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# Enhancing Drug-Drug Interaction Prediction with Auxiliary Drug Similarity Estimation using Convolutional Neural Networks

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## ABSTRACT

In the last few years, a rapid development of artificial intelligence has revealed its possible applications in many tasks. One of those areas where artificial intelligence showed great promise was predicting drug-drug interactions, which had an enormous amount of data to be interpreted through. Drug-drug interactions are caused by interactions between drugs; it can decrease the effectiveness, lead to serious emergencies of the patient, or have synergies that increase the effectiveness of both. The previous knowledge-based drug-drug interaction prediction methods were costly and time consuming. Thus, a model that can predict these interactions is highly demanded for patients' safety, furthermore, providing insights to scientists in medical fields. In this research, I propose a similarity aware drug-drug interaction predicting model. The proposed method consists of three modules: a drug feature extractor, a drug similarity estimator, and a drug-drug interaction predictor. The trained network is designed to be drug similarity-aware, which leads to significantly improved accuracy compared to the naive models. By incorporating drug similarity information, the model can provide more precise and reliable predictions for drug-drug interactions. The experimental result of the proposed deep-learning model achieved state-of-the-art performance compared to other previous methods.

## Introduction

### Problem Definition

Drug-Drug Interaction (DDI) is a change of a drug in its effects due to multiple medications at once. DDIs can have synergistic effects, but in most of the cases, it leads to unexpected side effects, adverse reactions, and toxicities, which all lead to patients in danger. Nowadays, as life expectancies of people are increasing and they are getting older, there are more and more people having multiple medications, which eventually leads to an exposure to the dangers of DDIs. By accurately identifying potential interactions between different drugs, researchers can gain valuable insights into their safety and efficacy profiles. The prediction of DDIs helps in assessing the risk associated with co-administration of multiple drugs and aids in making informed decisions during the drug development process. Due to these factors, the importance of predicting DDIs in drug discovery fields are at its peak. Numerous studies have been conducted to address the prediction of DDIs, with a particular focus on leveraging deep learning techniques that demonstrate comparable performance.

### Previous Methods

There have been numerous attempts to predict drug drug interactions using machine learning approaches. Shtar et al. (Shtar et al. 2019) developed a deep neural network using adjacency matrix factorization. The incorporation of classic graph similarity measures, which analyze the structural similarities between drugs, significantly contributed to the accuracy of the trained network. Feng et al. (2020) utilized graph convolutional neural networks to process three-dimensional chemical structures. While their approach yields accurate results, it is relatively slow in execution. Rozemberczki et al. (Rozemberczki et al. 2021) proposed a drug fair scoring framework to provide unification of drug-drug interaction and polypharmacy side effect and synergistic drug combination prediction tasks. Qiu et al. (Qiu et al. 2021) presents three categories of computational methods with outlines for each: literature-based extraction methods, machine learning based prediction methods, and pharmacovigilance-based data mining methods.

### Proposed Method

In this paper, I proposed a novel drug similarity-aware DDI prediction network to enhance the accuracy and efficiency of predicting potential drug-drug interactions. The proposed network consists of three modules: a drug feature extractor, consisting of a convolutional neural network, a drug similarity estimator, and a drug-drug interaction predictor. The drug similarity estimator takes the drug features produced by the drug feature extractor as input and outputs the similarity between two drugs. Similarly, the drug-drug interaction predictor utilizes the same drug features to make predictions about drug interactions. These three modules are trained jointly, and this unique framework yields more accurate and robust results compared to previous drug-drug interaction methods. The detailed steps of the development process will be further elucidated in Chapter 3.

## Related Work

### Drug-Drug Interaction

Drug-drug interactions is a change in an effect of a drug due to other drugs consumed together. There are mainly four types of effects: addition, permission, synergistic, and tachyphylactic. Addition is when the action of drug A is added to drug B. They do not affect each other, but perform their own effects. Permission is when the effect of drug A is highly increased by drug B. Only the effect of drug A is increased. Synergistic is when both of the drugs A and B are enhanced by each other. They both have increased effect. Tachyphylactic is tolerance, in which the body gains resistance and more drugs are needed to get the same effect.

Though there are many possible outcomes, interactions between drugs often lead to unexpected side effects, such as adverse reactions and toxicities. These unexpected side-effects caused by DDIs are preventable, but it often leads to an emergency for the patients because of unawareness of the underlying interaction between drugs. There are numerous machine learning models invented to predict drug-drug interactions, and common architecture of the task has been presented in Figure 1.

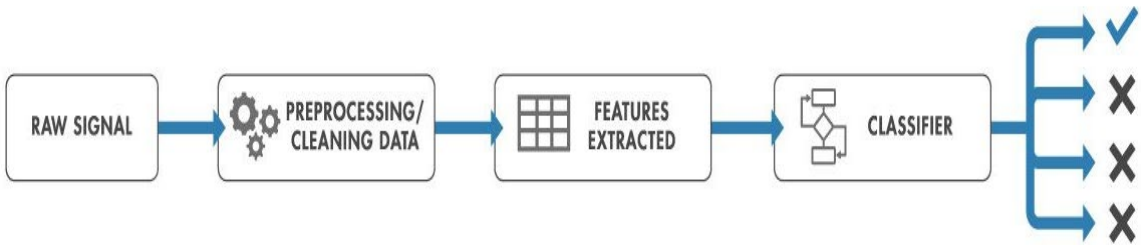


**Figure 1.** Schematic process for applying feature extraction to signals and time series data for a machine learning classifier. (MathWorks 2023)

Most of the architecture of state-of-the-art AI models for drug-drug interaction prediction tasks consists of preprocessing data, feature extraction, classifier, and scoring layer. Data preprocessing and feature extraction: a feature extractor represents a chemical formula of drugs into readable form for an AI, extracts a relevant feature from the drug to be used in training. Classifier: captures underlying interaction between drugs based on extracted features from the previous step. Scoring layer: predicts the probability of interactions occurring.

In addition, loss function is used after training, to measure the error of the model.

## Object Classification

Object classification in machine learning tasks is a technique of grouping input data under the category it belongs to. Classifying objects can be implemented using neural networks or convolutional neural networks. To outline the process, first, the data is preprocessed, so that a machine learning model can read through. For a neural network, data is flattened into 1-dimension. Then, weight and bias, which are hyperparameter values meaning that the values are randomly inputted by the person, are each multiplied and added to input data. Neural network has several layers of weight and bias to improve its accuracy, but still its accuracy is relevantly low compared to the convolutional neural networks.

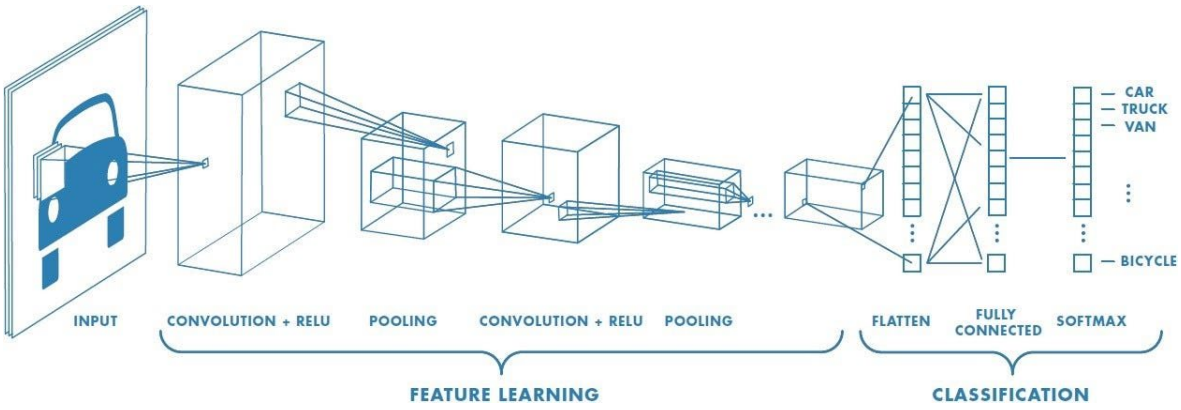


**Figure 2.** A Guide to Convolutional Neural Networks — the ELI5 way (Sumit Saha 2018)

Overall architecture of convolutional neural networks is presented in Figure 2. For a convolutional neural network, it is known for its high accuracy by preserving spatial structure of an input data. In the firsthand, a filter, which has a depth same with the dimension of input data and hyperparameter size of width and height, is multiplied over the data with a unique method called convolve operation.

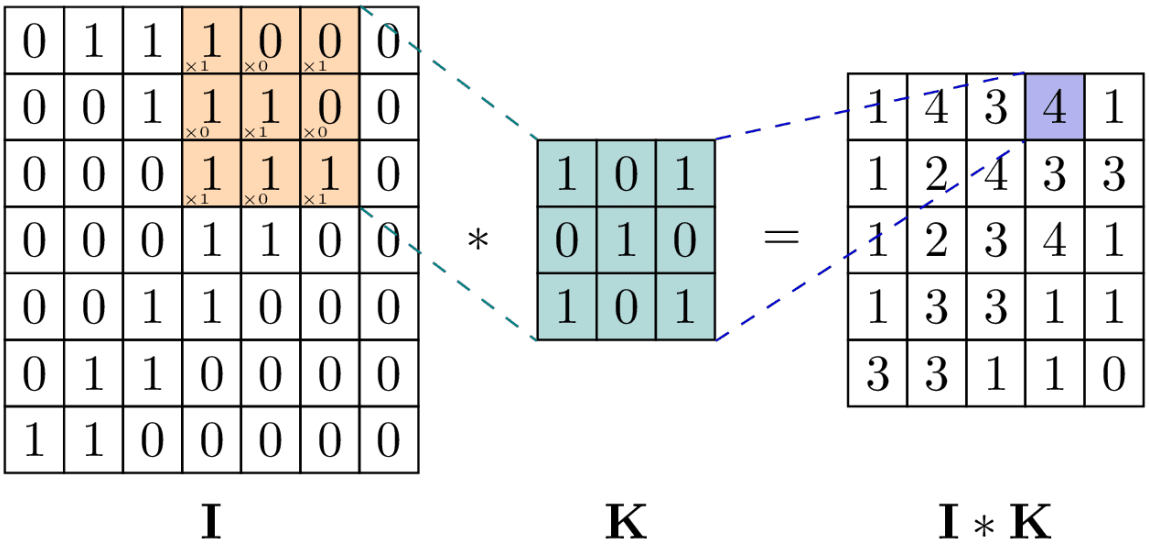


**Figure 3.** Convolution Operator (Janosh Riebesell 2022)

A convolve operation is multiplying the overlapping part of the data and a filter. The filter slides in a zig-zag motion from up-left until it reaches down-right of the data. The process eventually produces a whole new layer, called activation or feature map, consisting of outcomes from multiplication with an input data and filter of each local intersection. In figure 3, the data, I, is multiplied by filter, K, using convolve operation and outputs a feature map, I * K. After multiplying a filter to data, the ReLU function, which is one of the activation functions, adds non-linear properties to the model. Then, to make the model efficient by minimizing calculation amount, max pooling is performed to extract key features from the feature map. At the end, after repeating the process above, the input data will result in a deep feature map. Then the 3-dimensional feature map is flattened and put into a scoring layer to get scores. Then, the softmax function is used to convert scores into percent form, and possibilities that the input image belongs to certain categories.

AlexNet (Krizhevsky et al. 2012), VGGNet (Simonyan et al. 2014), and ResNet (He et al. 2016) are three well-known networks, which have immensely contributed to the development of convolutional neural network structure. AlexNet is a shallow model with 8 layers. It introduced multiple layered structures in the AI field. VGGNet is a modified version of AlexNet that discovered that if the model had more layers, then the accuracy increases. So it is deeper than Alexnet, which has 16 and 19 layers. Also it has consistent filter size and patterns with filter numbers. ResNet is an extremely deep AI model with 152 layers, and solves zero gradient problems, in which the gradient used for gradient descent algorithm for increasing accuracy vanishes and the model cannot be adjusted anymore, using a method called Residual block. In all, object classification is a popularly invested area. It can be implemented into various fields. One of the most popularly known fields is auto-driving vehicles. Using an object classification, a car can detect its surroundings and possibly drive by itself. Nevertheless, drug-drug interaction predicting tack is also an area worth to be invested in, which can save countless lives and provide insights to medical scientists in drug discovery pipeline.

In this research, I used a convolutional neural network as a drug feature extractor for extracting feature maps from the chemical formula of drugs. Then, with extracted feature maps, drug similarity estimation and DDI prediction are outputted.

### Drug Similarity

A drug similarity estimation is a task of evaluating the similarity between two drugs. The inputs are two feature maps extracted from the chemical formula of drugs, and those two feature maps are concatenated and output a value ranging from 0 to 1. The detailed procedure will be explained later on chapter 3. Similarity estimation between drugs can be performed by comparing pharmacokinetics of two drugs, in other words, a property of drug. There are three major categories that define the property of drugs: absorption, distribution, and excretion. All of the drugs have differences in their properties: how they are consumed, what is their target, and how they are excreted. These categories in one, are called drug metabolism. By comparing drug metabolism of drugs, it is possible to estimate the similarity between drugs.

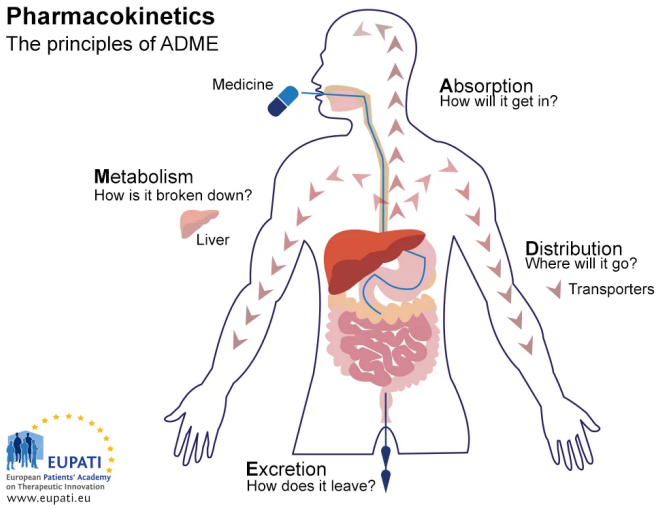


**Figure 4.** Pharmacokinetics (EUPATI 2020)

Figure 4 is an overall depiction of pharmacokinetics, or a drug metabolism. A drug can be absorbed through the mouth, blood vessel, or gut, and the chemicals are distributed in its target organ, and excreted through the digestive system.

## Proposed Method

In this chapter, a comprehensive explanation of the proposed method will be provided.

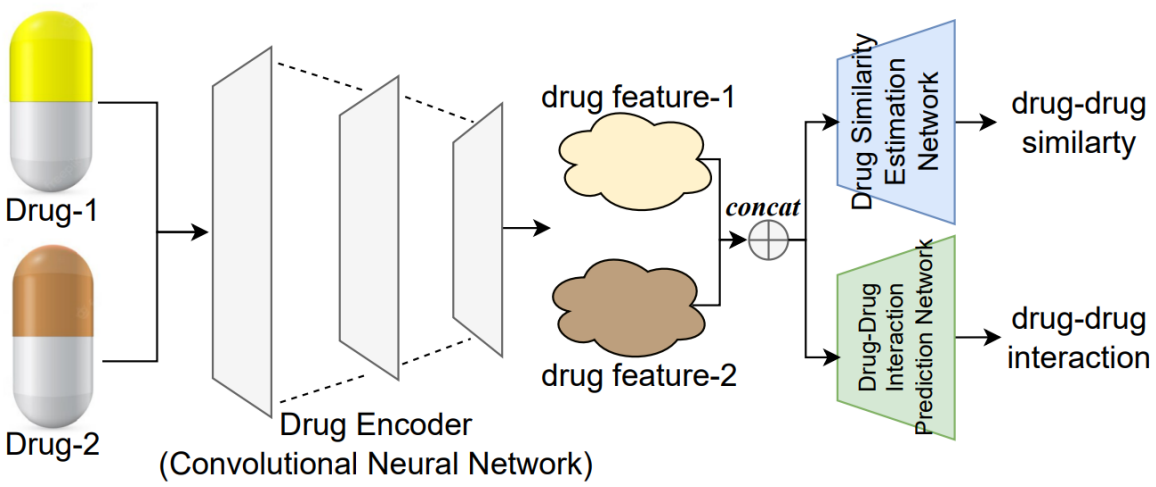


**Figure 5.** Overall architecture of the proposed method

Figure 5 demonstrates the overall architecture of the proposed method. The proposed drug-drug interaction prediction framework is composed of three modules: drug feature extractor, similarity estimator, and drug-drug interaction predictor.

The input drugs, D, are first placed into a drug encoder, C: a drug feature extractor, consisting of a convolutional neural network. This process converts chemical formulas into feature maps, F. The feature extractor can be defined as F = C(D). Then, concatenation, joining two feature maps to capture potential interactions, P, and estimate similarity, S, between drug features. The proposed architecture has an unique feature, in which it has two outcomes: similarity score and drug-drug interaction prediction. These two factors allow the model to consider drug similarity within its interaction prediction, and leads to higher accuracy.

## Drug-Drug Interaction Predictor

Drug feature maps, F, which are extracted from the drug feature extractor, are concatenated to identify potential interaction, I, between two drugs. It outputs a matrix with numbers ranging from 0 to 1 that indicates potential interactions. The closer the number is to 1, the higher possibility that an interaction occurs. The drug-drug interaction predictor, P, can be represented as, $P(F) \rightarrow I = [0,1]$.

The drug-drug interaction predictor is the most important layer of the DDI predicting model that performs the prediction. This predictor in the model can contribute to the future drug discovery pipeline with its screening process.

To train the drug-drug interaction prediction network, I utilize the cross-entropy function which is a common choice for training classification machine learning models. Equation 1 explains the mathematical expression of the cross-entropy loss function.

Equation 1: Cross-entropy loss function

$$L_{cross} = -ln\ P$$

Here, $P$ denotes the probability value of the predicted drug-drug interaction scores.

### Drug-Drug Similarity Estimator

The drug similarity estimator has an input of concatenated feature maps of drugs, F, it mainly estimates the similarity, S, between 3D structures of two drugs. The output ranges from 0 to 1, which the higher the number is to 1, the more similar the structures of drugs have. The similarity estimator, G, can be represented as, G(F) → S = [0,1]. The similarity estimator is the key component of the proposed method that differentiates this research from previous studies conducted. The information that 3D structure of drugs contain is important because those chemicals perform the action in our body, and by making my model aware of the similarity between two drugs gives an advantage in its prediction task. So, when the model faces unseen drugs, it can consider cases from other drugs that had similar structure with it to predict possible interactions that unseen drugs can make.

In order to train the proposed drug-drug similarity estimator, L-1 loss function is applied. The L-1 loss function calculates the absolute difference between two input arguments. I initially considered using the mean square error function as an alternative to the L-1 loss function, but the L-1 loss function ultimately yielded superior results. The L-1 loss function is explained in Equation 2.

Equation 2: L-1 loss function

$$\boldsymbol{L_1 = \left|similarity - \widehat{similarity}\right|_1}$$

In the equation 2, $\boldsymbol{\widehat{similarity}}$ and similarity represents the predicted drug similarity and its corresponding ground truth drug similarity.

Equation 3: Total loss function

$$L_{total} = L_{cross} + \boldsymbol{L_1}$$

Finally, the total loss function is defined by creating a linear combination of the cross-entropy loss function and the L-1 loss function as expressed in Equation 3.

## Experimental Results

### Dataset

**Table 1**. Dataset Distribution

| Dataset Name | Number of Drugs | Number of Drug Pairs | Number of Interactions |
|---|---|---|---|
| DS1 (Zhang et al. 2017) | 548 | 300304 | 97168 |
| DS2 (Wan et al. 2019) | 707 | 499849 | 34412 |
| DS3 (Gottlieb et al. 2012) | 807 | 651249 | 10078 |

In this research, three datasets will be used to train the model: DS1 (Zhang et al. 2017), DS2 (Wan et al. 2019), and DS3 (Gottlieb et al. 2012). Datasets each contain 548, 707, and 807 drugs; 300304, 499849, and 651249 pairs; 97168, 34412, and 10078 drugs with interactions; 203136, 465437, 641171 drugs without interactions. I

considered these datasets appropriate for the research because the datasets are not too small, but have sufficient numbers of drugs for the model to be trained and learn cases for predicting unseen drugs.

## K-Fold Cross Validation

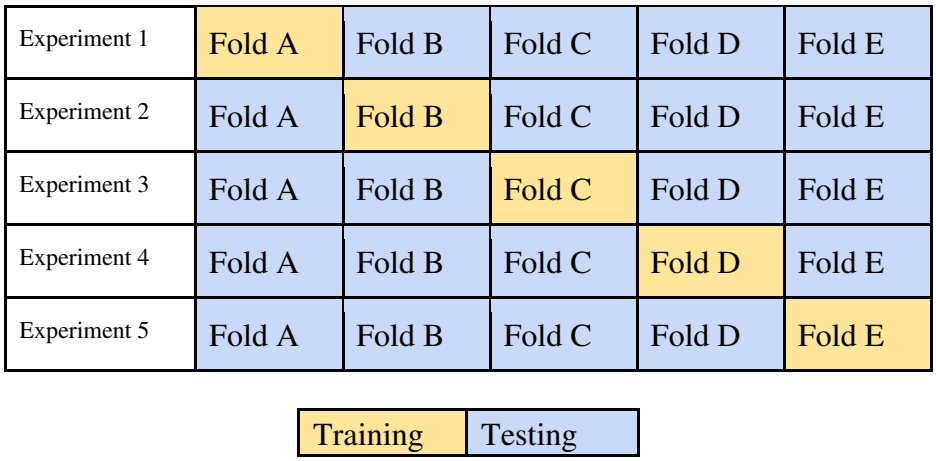


**Figure 6.** 5-Fold Cross Validation

K-fold cross validation is grouping dataset into k numbers and validating stability of the model's accuracy. One of the grouped dataset, folds, is used as a training set and other remaining data are used as a testing set. The process is repeated until all of the data groups are once used as a training set, and calculate the average accuracy from all of them. For example, In figure 6, a dataset is grouped into A, B, C, D, E, fold A is used as a training sample in the first experiment, and folds B, C, D, E are used for testing. Next, B is used for training in the second experiment, and the rest of the folds are used for testing. This is repeated until fold E is used as a training sample. Then, the average accuracy from five experiments are calculated. In this case, there are five grouped data, in which it can be called as 5-fold cross validation. Cross validation is an important process to prove that an accuracy of the model proposed in the research is stable. In figure 6, fold A and B could have harder samples than rest of the folds, resulting in the model to have an accuracy of 70% in the experiment using A and B as a testing sample. On the other hand, in the rest of the experiments, using other folds with easier samples for testing, the model could have accuracy around 90%. So, it is important to have stable accuracy, in other words, lower standard deviation from average accuracy. Using a k-fold cross validation method, it can be proven that the experiment was stably conducted and the model can perform well in both hard and easy testing samples.

## Experimental Results

**Table 2.** Accuracy Comparison with the Proposed Model and Previous Models

| | **F-score on each DDI type** | | | | **Overall performance** | | |
|---|---|---|---|---|---|---|---|
| | Advice | Effect | Mechanism | Int | Precision | Recall | F-score |
| (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 |
| (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 |
| (Molina et al. 2023) | 0.845 | 0.862 | 0.884 | 0.784 | 0.837 | 0.850 | 0.843 |
| **Proposed Method (ours)** | **0.874** | **0.879** | **0.899** | **0.842** | **0.867** | **0.880** | **0.867** |

Table 2 compares accuracy of the models in different categories of drug-drug interactions. There are four categories, or types, of drug-drug interaction: advice, effect, mechanism, and interaction. Advice is an increase in the effect of drugs by synergy. Effect is the occurrence of unexpected side-effects by combination of drugs. Mechanism is a change in the efficiency of a drug, so more observations and analyses are needed to check if the disease is cured or not. Interaction(Int) is a presence of interaction between drugs, but the type of it is not defined. There are three types of accuracy calculations: precision, recall, and F1-score(which is abbreviated as F-score in table 2). Precision is an accuracy of the model among all samples it has determined as positive. Recall is an accuracy of the model among all positive samples. F1-score is an accuracy of both precision and recall combined. It is clearly shown, in table 2, that the accuracy of the proposed method is exceeding all other previous methods in every column.

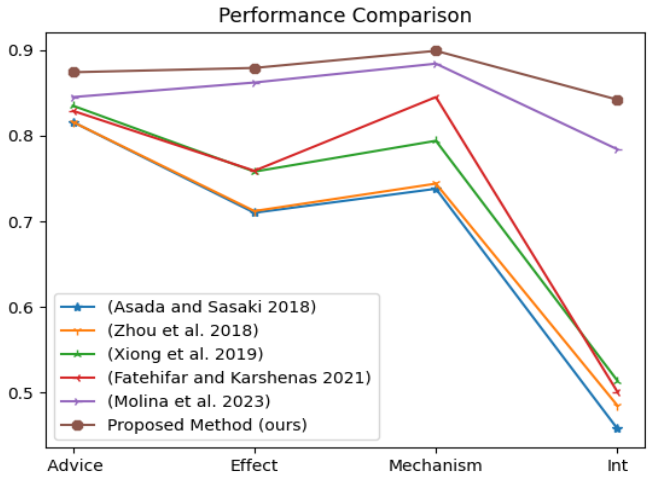


**Figure 7.** Visualized Accuracy Comparison with the Proposed Model and Previous Models

Figure 7 visualizes table 1, a comparison of accuracy of the proposed model with previous models. Previous models from 2018 to 2021, which do not have drug similarity estimation modules, have relatively low accuracies compared to the proposed model that contains a drug similarity estimation module. On the other hand, the proposed model has lower difference in accuracy with Molina et al. 2023, which has a drug similarity estimation module.

The relationship between a drug similarity estimation module and high accuracy is proved and explained in detail on 4.4.

## Ablation Study

Ablation study is used to measure the contribution of the proposed method in increasing the accuracy of the model. Ablation studies can be conducted by setting up two experiments: One with all modules and another one without the proposed method. Then, by calculating the difference between accuracy between two experiments, it is possible to measure how much the proposed method has contributed in increasing the accuracy of the model.

**Table 3.** Ablation Study Result

| | **Overall performance** | | |
|---|---|---|---|
| | Precision | Recall | F-score |
| without drug similarity estimation module | 0.792 | 0.778 | 0.772 |
| with drug similarity estimation module | **0.867** | **0.880** | **0.867** |

Table 2 is the result of ablation study. Two experiments, one with the similarity estimation and another without the similarity estimation, were conducted, then accuracies for precision, recall, and F1-score(abbreviated as F-score in the table) were calculated. The proposed method had boosted the accuracy of the model by 7.5% for precision, 10.2% for recall, and 9.5% for F1-score.

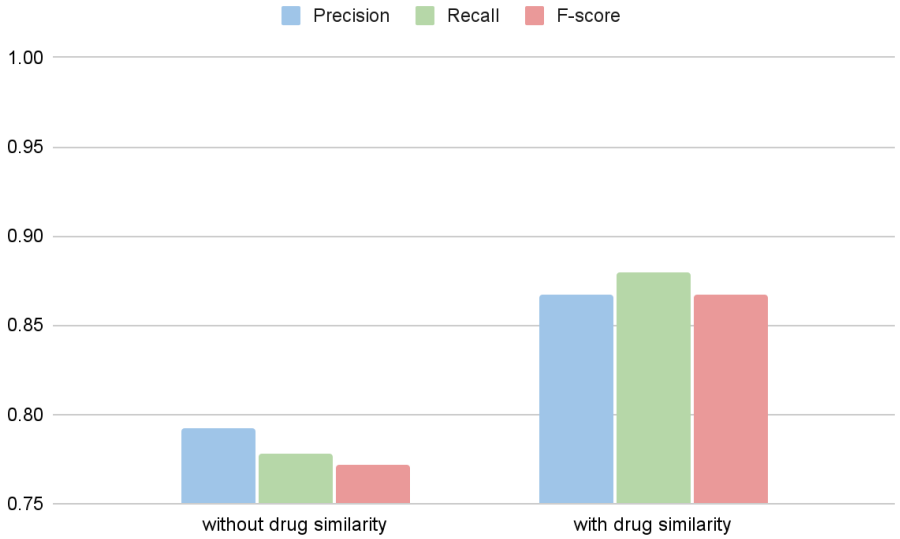


**Figure 8.** Visualized Ablation Study

Figure 8 is a visualized graph of the comparison of accuracy of two experiments. Compared to an experiment with a drug similarity module, the one without it had remarkably lower accuracy. In all, the ablation study proves that the proposed method contributes to significant increase in accuracy, and so the drug similarity estimation module is directly correlated with an increase of accuracy of the model.

## Conclusion

In this paper, I proposed a similarity aware drug-drug interaction prediction model. The overall structure of the proposed method has three modules: a drug feature extractor, drug similarity estimator, and drug-drug interaction predictor. The feature extractor converts chemical formulas of drugs into feature maps, and then those are concatenated and outputs similarity estimation and drug-drug interaction prediction. I conducted K-fold cross validation to validate the stability of the model's accuracy in different types of datasets, and an ablation study to prove and measure the contribution of the drug similarity estimation module in increasing the accuracy of the model. The accuracy of the proposed method has surpassed other previous methods. In the future, I hope the model will be applied in predicting drug-drug interactions with unseen drugs and contribute to medical discovery fields, and save people from unexpected side-effects caused by drug-drug interactions.

## Acknowledgments

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