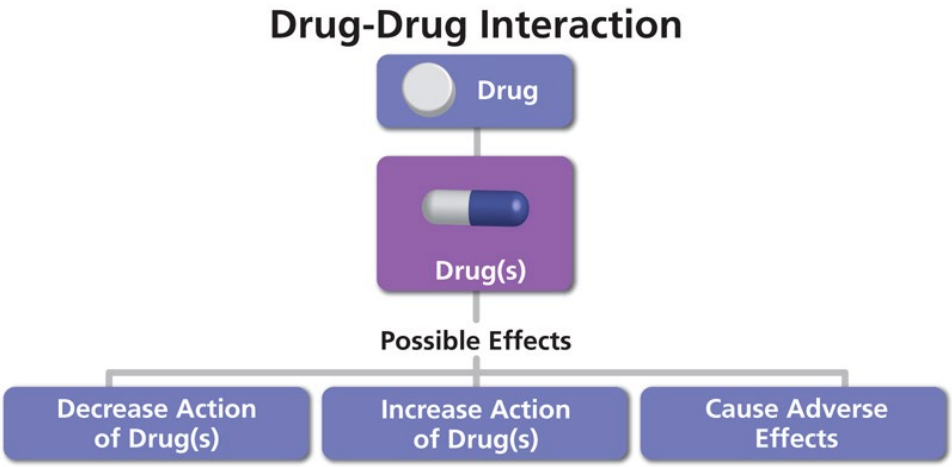

Figure 1. Possible drug interaction effects (NIH 2016).

DDI are the reactions between two or more drugs when used simultaneously. DDIs can lead to adverse drug reactions or drug ineffectiveness. There are various types of interactions including addition, permissive, synergistic, and tachyphylactic. Additional interactions occur when the effect of two drugs does not have an increase in the sum effect. For example, Aspirin has a blood thinning effect, however acetaminophen has analgesia effect, when they are used together, there are no additional side effects.

Permissive interactions occur when the effect of one drug is enhanced in the presence of another drug. Epinephrine itself can cause 40% vasoconstriction. When it is used with cortisol, the effect increases to 70%. Synergistic interactions are when the produced effect is greater than the sum of the individual effects of drugs. Clopidogrel and Aspirin both cause 30% of blood thinning. When they are taken together, the effect increases to 90%, which is larger than the sum of individual effects. Tachyphylactic interaction occurs when a drug's effect diminishes due to repeated use and a decreased effectiveness over time. Using drugs that provide short-term relief for extended periods decreases the effectiveness. Hence, it is crucial to understand the different types of drug interactions to avoid and identify adverse effects.

Object Classification

Object classification is a computer vision technique that determines a category of an object in an image or a video. The aim of object classification is to assign a class for objects based on its visual appearance. It is an essential task in the study of computer vision, as it holds significant importance in various fields such as object detection and medical image diagnosis.

Object classification involves training a machine learning model to recognize the features that are unique to each object category. The machine learning model is trained on a dataset of various images with category labels throughout the training process the model learns to extract and identify visual characteristics and associate them with correct categories. There are several methods in developing an object classification system. Convolutional neural network (CNN) is a type of deep learning model that is suitable for object classification. They are designed to use convolutional layers and to extract features from images.

There are various CNNs models that have been developed for various computer vision tasks. Some of the well known systems include: AlexNet (Krizhevsky et al. 2012), VGGNet (Simonyan et al. 2014), and ResNet (He et al. 2016). Figure 1 illustrates an example application of object classification, the facial expression recognition system. This system takes a facial image as input and outputs one of the several facial expressions.

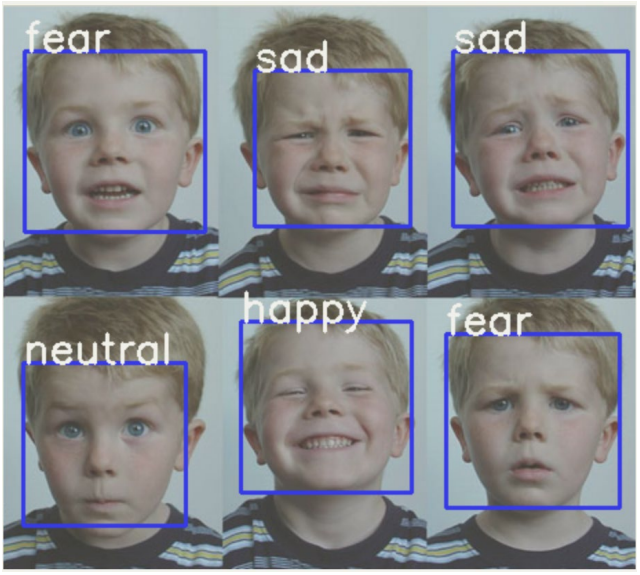

Figure 2. Example of an object classification (facial expression recognition) (Serengil 2018)

In this research, the concept of object classification will be utilized to investigate the drug-drug interactions between two specific drugs. Chapter 3 will provide a comprehensive explanation of the detail process and the input and output components of the system.

Drug Similarity

The drug similarity estimator has a crucial role in the model as it incorporates human-like reasoning. Its purpose is to evaluate the similarity between newly created drugs and existing drugs. By utilizing a drug similarity calculator, the model can efficiently predict the degree of similarity; which aids in predicting DDIs. This helps make informed decisions during development and minimize risks. The drug similarity takes two drugs as an input and outputs a number between 0~1. 0 indicates that there are no similarities between the drugs. 1 indicates that they are identical. The similarity estimator utilizes pharmacokinetics and drug related data to calculate their similarity.

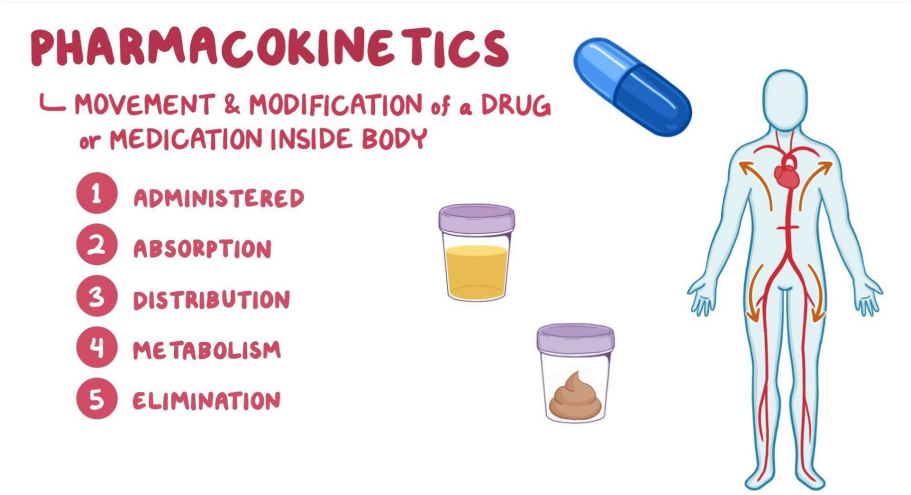

Figure 3. Four Key components of Pharmacokinetics (Paul 2021)

Pharmacokinetics is the study of how the body reacts with the drug. It consists of four key components: absorption, distribution, excretion, and metabolism. Absorption is the process where a drug enters the bloodstream to be absorbed. Distribution Involves the drug's transportation of various tissues and organs of the body. Metabolism is the process where the drug transforms into different compounds(metabolites). Elimination is a phase that removes the drug and its metabolites from the body. This is a crucial part of the intake of drugs because it can accumulate to toxic levels that lead to adverse effects.

Furthermore, the similarity calculator takes in the drug related data when calculating the similarity. Drug related data are: chemical structure, ATC code, target, side effect, drug-drug interactions, drug disease association, gene ontology, binding profiles, protein structures, etc,. Chemical structures are important as it provides information about the drug's chemical properties, functional groups and bonding patterns. It helps to determine the drug's behavior and interactions in the body.

ATC code is a classification system to categorize drugs based on their therapeutic use and pharmacological properties. It provides a standardized way to identify and organize drugs according to their specific indications and mechanisms of action. Target refers to the specific molecule within the body that the drug interacts to produce the therapeutic effect. Understanding it will help clarify its mechanism of action and predicting its efficiency. Side effects are unintended effects that can occur when taking a drug. They will help make informed decisions regarding its use and monitor for any potential adverse reactions that may occur. Drug-drug interactions are effects that occur when two or more drugs are used. understanding it would help avoiding the harmful effects and assess the compatibility of different drugs. Drug disease association refers to the relationships between specific drugs and particular disease or medical conditions. It helps to identify which drugs may be effective in treating certain diseases and guide treatments.

Gene ontology describes the gene functions and their relationships with the drug. It can be used to understand the genetic factors involved in drug responses, metabolism, and potential interactions. Binding profiles describe their interactions between drugs and their target molecules at a molecular level. This provides insight into dug's affinity, specificity and mode of binding, which aids in predicting its effects and potential side effects. protein structures are the three-dimensional arrangement of atoms in protein molecules. Understanding structures can help identify specific proteins to modulate their functions. These different types of drug-related data contribute to the understanding of properties, mechanisms of action, therapeutic uses, potential side effects and interactions. Hence, it is crucial in discovery and development of drug-drug interactions.

These pharmacokinetic and drug related data will be considered when calculating the similarity of the drugs. The model will calculate the similarities of each different factor and output a number between 0 and 1 which represents the similarities.

Proposed Drug-Drug Interaction Prediction System

This chapter presents a detailed review of the proposed method, addressing its functionality and the significance of the development of this network. The model functions by taking two drugs and extracting their unique features, which are then used to calculate a feature map. The model calculates the similarity between the two drugs based on this feature map and predicts potential DDIs as outputs.

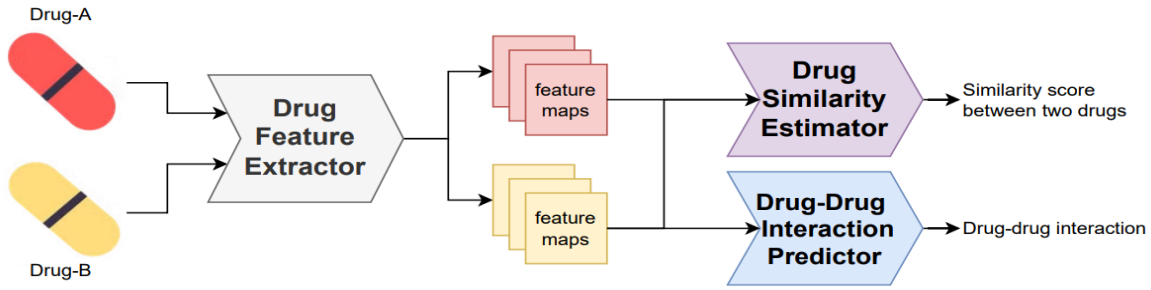

Figure 4. Overall architecture of the proposed method

Traditional techniques of identifying DDIs rely on comparing the chemical structures of drugs. The addition of a drug similarity estimator allows the model to account for a broader variety of characteristics that may impact drug interactions and deliver more accurate predictions. As a result, the model can generate more precise predictions.

Drug Feature Extractor

The proposed system takes two drug formulas, D_A and D_B, as its input. The drug formulas are placed into the Drug Feature Extractor (*DFE*), which is defined as *DFE* in this system. DFE: $D_k \rightarrow F$. *DFE* extracts features from D_A and D_B, resulting in feature maps F that represent the content of D_A and D_B. Then the information contained in F is used to calculate the similarity score S and predict drug-drug interactions P. The similarity score S is calculated by Drug Similarity Estimator (*DSE*), which compares the feature maps of D_A and D_B to those of other drugs in the dataset. Finally, the Drug-Drug Interaction Predictor (*DDIP*) predicts potential interactions between D_A and D_B based on their respective feature maps.

To evaluate the model's performance, it is critical to calculate the appropriate loss of each task. The proposed model consists of two neural networks. Each serves a distinct purpose in estimating drug similarity and drug-drug interaction.

The neural network responsible for drug similarity operates as a regression task. It aims to predict the exact value of the drug similarity input. The Mean Square Error (MSE) function is employed to evaluate the loss. The MSE loss function computes the mean of squared differences between the predicted and true values. By squaring the differences, it assigns higher penalties to larger errors due to the quadratic nature of the function. Thus ensuring the model's sensitivity to outliers or significant deviations from the true values.

Equation 1: Mean Square Error Loss Function

$$L_{mse} = \frac{1}{N}\sum_{i=1}^{N}\left(similarity^{i}_{gt} - similarity^{i}_{pred}\right)^{2}$$

Here, *N* represents the number of differences between the ground truth value and the predicted value Here, *i* denotes the specific predicted value and true value pair for each instance in the calculation of the squared difference. The variable gt and pred represents the ground truth value and predicted value of the input drug sample, respectively.

The MSE loss function operates on the mean of squared differences between the predicted and true values. Through squaring the difference, it penalizes larger errors more heavily than smaller errors. This emphasizes larger errors, making the model more sensitive to extreme deviations from the true values.

The Cross Entropy Loss Function is used to calculate the loss. The neural network for drug-drug interaction predictor is a classification program. It predicts the scores of each class and outputs the category with the largest value. Hence, Cross Entropy Loss Function is used.

On the other hand, the neural network addressing drug-drug interaction prediction is a classification program. It generates scores for each class and selects the category with the highest value as the prediction. The Cross-Entropy Loss Function is employed to assess the loss. The Cross-Entropy Loss Function calculates the negative logarithm of the predicted probabilities for the correct classes. By doing so, it encourages the model to assign higher probabilities to the correct classes and lower probabilities to incorrect classes during the training process.

Equation 2: Cross-Entropy Loss Function

$$L_{ce} = -\log_{e} P$$

Here, *P* represents the predicted value of potential drug-drug interaction. The Cross-Entropy Loss Function calculates the negative logarithm of the predicted probabilities for the correct classes. This encourages the model to assign higher probabilities to the correct classes and lower probabilities to incorrect classes during training. To assess the overall performance of the model, the losses calculated from the Mean Square Error Function (drug similarity) and the Cross-Entropy Loss Function (drug-drug interaction) are combined. This is achieved by adding the individual losses together.

Equation 3: Total Loss Function

$$L = L_{ce} + \alpha \cdot L_{mse}$$

Here, an additional parameter, denoted as α, is introduced to adjust the importance assigned to each task. The prediction of drug-drug interaction is considered more important compared to drug similarity. The value of "α" aids in reducing the loss, despite its potential to be large, by appropriately balancing the contributions of the two tasks. By utilizing these customized loss functions and considering the relative importance of each task, the model can effectively optimize its performance in both predictions.. The value of α is set as 0.8.

Experimental Results

Drug-Drug Interaction Dataset

Table 1. Dataset

Benchmark Name	Number of Drugs	Number of Pairs	Number of Interactions	Number of Non-interactions
DS1 (Zhang et al. 2018)	548	300,304	97,168	203,136
DS2 (Wan et al. 2019)	707	499,849	344,112	465,437
DS3 (Gottlieb et al. 2012)	807	651,249	10,078	641,171

The model was trained using three datasets. The first dataset, DS1, consists of 548 drugs with a total of 303,304 pairs. There are 97,168 drug-drug interactions and 2,023,136 pairs of non-interaction. The second dataset, DS2, includes 707 drugs with 499,849 pairs. There are 34,412 drug-drug interactions and 465,437 pairs of non-interaction. The third dataset, DS3:CYP, comprises 807 drugs and 651,249 pairs. There are 10,078 drug-drug interactions and 641,171 pairs of non-interaction. For each dataset, 80% of the data was used for training the model and the remaining 20% was used for testing and evaluating its performance.

Experiment Protocol

In this research, I applied the 5-fold cross validation technique to train and test the model. This method is often used due to its consistency. The data in one fold is divided into five pieces, where four subsets are utilized as training data, and one subset is used as validation Data set. This approach enables us to assess the model performance and make predictions by analyzing the errors. In the next fold, the validation set is changed. The subset that played the role of validation in the previous Fold becomes a part of the training set. This process is repeated 5 times as I have divided it into 5.

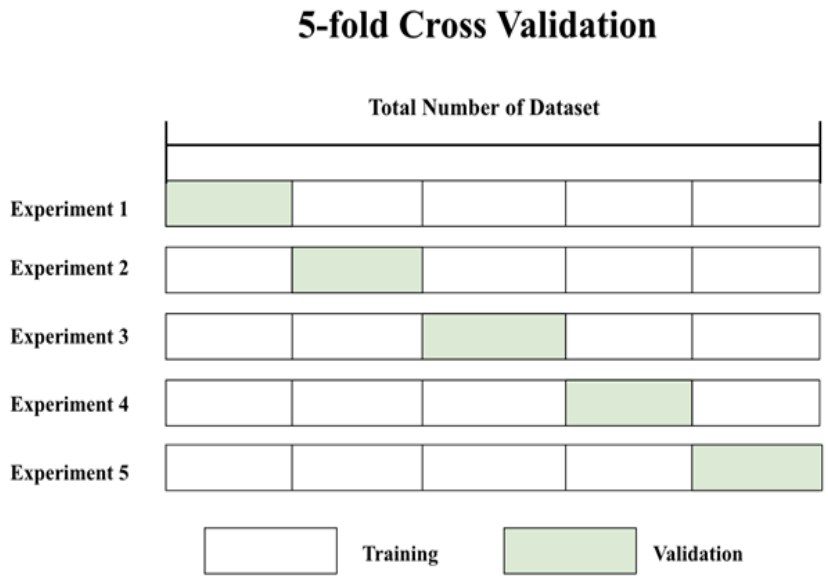

Figure 5. 5-fold Cross Validation

In this research, I employ a confusion matrix to evaluate the model's efficiency. It is utilized to evaluate the model's performance by categorizing the model's predictions into 4 parts. True positives, true negatives, false negatives, and false positives, represent instances that are correctly or incorrectly classified. In addition, the confusion matrix incorporates four evaluation metrics which are accuracy, recall, precision and F1-score.

True Positives (TP) denote the instances correctly predicted as the positive class. True Negatives (TN) represent the occasions correctly classified as the negative class. False Negatives (FN) refer to instances

incorrectly classified as negative. Lastly, False Positives (FP) signify occasions incorrectly classified as positive classes.

Equation 4: Precision

$$Precision = \frac{TP}{(TP + FN)}$$

The precision is calculated by dividing the true positives by the sum of true positives and false negatives. This represents the number of accurate predictions the model has made.

Equation 5: Recall

$$Recall = \frac{TP}{(TP + TN)}$$

The recall is calculated by dividing the true positive by the sum of true positive and true negative. This shows the number of accurate predictions the model has made.

Equation 6: F-Score

$$F1\text{-}Score = \frac{(2 \cdot Precision \cdot Recall)}{(Precision + Recall)}$$

The F-score is calculated by dividing the product of precision and recall by the sum of precision and recall.

Performance Comparison

Table 2. Performance comparison with state-of-the-art drug-drug interaction prediction methods

	F-score on each DDI type				Overall performance		
	Advice	**Effect**	**Mechanism**	**Int**	**Precision**	**Recall**	**F-score**
(Quan et al.2018)	0.782	0.628	0.722	0.510	0.760	0.653	0.702
(Liu et al.2016)	0.777	0.693	0.702	0.464	0.757	0.647	0.689
(Asada and Sasaki 2018)	0.816	0.710	0.738	0.458	0.733	0.718	0.725
(Zhou et al.2018)	0.816	0.712	0.744	0.485	0.758	0.703	0.729
(Sun et al.2019)	0.805	0.734	0.782	0.589	0.773	0.737	0.751
(Xiong et al.2019)	0.835	0.758	0.794	0.514	0.773	0.737	0.754
(Fatehifar and Karshenas 2021)	0.829	0.759	0.845	0.501	0.785	0.751	0.769
(Mollina et al.2023)	0.845	0.862	0.884	0.784	0.837	0.850	0.843
Proposed Method	**0.891**	**0.870**	**0.912**	**0.810**	**0.885**	**0.893**	**0.889**

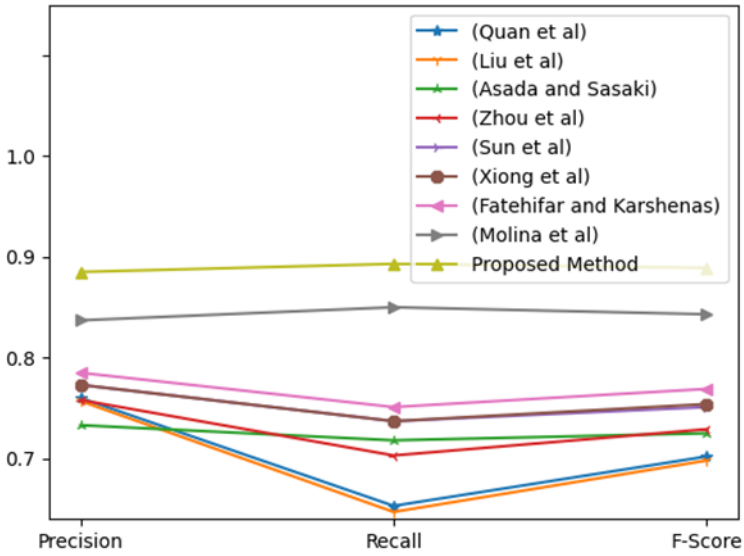

Figure 6. Performance comparison result (line graph)

In order to compare the proposed method's performance, a comparison with state-of-the-art drug-drug interaction prediction methods was run. Other prediction models included Quan et al.2016, Liu et al.2016, Asada and Sasaki 2018, Zhou et al.2018, Sun et al.2019, Xiong et al.2019, Fatehifar and Karshenas 2021, and Molina et al.2023. These methods were chosen due to their high accuracy. Excluding the most recent Molina et al.2023, the other methods do not include a similarity calculator. As shown in figure 3, the proposed method outperformed all the state-of-art methods. It has surpassed Molina et al. 2023 -the most recent and accurate DDI predictor- by 0.891, 0.012, 0.028, and 0.026 for Advice, Effect, Mechanism, and Int, respectively. It achieved a higher precision by 0.048, recall by 0.043, and F-score by 0.046. This solidifies its effectiveness in accurately predicting DDIs.

As represented in figure 6, the line on the graph is much higher than the other lines and is close to 1 - 1 is 100%, hence, the closer it is to 1, the higher the accuracy. The three points yield similar accuracy. Therefore, it can be seen that all parts show excellent results, with no one part being superior.

In terms of overall performance, the proposed method demonstrates its superiority over the most recent approach. Among the various models analyzed, the proposed model stands out by achieving the highest scores in each category. The categories are: Advice, Effect, Mechanism, Int, Precision, Recall, and F-score. This achievement indicates that the proposed method has superior accuracy in predicting drug-drug interactions compared to other models. Furthermore, the performance of the proposed model surpasses even the most recent model, Molina et al. 2023. It has surpassed specifically in terms of F-score for each type of drug-drug interaction. Molina et al.2023 is the most recent method that includes a drug similarity calculator. Although it consists of the same characteristics the proposed model has, the proposed model has more variety of topics that is taken in calculating the similarity calculation. This makes the model more advanced.

The proposed method resulted in higher accuracy due to its specialized drug similarity estimation network. Its diverse information in drug similarity calculators has led to a better quality compared to other state-of-art methods. This unique training strategy allows the Drug Feature Extractor to learn the patterns of inputs quickly and develops a higher accuracy, allowing our model to become superior.

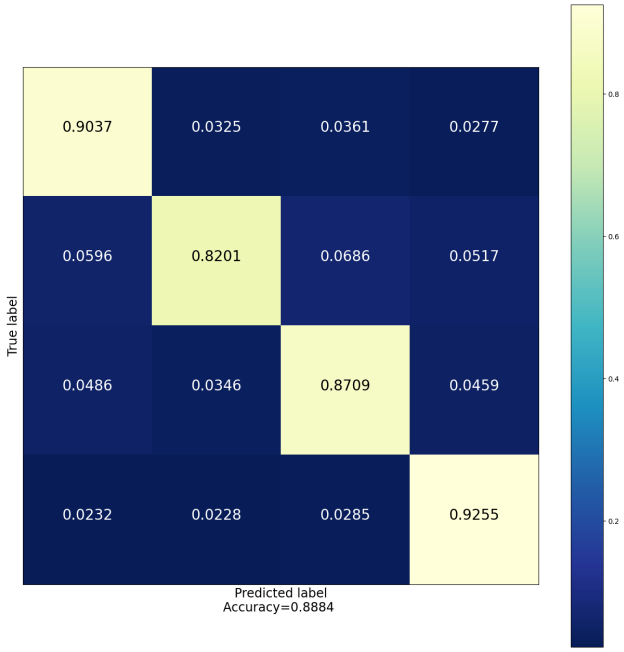

Figure 7. Confusion matrix of the proposed method

To clearly evaluate the accuracy of the model, experiment results were converted into a confusion matrix and a line graph. The table shown in figure two represents the experiment results that have been collected. A confusion above matrix is utilized to evaluate the model's performance by categorizing the model's predictions into true positives, true negatives, false negatives, and false positives. The four categories are: advice, effect, mechanism, and int(unknown interaction).

Advice is an output that is assigned when there could be recommendations or advice regarding the concomitant use of the input drugs. Hence, this suggests that the input drugs can be taken, as they do not have any adverse effects. The model has accurately predicted the class by 90.3%, indicating a strong ability to identify drugs with no adverse effects. Effect is an output that is assigned when the inputs contain pharmacodynamic mechanisms that include a clinical finding. Meaning that there is an increased toxicity or therapeutic failure. The second element represents the "Effect" category. The model has accurately predicted the class by 82%, which signifies the ability to recognise. Mechanism is an output that is assigned when the inputs contain pharmacokinetic mechanisms including changes in levels or concentration of the entities. Meaning, that there are adverse side effects when they are taken together. The third element represents the "Mechanism" category. The model has accurately predicted the class by 87%. Int, unknown interaction, is assigned when the inputs occur an interaction that does not provide any information about the interaction.

Indicating that the drugs cannot be taken, as there might be adverse side effects. The model has accurately predicted the class by 92.5%. Overall, the diagonal component of the confusion matrix has a high accuracy. Indicating that the model is classifying the inputs into corresponding classes.

Ablation Study

Table 3. Ablation study result (drug similarity replacement)

	Overall performance		
Mehtod	**Precision**	**Recall**	**F-score**

Baseline	0.781	0.720	0.724
DrugSimNet ATC[1]	0.824	0.817	0.845
DrugSimNet MS[2]	0.837	0.854	0.839
DrugSimNet GO[3]	**0.885**	**0.893**	**0.889**

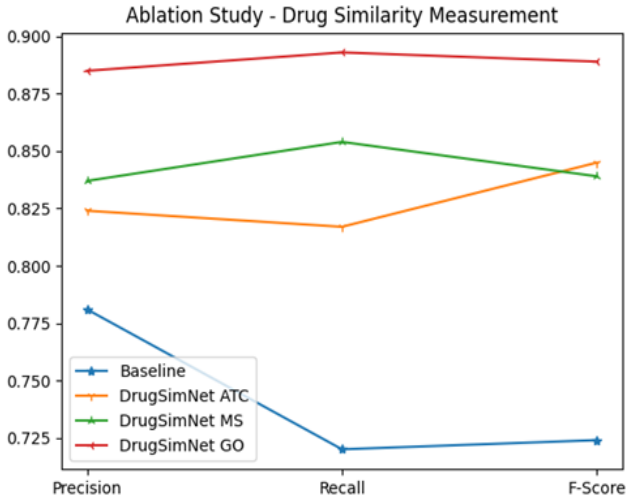

Figure 7. Ablation study result (line graph)

To improve the accuracy of the DDI prediction, I have incorporated a drug similarity calculator. The drug similarity calculator uses various metrics representing a drug's chemical characteristics. This model utilizes three metrics such as ATC code, molecular structure and gene ontology. These were used to calculate the similarity. The drug similarity calculator demonstrates a high accuracy - this was assessed by comparing with the ground truth values and finding the loss.

To evaluate the performance of the model, an ablation study was conducted. The model was tested 4 times. First, it was conducted without any similarity information. Second, it was conducted with similarity information based on ATC code. Third, it was conducted with similarity information based on molecular structure-based. Lastly, it was conducted with similarity information based on Gene Ontology. The ablation study revealed that the drug similarity network based on Genetic Ontology information resulted in the highest performance. It had 0.885 accuracy for precision, 0.893 for recall and 0.889 for F-score. Baseline had 0.781 for precision, 0.720 for recall and 0.724 for F-score, making it with the lowest accuracy. The similarity network that utilized ATC codes has 0,824 for precision, 0.720 for recall and 0,724 for F-score, making it the third accurate. The one that used Molecular structure had 0.837 for precision, 0.854 for recall and 0,839 for F-score. This is the second most accurate approach.

Conclusion

The main goal of this research study was to accurately predict DDIIn this study. I have proposed a drug-drug interaction calculator that incorporates a drug similarity calculator to enhance the accuracy. The proposed model takes two drugs as an input and outputs the predicted DDIs and the drug similarity. The study explored how deep learning Artificial Intelligence can enhance the accuracy and speed of drug-drug interactions. Through extensive experiments, I have explored the potential of deep learning and artificial intelligence to enhance the accuracy of DDI prediction. The results of the experiments have validated the superiority of our proposed

approach over the previous methods that did not integrate similarity calculators. This has enabled“human-like” thinking for our model. For future research, I plan to extend the application of the proposed method to find drug interactions between the FDA-approved new drugs and previous drugs.

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