*Journal Title Here*, 2024, pp. 1–8

doi: DOI HERE
Advance Access Publication Date: Day Month Year
Paper

PAPER

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

M.Amin Khodamoradi,[*,1,3] Bahareh Levian,[2] Changiz Eslahchi,[2] Maria Marques[3] and Ricardo Jardim-Gonçalves[1,3]

[1]Universidade NOVA de Lisboa, NOVA School of Science and Technology (FCT NOVA), Caparica,Portugal, [2]Department of Computer Sciences, Shahid Beheshti University, Tehran, Iran and [3] Center of Technology and Systems (UNINOVA-CTS) and Associated Lab of Intelligent Systems (LASI), Organization, Caparica, Portugal
[*]Corresponding author. A.khodamoradi@uninova.pt

## Abstract

**Motivation:** 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. This study introduces the Similarity Network Fusion and Convolutional Neural Networks (SNF-CNN) model, treating comprehensive DDIs as a signed network.
**Results:** 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 the superiority of SNF-CNN, not only in predicting DDIs but also in accurately forecasting non-DDIs. The graphical abstract of SNF-CNN is provided (Figure 1).
**Availability and implementation:** The SNF-CNN and data are available as open-source from GitHub at: https://github.com/aminkhod/SNF-CNN.
For inquiries or collaboration, please contact A.khodamoradi@uninova.pt.

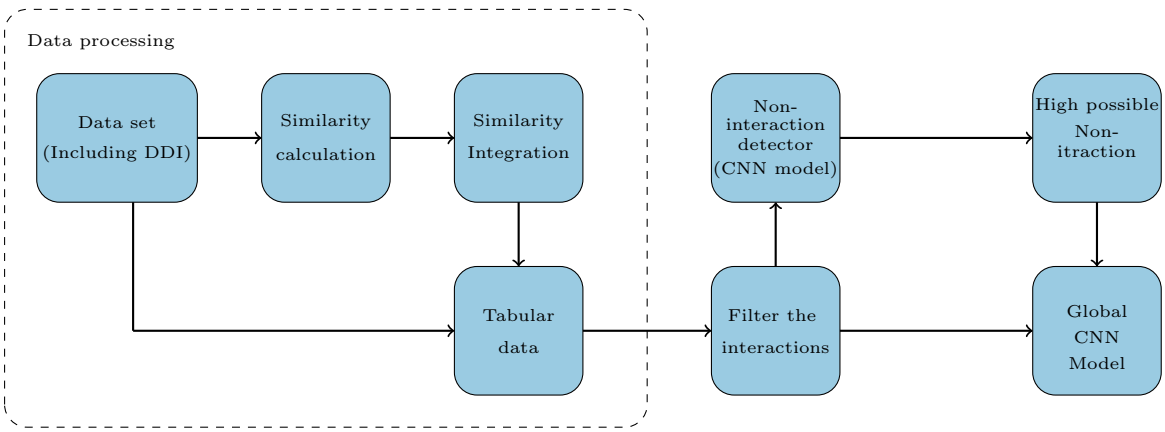


**Fig. 1.** Graphical abstract

## Introduction

When multiple drugs are taken together, their effects or behaviors may be unexpectedly influenced by each other [1]. 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 snowballing. For instance, among approved small molecular drugs listed in the DrugBank, approximately 15 out of every 100 drug pairs have known DDIs [2]. Such interactions pose risks to patients receiving multiple medications [3, 4, 5]. 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 [6]. 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 [7] or transporter-associated interactions [8], face challenges including high costs, time consumption, animal welfare concerns [9], 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 [10]. DDI 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 by the citizen for research (Research Platform – RP). CHDP utilizes the Health Level Seven (HL7®) Fast Healthcare Interoperability Resources (FHIR®) standard[2] to structure collected data, while RP adopts Observational Medical Outcomes Partnership (OMOP) Common Data Model (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 [11, 12]. Data mining-based computational methods have emerged to detect DDIs from diverse sources, including scientific literature [13, 14], electronic medical records [15], 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 [16], Network Recommendation-Based [9], Classification-Based [17]) can offer such alerts by leveraging pre-marketed or post-marketed drug attributes or drug similarities [18]. These approaches utilize various drug features to predict DDIs, including chemical structures [16], targets [19], hierarchical classification codes [17], as well as side effects and off-label side effects [9, 20].

Liu et al. proposed a dependency-based convolutional neural network (DCNN) in 2016 [21] to extract (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 [22], 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 Similarity Network Fusion (SNF) [23] is a competent method to integrate various similarities, which is used in other biological studies [24, 25, 26]. Neural networks represent a well-established approach, offering effective solutions, particularly for large datasets and nonlinear analyses [27]. They are widely utilized in critical problems across various domains [28, 29, 30].

Most existing approaches focus on predicting the typical two-classes 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 [31].

While enhancive and degressive DDIs are not arbitrary occurrences [32, 33], many current approaches have not leveraged this structural property, primarily focusing on conventional two-classes DDIs. However, uncovering this relationship is crucial for understanding DDI mechanisms, advancing the treatment of complex diseases [34], and aiding physicians in crafting safer prescriptions, especially for high-order drug interactions.

The TMFUF model, introduced by Shi et al. in 2018 [32], 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. [33], 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

[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

© The Author 2024. Published by Oxford University Press. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

2019 [35], utilizes Semi-NMF to predict these interactions more accurately, particularly in cold start scenarios [36]. This method leverages Drug Binding Protein (DBP) features to map new drugs with known drugs, resulting in drug communities with more moderate sizes.

Certainly! This study introduces a novel recommendation system designed to predict DDIs and accurately identify non-interaction drug pairs. The system, known as SNF-CNN, combines drug similarities and employs deep learning techniques to predict Drug-Drug Interactions (DDIs) within a triple-class model. This innovative approach aims to uncover previously unnoticed DDIs by leveraging off-label side effects and drug chemical structures for valuable insights. SNF-CNN utilizes a similarity integration method followed by a convolution neural network, diverging from conventional approaches. While acknowledging alternative methods, it is important to highlight that this study represents a distinct exploration within the domain of triple-class data, setting it apart from existing research in the field.

## 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 [37, 38]. 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 well-proven approach to verify the algorithms' resolution ability, model selection, and feature engineering in machine learning. The CV is carefully designed to propose a robust and confident model, and also proper accuracy comparison to other methods. In the CV process, precision, recall, and F-measure are collected.

Since precision, recall, and F-measure are threshold-dependent, methods are also evaluated via Area Under the Curve (AUC) and Area Under the Precision-Recall Curve (AUPR). In cases where imbalanced data, AUPR is the better criterion for evaluation.

The more details are provided in the supplementary.

## Methods and Materials

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

### Dataset and features

This study utilizes the dataset introduced by Yu et al. in 2018 [33], 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 ($F_{str}$) derived from PubChem chemical structure descriptors.
2. A 9149-dimensional feature vector ($F_{se}$) based on off-label side effects sourced from the OFFSIDES database [39].

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 each drug's structural attributes and off-label side effects, forming the foundational elements for subsequent analyses in this investigation.

### Data preparing

Since the new drugs are isolated nodes in the interaction network, it is impossible to infer their potential interaction from topological information alone. Therefore, additional information, such as chemical structure or off-label side effects, is necessary and is referred to as a drug feature in machine learning. First, feature matrix data is prepared as input for machine learning methods, and then a deep learning model is devised and trained to predict potential interactions.

### Integration drug similarity matrices

SNF [23] is a computational method for integrating diverse data types, 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 non-linearly, SNF leverages both common and complementary information. 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 ($S_{snf}$) output has dimensions of $568 \times 568$, with elements ranging from 0 to 1. The SNFPy [40] package of Python was used for network similarity integration.

### Input matrix format

A matrix is formed at this stage with 1139 columns and 322056 rows. Figure 2 displays the input data header, including two columns for drug pair names (the names of $d_i$ and $d_j$) and

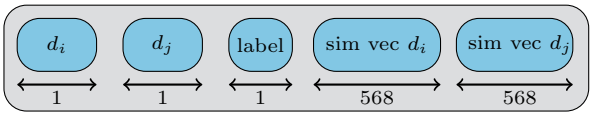


**Fig. 2.** Matrix scheme of tabular input data ($B$ matrix)

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 ($(568 \times 568) - 568 = 322056$). Consequently, a matrix with dimensions of $322056 \times 1139$ forms the input for the model, referred to as the $B$ matrix.

SNF processes [23]: 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, by employing deep learning techniques. While positive and negative DDIs are labeled distinctly, the zero label does not denote the absence of interaction between a drug pair. Instead, it indicates that no interaction has been identified for that specific drug pair. The method of identifying pairs of non-interaction drugs is outlined in the next section. These drug pairs are then utilized as zero-labeled data in the subsequent training phase.

## Selecting model

The matrix of $B$ as shown in Figure 2, formed the basis for training a DNN model. Rows of $B$ are divided to isolate positive and negative interaction instances, creating a new matrix with $42,702$ drug pairs showing degressive and enhancive interactions. Interaction data, labeled as $+1$ and $-1$, comprises feature vectors of 1136 elements. After considering various models, the selected one underwent a rigorous 10-fold CV. Drug pairs ($d_i$, $d_j$) and ($d_j$, $d_i$) were treated as dual identical to ensure methodological integrity. The final DNN model shown in 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 [41]. 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 [42].

| Layer (type) | Output Shape | Param # |
|---|---|---|
| conv2d_1 (Conv2D) | (None, 13, 68, 128) | 2176 |
| conv2d_2 (Conv2D) | (None, 10, 65, 32) | 65568 |
| conv2d_3 (Conv2D) | (None, 7, 62, 8) | 4104 |
| flatten_1 (Flatten) | (None, 3472) | 0 |
| dense_1 (Dense) | (None, 64) | 222272 |
| dropout_1 (Dropout) | (None, 64) | 0 |
| dense_2 (Dense) | (None, 16) | 1040 |
| dense_3 (Dense) | (None, 2) | 34 |

Total params: 295,194
Trainable params: 295,194
Non-trainable params: 0

**Fig. 3.** CNN model structure with Learnable parameters

Convolution layers are followed by a flattened layer, which converts a 2-dimensional(2-D) matrix into a 1-D vector. The vector is fed into 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 [43]. This layer helps prevent overfitting by randomly ignoring 20 percent of the features.

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 $17 \times 16$.

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

1. TensorFlow [44] (version 1.14.0) and KERAS [45] are used (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 [46, 47, 48].
3. ADAM optimization [49] 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 $10^{-5}$ was used.

## Hyper-parameters Optimization

Note that the hyper-parameters of the network have not been optimized, so the specified parameters may not represent the best configuration. There are two reasons for not optimizing hyper-parameters:

1. Model Overfitting: Optimizing hyper-parameters for the best performance on specific data may increase the risk of overfitting. While this can enhance the results, it does not ensure the learned features will generalize effectively to new unseen data. Overfitting diminishes the model's utility in real-world scenarios.

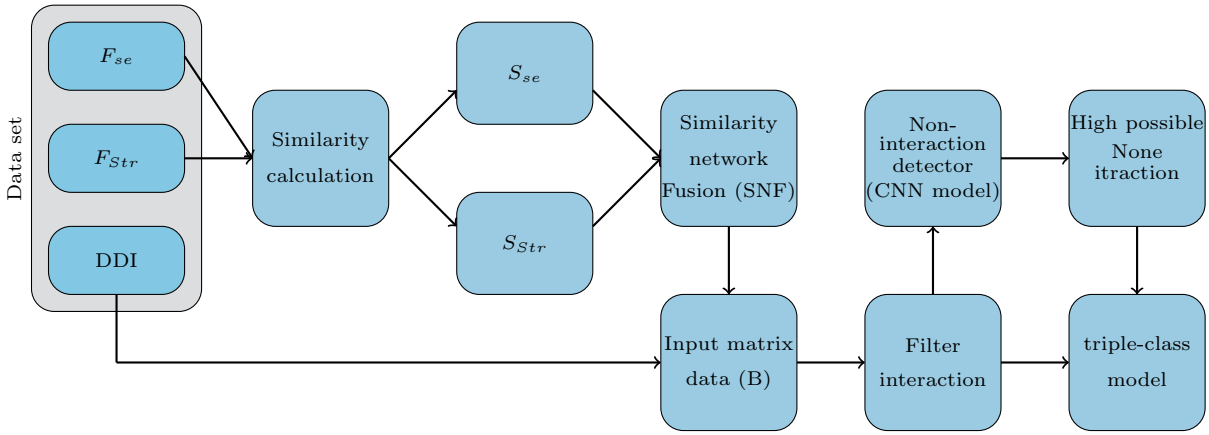


**Fig. 4.** Flowchart of the comprehensive DDI prediction from raw data to the end model (SNF-CNN)

**Algorithm 1** Final model selection (SNF-CNN) pseudocode

**Require:** Input: Drug pairs features (+1, -1, real 0)
Features matrices of chemical and off-label

1: Drug similarity calculation on feature matrices via cosine.
2: Integrate drug similarity matrices with the SNF method.
3: Built the input matrix of $B$.
4: Select known interactions and train the CNN.
5: Predict probable zeros using the model from step 4.
6: Select the known interactions from step 4 and zeros from the step 5 model to train a new CNN.
7: Predict on unknown drug pairs.

**Ensure:** Output: triple-class diagnostic model

2. Robustness: While Optimal hyper-parameters yield better results on the current data, they may not generalize well for a new drug with outlier drug similarities 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.

While hyper-parameter optimization is a common step 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 SNF-CNN method's steps are presented in the form of Algorithm 1, and also Figure 4 shows the visual process which includes data preparation, model selection, non-DDI detection, and the final comprehensive recommender system.

## Implementation

### two-classes model's training trend

The training data for the two-class model is generated by randomly selecting 90% of the enhancive and degressive interactions. The remaining 10% is allocated for testing. In the training phase, the model is selected, and certain hyper-parameters for instance, the number of epochs are determined by 5. The selection process of 5 is elaborated in the supplementary file.

| | Precision | Recall | F-measure | Support |
|---|---|---|---|---|
| Degressive | 0.94 | 0.83 | 0.88 | 3902 |
| Enhancive | 0.95 | 0.99 | 0.97 | 3902 |

**Table 1.** Interaction type classification report.

### Reliability of the two-classes model

The proposed model is examined in the 10-fold CV from three perspectives:

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.

   Table 1 presents an example result of the implemented model, showcasing its precision, recall, and F-measure in detecting the different types of interactions. As per Table 1, the model achieved 95% precision 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 $\pm 0.002$, and only the AUPR was in the range of $\pm 0.005$ for the degressive interaction. The low variance of the model is evidence robustness of the proposed model.
3. Separability: By plotting the output probability distribution diagram, as shown in Figure 5, values $+1$ and $-1$ are well separated, and probability distribution degressive and enhancive have a smaller intersection.

### Detecting of non-interaction drug pairs

In the previous step, a precise model was introduced to detect potential interactions between drug pairs, both enhancive and degressive interactions. This model can also identify non-interactions or 'real zeros'. If a drug pair shows little likelihood of interaction, it is classified as a 'real zero'.

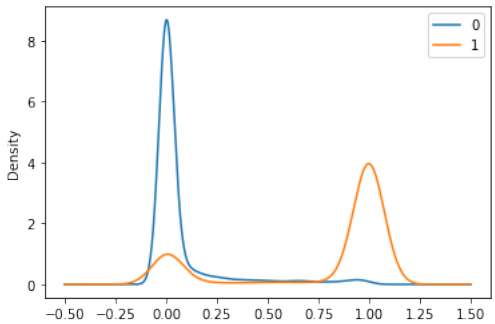


**Fig. 5.** Probability density distribution of degressive and enhancive. Here, 0 is the same as the −1 label (for technical reasons), and 1 is the same as +1.

To apply this rule, the model was used to predict interactions among 270,000 drug pairs with unknown labels. Pairs with both enhancive and degressive probabilities below 0.4 were classified as non-interaction. Approximately 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 considered as non-interactions.

## Triple-class model training trend

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-interaction candidate drug pairs, 30,000 are randomly selected, ensuring each pair and its dual are included. The zero group is split into ten parts, aligned with the +1s and −1s. These parts are merged, resulting in a dataset of approximately 72,702 drug pairs evenly divided and suitable for training and testing the final recommender system.

Then, the previous model is trained and validated in a 10-fold CV procedure for triple-class prediction. Only the output layer is adapted to have three categorical outputs. The number of epochs was determined by 9. The process of selecting 9 is elaborated in the supplementary file.

# Discussion

Every combination of model and feature set has to undergo a validation process. Depending on the nature of the problem and the chosen methodology, two variants of 10-fold CV were employed 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 triple-class model

In this study, drug pairs are classified into three classes based on interaction type for performance comparison. Methods are evaluated via adapted AUC and AUPR for the triple-class model using the confusion matrix table in the supplementary file with detail.

| | Precision | Recall | F-measure | 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 |

**Table 2.** triple-class 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 3.** 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 [36] | 0.796 | 0.579 |
| TMFUF [32] | 0.842 | 0.526 |

**Table 4.** Comparison of the results of triple-class prediction algorithms based on criteria AUC and AUPR

## 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 triple-class model is introduced, utilizing the most probable non-interactions as zeros. The SNF-CNN model undergoes evaluation through a 10-fold CV to assess its robustness and efficiency. In this section, the results of the SNF-CNN model are compared with those of other methods, and the findings are discussed. In Table 2 the triple-classes 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 F-measures are 96%, 96%, and 86%. The model power in the triple-classes mode decreases slightly compared to the two-classes mode, which can be due to two reasons:

1. The triple-class mode is more difficult than the two-classes mode.
2. The suggested non-interactions or zeros are not necessarily real or pharmacologically proven, so some disturbance is possible.

For the above reasons, a reduction in the detection ability of the triple-class model was expected. Since the previous three-classes of DDI models reported AUC and AUPR for comparison, the SNF-CNN results (Table 3) are presented based on these criteria, including the error margin of a 95% confidence interval. The small margin of the SNF-CNN in the 10-fold CV underscores the robustness and reliability of the proposed algorithm. Table 4 compares the SNF-CNN result with other existing triple-classes algorithms. The proposed algorithm exhibits a notable performance improvement compared to the state-of-the-art algorithms in addressing the ternary problem, showcasing its competitive performance.

## Conclusions

Modern machine learning methods effectively identify potential drug interactions using large datasets but struggle with comprehensive triple-class 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.

This study aimed to fill this gap by utilizing extensive DDI data and drug features to create a novel algorithm inspired by recommender systems. While the proposed algorithm showed promising performance, there is still room for improvement, as indicated by false 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.

The SNF-CNN approach shows promising results that can 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-classes to triple-classes data aims to enhance representation and problem-solving capabilities, it is recognized that triple-classes data may not inherently provide sufficient biological insights. Therefore, collecting datasets featuring degressive and enhancive labels across pharmacokinetics and pharmacodynamics 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.

## Declarations

### Funding

This work was partially funded by the European Union's Horizon 2020 research and innovation program in the scope of the Smart4Health under grant agreement No 826117 and by the Portuguese FCT program, Center of Technology and Systems (CTS) UIDB/00066/2020 / UIDP/00066/2020.

## References

1. Larry C. Wienkers and Timothy G. Heath. Predicting in vivo drug interactions from in vitro drug discovery data, 10 2005.
2. Drugbank 4.0: Shedding new light on drug metabolism. *Nucleic Acids Research*, 42, 1 2014.
3. L. L. Leape. Systems analysis of adverse drug events. ade prevention study group. *JAMA: The Journal of the American Medical Association*, 274:35–43, 7 1995.
4. Agnieszka Karbownik, Edyta Szałek, Katarzyna Sobańska, Tomasz Grabowski, Anna Wolc, and Edmund Grześkowiak. Pharmacokinetic drug-drug interaction between erlotinib and paracetamol: A potential risk for clinical practice. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*, 102:55—62, May 2017.
5. Eoin Mulroy, John Highton, and Sarah Jordan. Giant cell arteritis treatment failure resulting from probable steroid/antiepileptic drug-drug interaction. *NZMJ*, 130:1450, 2017.
6. Xing-Ming Zhao, Murat Iskar, Murat Iskar, Georg Zeller, Michael Kuhn, Vera van Noort, and Peer Bork. Prediction of drug combinations by integrating molecular and pharmacological data. *PLoS computational biology*, 7(12):e1002323, December 2011.
7. Comprehensive characterization of cytochrome p450 isozyme selectivity across chemical libraries. *Nature Biotechnology*, 27:1050–1055, 11 2009.
8. S. M. Huang, R. Temple, D. C. Throckmorton, and L. J. Lesko. Drug interaction studies: Study design, data analysis, and implications for dosing and labeling, 2 2007.
9. Ping Zhang, Fei Wang, Jianying Hu, and Robert Sorrentino. Label propagation prediction of drug-drug interactions based on clinical side effects. *Scientific Reports*, 5, 7 2015.
10. Md Rezaul Karim, Michael Cochez, Joao Bosco Jares, Mamtaz Uddin, Oya Beyan, and Stefan Decker. Drug-drug interaction prediction based on knowledge graph embeddings and convolutional-lstm network. pages 113–123. Association for Computing Machinery, Inc, 9 2019.
11. Barbara Wiśniowska and Sebastian Polak. The role of interaction model in simulation of drug interactions and qt prolongation, 12 2016.
12. D. Zhou, K. Bui, M. Sostek, and N. Al-Huniti. Simulation and prediction of the drug-drug interaction potential of naloxegol by physiologically based pharmacokinetic modeling. *CPT: Pharmacometrics and Systems Pharmacology*, 5:250–257, 5 2016.
13. Quoc Chinh Bui, Peter M.A. Sloot, Erik M. Van Mulligen, and Jan A. Kors. A novel feature-based approach to extract drug-drug interactions from biomedical text. *Bioinformatics*, 30:3365–3371, 12 2014.
14. Yaoyun Zhang, Heng Yi Wu, Jun Xu, Jingqi Wang, Ergin Soysal, Lang Li, and Hua Xu. Leveraging syntactic and semantic graph kernels to extract pharmacokinetic drug drug interactions from biomedical literature. *BMC Systems Biology*, 10, 8 2016.
15. Yoshihiro Yamanishi, Michihiro Araki, Alex Gutteridge, Wataru Honda, and Minoru Kanehisa. Prediction of drug-target interaction networks from the integration of chemical and genomic spaces. *Bioinformatics*, 24, 2008.
16. Santiago Vilar, Eugenio Uriarte, Lourdes Santana, Tal Lorberbaum, George Hripcsak, Carol Friedman, and Nicholas P. Tatonetti. Similarity-based modeling in large-scale prediction of drug-drug interactions, 2014.
17. Feixiong Cheng and Zhongming Zhao. Machine learning-based prediction of drug-drug interactions by integrating drug phenotypic, therapeutic, chemical, and genomic properties. *Journal of the American Medical Informatics Association : JAMIA*, 21, 2014.
18. Tapio Pahikkala, Antti Airola, Sami Pietilä, Sushil Shakyawar, Agnieszka Szwajda, Jing Tang, and Tero Aittokallio. Toward more realistic drug-target interaction predictions. *Briefings in Bioinformatics*, 16:325–337, 3 2015.

19. Heng Luo, Ping Zhang, Hui Huang, Jialiang Huang, Emily Kao, Leming Shi, Lin He, and Lun Yang. Ddi-cpi, a server that predicts drug-drug interactions through implementing the chemical-protein interactome. *Nucleic Acids Research*, 42, 7 2014.
20. Jian-Yu Shi, Hua Huang, Jia-Xin Li, Peng Lei, Yan ning Zhang, and Siu-Ming Yiu. Predicting comprehensive drug-drug interactions for new drugs via triple matrix factorization. In Ignacio Rojas and Francisco M. Ortuño Guzman, editors, *Bioinformatics and Biomedical Engineering - 5th International Work-Conference, IWBBIO 2017, Granada, Spain, April 26-28, 2017, Proceedings, Part I*, volume 10208 of *Lecture Notes in Computer Science*, pages 108–117, 2017.
21. et. al Shengyu Liu, Kai Chen. Dependency-based convolutional neural network for drug-drug interaction extraction. *Proceedings, 2016 IEEE International Conference on Bioinformatics and Biomedicine: Dec 15-18, 2016, Shenzhen, China*, 2016.
22. Jae Yong Ryu, Hyun Uk Kim, and Sang Yup Lee. Deep learning improves prediction of drug–drug and drug–food interactions. *Proceedings of the National Academy of Sciences of the United States of America*, 115:E4304–E4311, 5 2018.
23. Bo Wang, Aziz M. Mezlini, Feyyaz Demir, Marc Fiume, and et. al Zhuowen Tu. Similarity network fusion for aggregating data types on a genomic scale. *Nature Methods*, 11:333–337, 2014.
24. Rawan S. Olayan, Haitham Ashoor, and Vladimir B. Bajic. Ddr: Efficient computational method to predict drug-target interactions using graph mining and machine learning approaches. *Bioinformatics*, 34:1164–1173, 4 2018.
25. Zhen Tian, Maozu Guo, Chunyu Wang, Lin Lin Xing, Lei Wang, and Yin Zhang. Constructing an integrated gene similarity network for the identification of disease genes. *Journal of Biomedical Semantics*, 8, 9 2017.
26. Yoo Ah Kim, Dong Yeon Cho, and Teresa M. Przytycka. Understanding genotype-phenotype effects in cancer via network approaches. *PLoS Computational Biology*, 12, 3 2016.
27. Yiheng Wang, Tong Liu, Dong Xu, Huidong Shi, Chaoyang Zhang, Yin Yuan Mo, and Zheng Wang. Predicting dna methylation state of cpg dinucleotide using genome topological features and deep networks. *Scientific Reports*, 6, 1 2016.
28. Qian Ru HUANG, Feng HU, Shan HUANG, Hui Xin LI, Ying Hong YUAN, Gen Xing PAN, and Wei Jian ZHANG. Effect of long-term fertilization on organic carbon and nitrogen in a subtropical paddy soil. *Pedosphere*, 19:727–734, 2009.
29. Laiyi Fu and Qinke Peng. A deep ensemble model to predict mirna-disease association. *Scientific Reports*, 7, 12 2017.
30. Xiaoyong Pan, Yong Xian Fan, Junchi Yan, and Hong Bin Shen. Ipminer: Hidden ncrna-protein interaction sequential pattern mining with stacked autoencoder for accurate computational prediction. *BMC Genomics*, 17, 8 2016.
31. Jan Koch-Weser. Serum drug concentrations in clinical perspective. *Therapeutic Drug Monitoring*, 1981.
32. Jian Yu Shi, Hua Huang, Jia Xin Li, Peng Lei, Yan Ning Zhang, Kai Dong, and Siu Ming Yiu. Tmfuf: A triple matrix factorization-based unified framework for predicting comprehensive drug-drug interactions of new drugs. *BMC Bioinformatics*, 19, 11 2018.
33. Hui Yu, Kui Tao Mao, Jian Yu Shi, Hua Huang, and et. al Zhi Chen. Predicting and understanding comprehensive drug-drug interactions via semi-nonnegative matrix factorization. *BMC Systems Biology*, 12, 4 2018.
34. Murat Cokol, Nurdan Kuru, Ece Bicak, Jonah Larkins-Ford, and Bree B Aldridge. Efficient measurement and factorization of high-order drug interactions in mycobacterium tuberculosis, 2017.
35. Jian Yu Shi, Kui Tao Mao, Hui Yu, and Siu Ming Yiu. Detecting drug communities and predicting comprehensive drug–drug interactions via balance regularized semi-nonnegative matrix factorization. *Journal of Cheminformatics*, 11, 2019.
36. Lesly Alejandra Gonzalez Camacho and Solange Nice Alves-Souza. Social network data to alleviate cold-start in recommender system: A systematic review. *Information Processing and Management*, 54:529–544, 7 2018.
37. Shikui Tu et. al Wen Zhang, Yanlin Chen. Drug side effect prediction through linear neighborhoods and multiple data source integration. *IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, 2016.
38. Wen Zhang, Yanlin Chen, Dingfang Li, and Xiang Yue. Manifold regularized matrix factorization for drug-drug interaction prediction. *Journal of Biomedical Informatics*, 88:90–97, 12 2018.
39. Nicholas P. Tatonetti, Patrick P. Ye, Roxana Daneshjou, and Russ B. Altman. Data-driven prediction of drug effects and interactions. *Science Translational Medicine*, 4, 3 2012.
40. Ross Markello. snfpy 0.2.2, 3, March, 2020.
41. Vinod Nair and Geoffrey E Hinton. Rectified linear units improve restricted boltzmann machines. 2010.
42. Deep neural networks for acoustic modeling in speech recognition: The shared views of four research groups. *IEEE Signal Processing Magazine*, 29:82–97, 2012.
43. Nitish Srivastava, Geoffrey Hinton, Alex Krizhevsky, and Ruslan Salakhutdinov. Dropout: A simple way to prevent neural networks from overfitting, 2014.
44. Martín Abadi, Paul Barham, Jianmin Chen, Zhifeng Chen, Andy Davis, Jeffrey Dean, Matthieu Devin, Sanjay Ghemawat, Geoffrey Irving, Michael Isard, Manjunath Kudlur, Josh Levenberg, Rajat Monga, Sherry Moore, Derek G. Murray, Benoit Steiner, Paul Tucker, Vijay Vasudevan, Pete Warden, Martin Wicke, Yuan Yu, and Xiaoqiang Zheng. Tensorflow: A system for large-scale machine learning. 5 2016.
45. François Chollet and et.al. Keras, 28, 3, 2015.
46. Tirthankar Ghosal, Vignesh Edithal, Asif Ekbal, Pushpak Bhattacharyya, Srinivasa Satya Sameer Kumar Chivukula, and George Tsatsaronis. Is your document novel? let attention guide you. an attention-based model for document-level novelty detection. *Natural Language Engineering*, 27(4):427–454, 2021.
47. Yosuke Toda and Fumio Okura. How convolutional neural networks diagnose plant disease. *Plant Phenomics*, 2019:1–14, 03 2019.
48. Giseop Kim, Byungjae Park, and Ayoung Kim. 1-day learning, 1-year localization: Long-term lidar localization using scan context image. *IEEE Robotics and Automation Letters*, 4(2):1948–1955, 2019.
49. Diederik P. Kingma and Jimmy Ba. Adam: A method for stochastic optimization. 12 2014.