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SNF-CNN: Predicting Comprehensive Drug-Drug Interaction via Similarity Network Fusion and Convolutional Neural Networks

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Abstract

This research addresses the critical need to identify drug-drug interactions (DDIs) before market entry. Existing preclinical detection methods are resource-intensive, prompting the use of computational models based on premarket drug properties. However, current models often oversimplify interactions, neglecting nuanced alterations in pharmacological effects. DDIs, rooted in the structural features of the DDI graph, are non-random, and understanding these relationships is vital for making comprehensive predictions and uncovering structural patterns in the DDI graph. The study introduces the Similarity Network Fusion and Convolutional Neural Networks (SNF-CNN) model, treating comprehensive DDIs as a signed network. SNF-CNN excels in predicting degressive (AUC = 0.975, AUPR = 0.967), enhancive (AUC = 0.969, AUPR = 0.822) and Unknown DDIs (AUC = 0.971, AUPR = 0.948). A comparative analysis against state-of-the-art methods highlights SNF-CNN's superiority, not only in predicting DDIs but also in accurately forecasting non-DDIs. The SNF-CNN code and data are available on GitHub.
For inquiries or collaboration, please contact A.khodamoradi@uninova.pt.

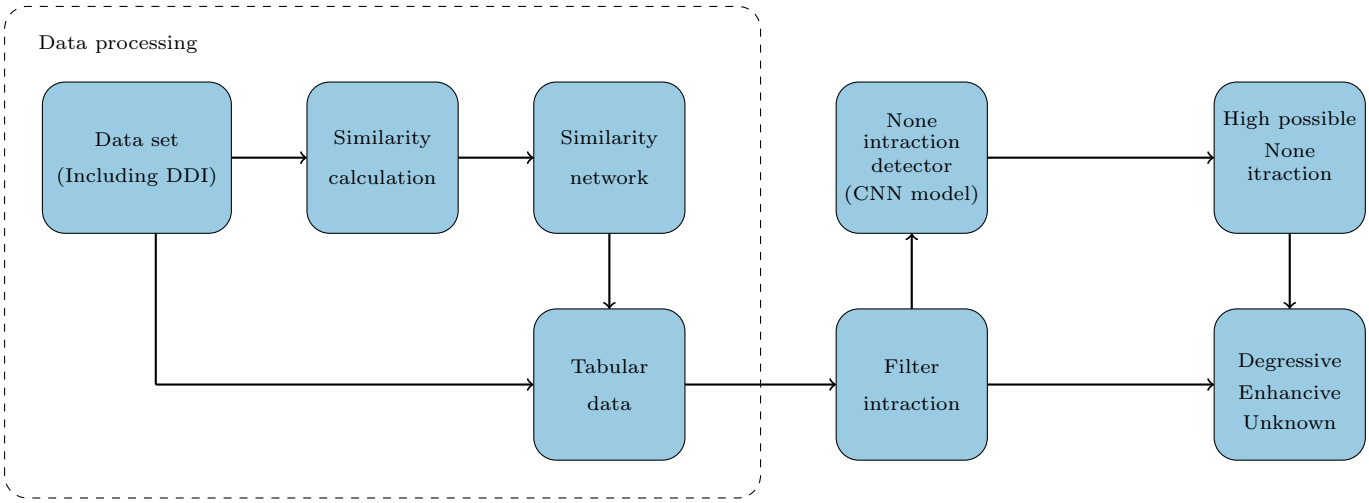

Fig. 1. Graphical abstract

Key words: Drug-Drug Interaction, Drug Similarity, Drug Similarity Integration, Feature Selection, Recommender System

Abbreviations: DDI:Drug-drug interactions; CV:cross-validation; SNF:Similarity Network Fusion

Introduction

When multiple drugs are taken together, their effects or behaviors may be unexpectedly influenced by each other [37]. This phenomenon is known as Drug-Drug Interaction (DDI), which can lead to reduced drug efficacy, increased toxicity, or other adverse reactions between the co-prescribed drugs. With the rising number of approved drugs, the incidence of unidentified DDIs is also increasing rapidly. For instance, among approved small molecular drugs listed in the Drug Bank, approximately 15 out of every 100 drug pairs have known DDIs [2]. Such interactions pose risks to patients receiving multiple medications [17, 11, 19]. Understanding DDI is crucial as it is the first step in exploring drug combinations, which are increasingly seen as promising solutions for treating complex diseases [44]. Therefore, there is an urgent need for screening and analyzing DDIs before administering clinical co-medications. However, traditional DDI identification approaches, such as testing Cytochrome P450 or transporter-associated interactions, face challenges including high costs, lengthy duration, animal welfare concerns [41], limited trial participants, and a multitude of drug combinations undergoing screening in clinical trials. Consequently, only a few DDIs are identified during drug development, often in the clinical trial phase. Some are reported post-approval, while many are discovered during post-marketing surveillance [12].

DDIs can be significantly influenced by a patient's medical history and genetics. To bridge these aspects, the Smart4Health project[1] developed two platforms: one personal, containing health information from the citizen (Citizen Health Data Platform – CHDP), including medical conditions, allergies, intolerances, medication use, and genetic data, and one de-identified, containing data donated for research by the citizen (Research Platform – RP). CHDP utilizes HL7 FHIR[2] to structure collected data, while RP adopts OMOP CDM to convey data from CHDP and make it reusable by third-party research infrastructures (e.g., ELIXIR[3]). The concept involves citizens collecting and aggregating data generated from interactions with medical institutions (e.g., medication prescriptions, laboratory results, discharge letters) into a single, interoperable EHR. This data may also encompass genetic data if available. This data can be donated to the RP at the citizens' discretion. Specifically regarding medication intake and genetic data, these are linked to drug exposure and outcome data within the OMOP CDM[4]. This mechanism has the potential to streamline data collection and contribute to ensuring data quality. Moreover, placing the citizen at the center of this process may expedite and broaden the identification of DDIs, facilitating a more comprehensive understanding of their mechanisms.

Computational approaches offer a promising avenue for discovering potential DDIs on a large scale, garnering recent attention from academia and industry [38, 45]. Data mining-based computational methods have emerged to detect DDIs from diverse sources, including scientific literature [4, 43], electronic medical records [39], and the Food and Drug Administration's Adverse Event Reporting System (FDA[5]). However, these approaches rely on post-market clinical evidence, limiting their ability to provide alerts of potential DDIs before administering clinical medications. In contrast, machine learning-based computational methods (e.g., Naive Similarity-Based Approach [33], Network Recommendation-Based [41, 12], Classification-Based [6]) can offer such alerts by leveraging pre-marketed or post-marketed drug attributes, such as drug features or similarities [22]. These approaches utilize various drug features to predict DDIs, including chemical structures [33], targets [18], hierarchical classification codes [6], as well as side effects and off-label side effects [41, 12, 26].

Liu et al. introduced a dependency-based convolutional neural network (DCNN) in 2016 [25] to extract drug-drug interactions (DDIs) from biomedical literature and knowledge bases. DCNN analyzes word sequences and dependency parsing trees using convolution layers. Ryu et al. developed DeepDDI in 2018 [24], integrating structural similarity profiles and a Deep Neural Network (DNN) to predict DDIs based on chemical structures and names of drug pairs. DeepDDI aids in identifying adverse drug events and understanding potential causal mechanisms, providing informative output sentences.

While previous methods have made significant advances, achieving greater prediction accuracy remains a priority. Leveraging additional similarities could potentially lead to further advancements in this area. Similarity Network Fusion (SNF) [21, 31, 14]. Neural networks represent a well-established approach, offering effective solutions, particularly for large datasets and nonlinear analyses [35]. They are widely utilized in critical problems across various domains [10, 8, 23].

Most existing machine-learning approaches focus on predicting the typical two-class problem, indicating the likelihood of a drug pair being a DDI. However, in vivo, interacting drugs may alter their pharmacological behaviors or effects, such as increasing or decreasing serum concentration. For example, Flunisolide (DB00180) exhibits decreased serum concentration with Mitotane (DB00648) and increased concentration with Roxithromycin (DB00778), representing degressive and enhancive DDIs, respectively. Understanding these interactions is crucial for optimal patient care, drug dosage, prophylactic therapy design, and identifying therapy resistance [16].

While enhancive and degressive DDIs are not arbitrary occurrences [27, 40], many current approaches have not leveraged this structural property, primarily focusing on conventional two-class DDIs. However, uncovering this relationship is crucial for understanding DDI mechanisms, advancing the treatment of complex diseases [7], and aiding physicians in crafting safer prescriptions, especially for high-order drug interactions.

Recent research has focused on addressing two key issues: 1) predicting three-class DDIs instead of the traditional two-class prediction, and 2) extracting the topological information of drugs in a DDI network.

The TMFUF model, introduced by Shi et al. in 2018 [27], predicts enhancive and degressive DDIs for scenarios involving new drugs with no known DDI history. In contrast, the DDINMF model, proposed by Yu et al. [40], predicts DDIs and assigns drugs to communities, establishing correlations between drug communities and the numbers of enhancive, degressive, sum, and difference of DDIs for each drug.

These observations suggest that enhancive or degressive DDIs exhibit specific topological features in the DDI network. The BRSNMF model, proposed by Shi et al. in 2019 [28], utilizes Semi-NMF to predict these interactions more

[1] http://www.smart4health.eu

[2] https://hl7.org/fhir

[3] https://elixir-europe.org

[4] https://www.ohdsi.org/data-standardization

[5] http://www.fda.gov

accurately, particularly in cold start scenarios [5]. This method leverages Drug Binding Protein (DBP) features to map new drugs with known drugs, resulting in drug communities with more moderate sizes.

All three introduced models utilize matrix factorization methods within a network recommender-based approach. While matrix factorization has gained attention for predicting DDIs, these methods do not consider potential DDIs crucial for safe drug prescribing.

This study details the data preparation process and introduces a recommendation system for accurately identifying pairs of non-interacting drugs. Additionally, we present the SNF-CNN algorithm, which integrates drug similarities and employs deep learning recommendation systems to predict Drug-Drug Interactions (DDIs) within a comprehensive three-class model. This groundbreaking approach aims to uncover previously undetected DDIs, leveraging off-label side effects and chemical structures of drugs for valuable insights. We utilize Similarity Network Fusion (SNF) to leverage similarity features effectively. This approach diverges from conventional methods by leveraging deep neural networks, particularly a convolutional neural network, instead of matrix factorization techniques. While we briefly acknowledge alternative methods, it's essential to emphasize that our work represents a unique exploration within the realm of three-class data, distinguishing it from existing studies.

System and methods

Problem formulation

Let $D = \{d_i : i = 1, 2, \ldots, m\}$, represent a set of m approved drugs. Each drug d_i in D is denoted by a p-dimensional feature vector $f_i = \left[f_1, f_2, \ldots, f_k, \ldots, f_p\right]$, where $f_k = 1$ indicates the presence of the k^{th} specific chemical structure fragment or occurrence of an off-label side effect, and $f_k = 0$ otherwise. Given that each drug has two feature vectors representing chemical structure and off-label side effects, two feature matrices F are constructed with dimensions $m \times p$ (where the magnitude of p depends on the feature type). The matrices F_{str} and F_{se} correspond to the feature matrices of chemical structure and off-label side effects.

Drug-drug interactions can be represented by a symmetric interaction matrix $A_{m\times m} = (a_{ij})_{m\times m}$. For conventional binary DDIs, $a_{ij} = 1$ if d_i interacts with d_j, and $a_{ij} = 0$ otherwise. In the case of comprehensive DDI, similar to the binary formulation, if d_i and d_j do not interact, $a_{ij} = 0$. However, if there is an enhancive DDI or a degressive DDI between d_i and d_j, $a_{ij} = +1$ or $a_{ij} = -1$, respectively.

A common method of calculating similarity called Cosine Similarity is used in machine learning articles such as [36, 42]. If the feature vectors of the drug of d_i and d_j are named x_i and x_j, Cosine Similarity between x_i and x_j is defined as follows

$$S_{Cos}(x_i, x_j) = \frac{x_i \cdot x_j}{||x_i||_2||x_j||_2} \tag{1}$$

Where $||\cdot||_2$ is the Euclidean Norm, and $x_i \cdot x_j$ is the inner product of two vectors.

Evaluation process

K-Fold cross-validation (CV) is a common method in machine learning for algorithm evaluation, model selection, and feature engineering. The dataset is divided into K equal parts, maintaining related pairs together. One part is for testing, and the rest are for training, repeated K times. The average performance across rounds gives the final classifier evaluation. While K-Fold CV enhances classifier accuracy and dataset understanding, it lengthens validation time.

	Actual Enhancive	Actual Degressive
Classified Enhancive	TP	FP
Classified Degressive	FN	TN

Table 1. The confusion matrix for interaction type (Degressive or Enhancive) and relevant evaluation index. True Positive (TP): The number of drug pairs classified as enhancive interaction correctly, False Positive (FP): The number of drug pairs classified as enhancive interaction incorrectly, False Negative (FN): The number of drug pairs classified as degressive interaction incorrectly, True Negative (TN): The number of drug pairs classified as degressive interaction correctly.

If degressive interaction is as Negative (N) and enhancive interaction as a Positive (P) sample, then the confusion matrix for interaction type (Degressive or Enhancive) and relevant evaluation index is shown in Table 1. By using Table 1, four evaluation criteria are defined in the following order:

Accuracy: The fraction of all correct predictions (TP and TN) to all predictions. Expressed as:

$$\text{Accuracy} = \frac{TP + TN}{TP + FP + TN + FN} \tag{2}$$

Precision: The fraction of correct predicted (enh/deg) interactions among all predicted (enh/deg) interactions. Expressed as:

$$\text{Precision}_{(enh/deg)} = \frac{TP}{TP + FP} \tag{3}$$

Recall: The fraction of correct predicted (enh/deg) interactions among all true (enh/deg) interactions. Expressed as:

$$\text{Recall}_{(enh/deg)} = \frac{TP}{TP + FN} \tag{4}$$

Precision and recall have a trade-off; thus, improving one may lead to a reduction in another. Therefore, utilizing the F-measure is more reasonable.

F-measure: The geometric mean of precision and recall. Expressed as:

$$\text{F-measure}_{(enh/deg)} = \frac{2\text{Precision}_{(enh/deg)}\text{Recall}_{(enh/deg)}}{\text{Precision}_{(enh/deg)} + \text{Recall}_{(enh/deg)}} \tag{5}$$

Since precision, recall, and F-measure values depend on the threshold value, we also evaluate methods via AUC, the area under the receiver operating characteristic (ROC) curve, and AUPR, the area under the precision-recall curve. These criteria indicate the efficiency of methods independent of the threshold value. In cases where the fraction of negative and positive samples are not equal, AUPR is the fairer criterion for evaluation.

Algorithm

A deep learning model is designed to predict the possible non-interaction drug pairs and then used to design a three-class model. High resolution in detecting these zeros can help provide a more accurate and confident three-class model.

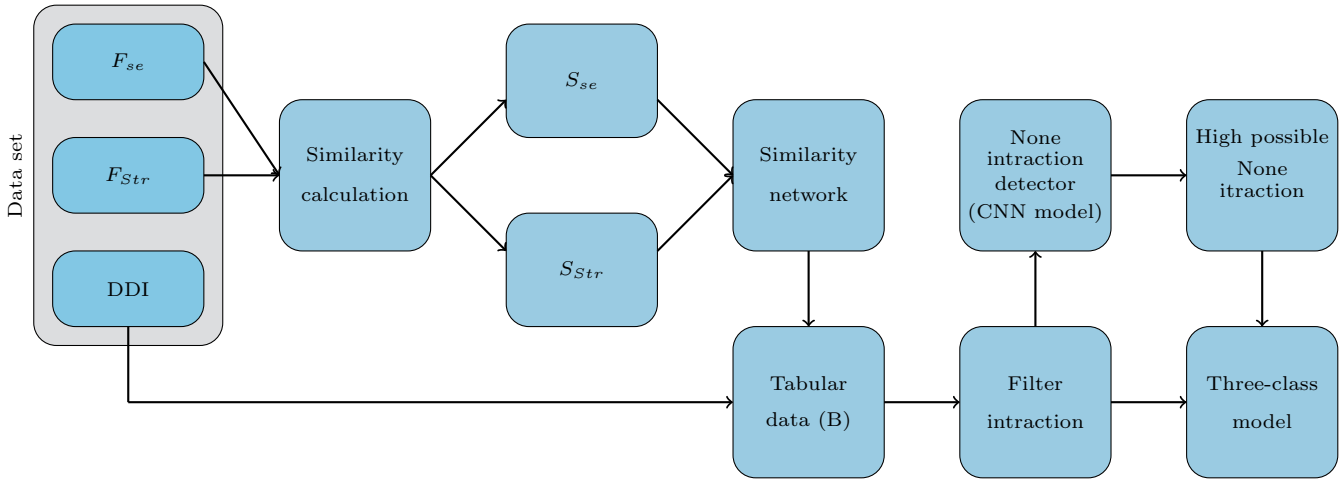

Fig. 2. Algorithm

Selecting model

We divided matrix B rows to isolate positive and negative interaction instances, creating a new matrix with 42, 702 drug pairs showing degressive and enhancive interactions. This dataset formed the basis for training a robust deep neural network model with convolutional and fully connected layers. Interaction data, labeled as $+1$ and -1, comprises feature vectors of 1136 elements. After considering various models, the selected one underwent rigorous 10-fold cross-validation with 90% for training and 10% for evaluation. Drug pairs (d_i, d_j) and (d_j, d_i) were treated as identical to ensure methodological integrity. The final deep neural network model (Figure 3) includes three 2D convolution layers followed by three fully connected layers, with the last layer predicting degressive or enhancive interactions. Convolution layers use 4-dimensional square filters with a Stride of 1 and ReLU activation function [20] as follows.

$$\text{ReLU}(x) = \max\{x, 0\} \tag{6}$$

The convolution filters are sized at 128, 32, and 8. The connected layers consist of 64, 16, and 2 nodes, respectively. The first two layers utilize the ReLU activation function, while the final layer with two nodes uses the Sigmoid activation function [1], defined as follows:

$$\text{Sigmoid}(x) = \frac{1}{1 + e^{-x}} \tag{7}$$

Convolution layers are followed by a flattened layer, which converts a two-dimensional matrix into a one-dimensional vector. The output from this layer serves as the input for the first fully connected layer. Additionally, a Dropout layer with a dropout rate of 0.2 is inserted between the fully connected layers of 64 and 16 nodes [29]. This layer helps prevent overfitting by randomly ignoring 20 percent of the features, encouraging the model to utilize a wider range of features for prediction.

Our experiments have demonstrated that two-dimensional convolution layers outperform their one-dimensional counterparts, as they can detect more drug similarities and extract more robust features. Thus, the 1136-dimensional feature vectors are transformed into matrices with dimensions of 17×16. Figure 4 illustrates the number of learnable weights for each layer, along with the total number of weights, reflecting the overall complexity of the model.

The following settings are used in the construction of the convolution neural network:

1. TensorFlow [3] (version 1.14.0) and KERAS are used [45] (version 2.2.5) packages to implement the neural network.
2. The categorical-cross entropy loss function was considered an objective function for the neural network, which is generally used to train a classification network [9, 32, 13].
3. ADAM optimization [15] was used to manipulate the neural network weights to find a promising optimal (minimum) state of the loss function.
4. The number of epochs was considered 5.
5. A learning rate of 1.010^{-5} was used.

Hyper-parameters Optimization

It's important to note that the hyperparameters of the network have not been fully optimized, and the specified parameters may not represent the best possible configuration. There are two primary reasons for not optimizing hyperparameters:

1. Model Overfitting: Optimizing hyperparameters to achieve the best performance on the current dataset may lead to overfitting. While this could improve performance on the current data, it does not guarantee that the learned features generalize well to new, unseen cases. Overfitting can be detrimental to the model's effectiveness in practical applications.
2. Robustness: While optimal hyperparameters may yield better results on the current dataset, they may not generalize well to different drug similarities or new data in the future. A model that lacks robustness may fail to perform adequately when applied to novel scenarios, undermining its credibility and acceptance within the pharmaceutical and pharmacological community.

Thus, while hyperparameter optimization is an important aspect of model development, it must be approached cautiously to balance performance on current data with the model's ability to generalize to unseen cases and maintain robustness over time.

The proposed SNF-CNN method's general process is presented in the form of Pseudocode 1, which includes the steps of preparation, model selection, real zero detection, and the presentation of a comprehensive recommender system.

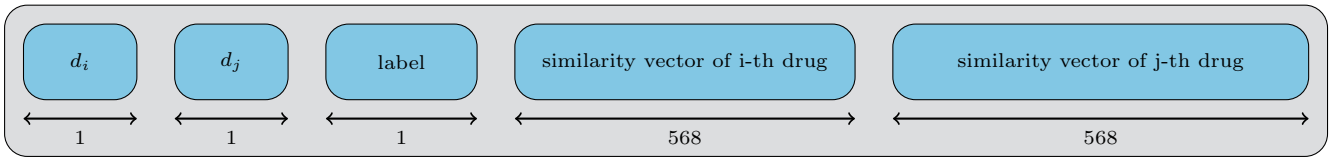

Fig. 3. Matrix scheme of tabular input data (table of B)

Algorithm 1 Final model selection (SNF-CNN) pseudocode

Require: Input: Drug pairs features (+1, -1, real 0)
1: Calculate drug similarity matrices with the cosine method.
2: Integrate drug similarity matrices with the similarity network fusion (SNF) method.
3: Built the input matrix of the model.
4: Select the fit known interactions model and train it.
5: Predict probable zeros by using step 4.
6: Select the fit known interactions and zeros of the step 5 model and train it.
7: Predict on unknown drug pairs.
Ensure: Output: Diagnostic model for interaction and non-interaction

Implementation

Dataset and features

This study utilizes the dataset introduced by Yu et al. in 2018 [40], comprising 568 approved small-molecule drugs. Each drug within the dataset exhibits at least one interaction with other drugs, resulting in a total of 21,351 Drug-Drug Interactions (DDIs). Notably, these interactions are further categorized into 16,757 enhancive DDIs and 4,594 degressive DDIs. Each drug in the dataset is uniquely characterized by two feature vectors:

1. An 881-dimensional feature vector (Fstr) derived from PubChem chemical structure descriptors.
2. A 9149-dimensional feature vector (Fse) based on off-label side effects sourced from the OFFSIDES database [30].

The elements in these vectors are binary, assigned a value of one if the corresponding side effect or chemical structure is reported or observed for the drug and zero otherwise. This dual-feature representation encapsulates both the structural attributes and off-label side effects of each drug, forming the foundational elements for subsequent analyses in our investigation.

Data preparing

Since the new drugs are isolated nodes in the interaction network, we cannot infer their possible interaction from topological information alone. Therefore, additional information (such as chemical structure or off-label side effects) is needed, called a drug feature in machine learning. First, we prepare feature matrix data to be proper input for machine learning methods, and then we devise and train a deep learning model to predict potential interactions.

Integration drug similarity matrices

Similarity Network Fusion (SNF) [34] is a computational method for integrating diverse types of data, such as chemical structure, off-label side effects, clinical data, questionnaires, and image data, for a given set of samples (e.g., drugs). SNF constructs sample similarity networks for each data type and iteratively integrates these networks using a novel fusion method. Operating in the sample network space enables SNF to handle different scales, collection bias, and noise across data types. By integrating data nonlinearly, SNF leverages both common and complementary information. Figure 1 illustrates the SNF process used in our method. In this section, similarity matrices of the chemical structure and off-label side effects of drugs were integrated using the SNF method. The new similarity matrix (Ssnf) output has dimensions of 568568, with elements ranging from 0 to 1. The SNFPy package, implemented in Python and available at [40], was used for network similarity integration.

Input matrix format

At this stage, a matrix is formed with 1139 columns and 322056 rows. Figure 2 displays the input data header, including columns for drug pairs (the names of the i-th and j-th drugs) and the type of interaction (degressive (-1), enhancive (+1), and unknown (0)). Each similarity vector from the Ssnf matrix for drug i and drug j has 568 elements. The dataset comprises 568 drugs. However, interactions of a drug with itself are disregarded. Drug pairs (d_i, d_j) and (d_j, d_i) share the same label, augmenting the training data and improving prediction accuracy. Hence, the matrix has 322056 data samples or rows ($568568 - 568 = 322056$). Consequently, a matrix with dimensions of 3220561139 forms the input for our model, referred to as the B matrix.

SNF processes [34]: A detailed example of SNF steps:

1. Illustration of chemical structure and off-label side effect features for the same set of drugs.
2. Drug-drug similarity matrices for each feature type.
3. Drug-drug similarity networks correspond to the data, with nodes representing drugs and edges representing pairwise similarities.
4. Network fusion through SNF iteratively updates each network with information from the others, increasing their similarity.
5. Iterative network fusion converges to the final fused network, with edge color indicating the contributing data type.

Devising of Recommender System

The data was meticulously prepared in the earlier stages to cater to various learning machines, including those employing deep learning techniques. While positive and negative DDIs are labeled distinctly, the zero label doesn't denote the absence of interaction between a drug pair. Instead, it indicates that no interaction has been identified for that specific drug pair. In the following sections, we outline a method for identifying pairs of non-interacting drugs. These drug pairs are then utilized as zero-labeled data in the subsequent training phase.

	Precision	Recall	F-measure	Accuracy	Support
Degressive	0.94	0.83	0.88		3902
Enhancive	0.95	0.99	0.97		3902
Macro Avg	0.95	0.91	0.93	0.95	3902
Weighted Avg	0.95	0.95	0.95	0.95	3902

Table 2. Interaction type classification report.

Two-class model's training trend

Ninety percent of the enhancive and degressive interactions are randomly selected for the training set, while the remaining 10% are allocated to the testing set. In the testing phase, the model is selected, and certain hyperparameters, such as the number of epochs, are determined. Figure 5 illustrates the training process for the chosen model. As expected, the model's accuracy steadily increases with training data, but fluctuations occur for testing data after Epoch 5. In the loss function graph, both training and testing loss decrease until the end of Epoch 5. However, beyond Epoch 5, while the training trend continues, the testing trend reverses, indicating overfitting. Thus, based on the graphs, the appropriate number of epochs for this step is determined to be 5.

Evidence of reliability of the two-class model

Finally, we examine the results of the proposed model in the 10-fold CV from three views:

1. Model Resolution: In a 10-fold CV, the model obtained AUC = 0.97, AUPR = 0.93 for degressive interactions, and AUC = 0.97, AUPR = 0.99 for enhancive interactions. These results indicate the high resolution and detection power of the selected model. The selected model resolution results are presented in Table 2, which identifies the type of degressive and enhancive interactions.

   Table 2 presents an example result of the implemented model, showcasing its precision, recall, and F-measure in detecting different types of interactions. As per Table 2, the model achieves a precision of 95% for detecting enhancive interactions and 94% for degressive interactions, with recall rates of 99% and 83%, respectively. Additionally, the F-measure stands at 97% for enhancive interactions and 88% for degressive interactions. The model's superior ability to detect degressive interactions stems from their higher prevalence, with a ratio of approximately 4 degressive interactions to 1 enhancive interaction.
2. Variance: The confidence interval for the reported values with a reliability coefficient above 95 percent was narrow and close to each other. Out of four reported confidence interval values, three values were less than 0.002, and only the AUPR was in the range of 0.005 for the degressive interaction. The low amount of variance obtained from the model shows that the proposed model is robust.
3. Separability: By plotting the output probability distribution diagram, as shown in Figure 6, it is clear that values $+1$ and -1 are well separated, and probability distribution degressive and enhancive have slight Subscriptions. Pseudocode 1 shows the step-by-step model selection process.

Algorithm 2 Model selection process

Require: Input: +1 and -1 drug pairs features
1: Apply 10-fold CV to the features of +1 and -1 drug pairs.
2: Select the right model.
3: Test the model results in a 10-fold CV.
4: If (3) is correct, select the model; else, go to (2).
Ensure: Output: +1 and -1 diagnostic model

Detecting of non-interaction drug pairs

In the previous step, a precise model was introduced to detect potential interactions between drug pairs, both enhancing and diminishing effects. This model can also identify non-interactions or 'real zeros.' If drug pairs show little likelihood of interaction, they are treated as real zeros.

Applying this hypothesis, the model was used to predict interactions among 270,000 unknown drug pairs. Pairs with both enhancing and diminishing probabilities below 0.4 were classified as non-interacting. Around 65,000 pairs met these criteria and were considered candidates for non-interaction. Given the model's accuracy, consistent results, and high resolution, these pairs are confidently regarded as non-interacting.

This section focuses on selecting and training models using both known interactions and potential non-interaction candidates. Non-interaction candidate drug pairs are treated as real zeros. The recommender system introduced in the previous section is utilized for the final model.

As detailed previously, the B matrix rows with +1 and -1 interactions are divided into ten parts. From the $65,000$ non-interacting candidate drug pairs, $30,000$ are randomly selected, ensuring each pair and its dual are included. The zero group is also split into ten parts, aligned with the +1s and -1s. These parts are then merged, resulting in a dataset of approximately $72,702$ drug pairs evenly divided and suitable for training and testing the final recommender system.

Three-class model training trend

In this case, we divide the set of all interactions (enhancive, degressive, and zeros of the first step) into ten equal parts. We consider one part of the testing set and the other nine parts of the training data set. Divide all the zeros in the previous step into ten parts and add a 1 to 9 ratio to both testing and training sets. In the second case, the previous model's 10-fold CV procedure was trained to predict the three classes with the least changes. Besides the hyper-parameter, the number of epochs was determined. Figure 8 shows the training process. The model's accuracy on training data increases steadily with the increase of epochs. Still, the model after epoch 9 reduces a constant and decreases the accuracy a little for testing data.

	Actual Enhancive	Actual Degressive	Actual Non-interaction
Predicted Enhancive	$cell_1 : T_{Enh}$	$cell_2 : F_{Enh}$	$Cell_3 : F_{Enh}$
Predicted Degressive	$cell_4 : F_{Deg}$	$cell_5 : T_{Deg}$	$cell_6 : F_{Deg}$
Predicted Non-interaction	$cell_7 : F_{Non-Int}$	$cell_8 : F_{Non-Int}$	$cell9 : T_{Non-Int}$

Table 3. The confusion matrix and relevant evaluation index for predicting triple classes whose cell names start with T (True). The main diagonal amounts of the matrix show correct predictions for each class. The other cells show drug pairs classified by mistake whose cell names start with F (False)..

Enhancive	Degressive	Non-interaction
$TP = cell_1$	$TP = cell_5$	$TP = cell_9$
$FP = cell_2 + cell_3$	$FP = cell_4 + cell_6$	$FP = cell_7 + cell_8$
$FN = cell_4 + cell_7$	$FN = cell_2 + cell_8$	$FN = cell_3 + cell_6$
$TN = cell_5 + cell_6 + cell_8 + cell_9$	$TN = cell_1 + cell_3 + cell_7 + cell_9$	$TN = cell_1 + cell_2 + cell_4 + cell_5$

Table 4. The new definition of TP, TN, FP, and FN in the triple class mod.

Discussion

Each combination of model features and data sets requires a thorough validation process. Depending on the nature of the problem and the chosen methodologies, we employed two variants of 10-fold cross-validation to ascertain the most suitable model and validate its results. The selection and evaluation of models were conducted with meticulous attention to the specific metrics detailed below.

Evaluation criteria for the final three-class model

In this study, drug pairs are classified into three classes based on interaction type for performance comparison with existing methods. Four measurement criteria—F-measure, accuracy, Area Under Roc Curve (AUC), and Area Under Precision-Recall curve (AUPR)—are utilized, defined using a confusion matrix (Table 3). The confusion matrix for the triple class case requires the redefinition of TP, TF, TN, and FP, as well as accuracy, precision, recall, and F-measure. $\text{Accuracy}_{(enh/deg/nonInt)}$: The fraction of all correct predictions (TPs) to all predictions.

$$\text{Accuracy} = \frac{\text{All correctly predicted}(cell_1 + cell_5 + cell_9)}{\text{Summation all nine cells}(\sum_{i=1}^{9} cell_i)} \quad (8)$$

Based on Table 3, TP, TF, TN, and TP will be defined in Table 4 for the triple-classes scenario. The other three evaluation criteria for each class are defined as follows:

Precision: The ratio of correct predicted ($TP_{Enh/Deg/Non-Int}$) interactions among all predicted (Enh/Deg/Non-Int) interactions.

$$\text{Precision}_{(Enh/Deg/Non-Int)} = \frac{TP_{(Enh/Deg/Non-Int)}}{TP_{(Enh/Deg/Non-Int)} + FP_{(Enh/Deg/Non-Int)}} \quad (9)$$

Recall: The ratio of correct predicted ($TP_{Enh/Deg/Non-Int}$) interactions among all true (Enh/Deg/Non-Int) interactions.

$$\text{Recall}_{(Enh/Deg/Non-Int)} = \frac{TP_{(Enh/Deg/Non-Int)}}{TP_{(Enh/Deg/Non-Int)} + FN_{(Enh/Deg/Non-Int)}} \quad (10)$$

Precision and recall for each class have a trade-off; Therefore, the F-measure can show the resolution ability of the model in each class. F-measure: The geometric mean of precision and recall in three- classes:

$$\text{F-measure}_{(Enh/Deg/Non-Int)} = \frac{2 \times \text{Precision}_{(Enh/Deg/Non-Int)} \times \text{Recall}_{(Enh/Deg/Non-Int)}}{\text{Precision}_{(Enh/Deg/Non-Int)} + \text{Recall}_{(Enh/Deg/Non-Int)}} \quad (11)$$

Also, we evaluated methods via modified AUC and AUPR for the three-class model.

Comparison of results

The binary interaction type detection model is developed and trained following the validation procedure outlined in the previous section. Subsequently, the final three-class model is introduced, utilizing the most probable non-interactions as zeros. The SNF-CNN model undergoes evaluation through a 10-fold cross-validation to assess its robustness and efficiency. Results of SNF-CNN and other methods for comparison are presented and discussed in this section. Table 5 three-class interaction classification is displayed. In this implementation, the precision of the model in detecting degressive interactions, non-interactions, and enhancive interactions are 95%, 96%, and 88%, respectively. The recalls are 97%, 95%, and 84%, respectively, and finally, F-measures are 96%, 96%, and 86%. The model power in the three-class mode decreases slightly compared to the two-class mode, which can be due to two reasons.

1. The problem of three-classes is more difficult than two-classes.
2. The suggested non-interactions or zeros are not necessarily real or pharmacologically proven, so some disturbance is possible.

For the above reasons, the detection ability reduction of the three-classes model was not unexpected. Since the previous three- classes of DDI models reported AUC and AUPR for comparison, the SNF-CNN results (Table 6) are presented based on these criteria, along with the margin of error at a 95% confidence interval. The small margin in the 10-fold CV underscores the robustness and reliability of the proposed algorithm. Table 7 compares SNF-CNN results averaged across the three classes with other existing three-class algorithms. The proposed algorithm exhibits a notable difference compared to superior algorithms in addressing the ternary problem, showcasing its competitive performance.

	Precision	Recall	F-measure	Accuracy	Support
Enhancive	0.88	0.84	0.86		850
Non-interaction	0.96	0.95	0.96		3000
Degressive	0.95	0.97	0.96		3052
Macro Avg	0.93	0.92	0.93	0.95	6902
Weighted Avg	0.95	0.95	0.95	0.95	6902

Table 5. Three-Classes interaction classification report.

	AUC	AUPR
Degressive	0.9747 ± 0.0033	0.9666 ± 0.0045
Enhancive	0.9686 ± 0.0028	0.8221 ± 0.0184
Non-interaction	0.9714 ± 0.0040	0.9480 ± 0.0083

Table 6. Results of SNF-CNN algorithm in predicting three- classes based on AUC and AUPR criteria and their confidence interval

	AUC	AUPR
SNF-CNN	0.971	0.912
BRSNMF [35]	0.805	0.644
Semi-NMF [33]	0.796	0.579
TMFUF [32]	0.842	0.526

Table 7. Comparison of the results of three-classes prediction algorithms based on criteria AUC and AUPR

Conclusions

Modern machine learning methods effectively identify potential drug interactions using large datasets but struggle with comprehensive three-class Drug-Drug Interactions (DDIs), including degressive, enhancive, and non-interactions. Current approaches often focus solely on binary classifications, overlooking pharmacological nuances. The distinct patterns of degressive and enhancive DDIs highlight the limitations of existing methodologies in capturing the complexities of drug interactions and disease dynamics.

In this study, we aimed to fill this gap by utilizing extensive DDI data and drug features to create a novel algorithm inspired by recommender systems. While our algorithm showed promising performance, there is still room for improvement, as indicated by inaccuracies in DDI predictions upon closer examination. A detailed investigation into model predictions, conducted through a case-by-case analysis of the latest versions of the DrugBank database, revealed three main reasons for erroneous predictions, all stemming from differences between DrugBank versions 4 and 5.

1. Removal of interactions in DrugBank version 5, leading to discrepancies in labeled data compared to version 4.
2. Inconsistencies in DDI labeling between DrugBank versions 4 and 5, resulting in misclassification of certain drug pairs.
3. Alterations in classifying DDIs between enhancive and degressive types between DrugBank versions 4 and 5.

We anticipate that the SNF-CNN approach will deliver superior DDI predictions with an improved dataset, minimizing erroneous or missing information on drug pairs. Future research should prioritize acquiring drug-related data from the latest DrugBank version.

While transitioning from two-class to three-class data aims to enhance representation and problem-solving capabilities, it's recognized that three-class data may not inherently provide sufficient biological insights. Therefore, collecting datasets featuring degressive and enhancive labels across pharmacokinetic and pharmacodynamic steps is recommended. These datasets hold promise for developing nuanced pharmacological models, offering valuable insights for pharmacists and advancing human health objectives.

As a prospect for future research, the authors are investigating potential synergies between the findings presented here and those from the Smart4Health project's pharmacogenomics investigations for personalized health. This collaborative effort aims to understand DDI mechanisms across patient profiles, contributing to personalized treatment regimens.

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