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Research Article

Exploiting Hypergraph Topologies: Advancing Explainable AI for Predicting Drug Synergies

Bareq Kadhim Faraj[1,*], Amir Lakizadeh[1]

[1] Computer Engineering and Information Technology Department, University of Qom, Qom, Iran
*Corresponding Author. Email: b.alghanimi@stu.qom.ac.ir

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ABSTRACT

Background: Considering the importance of drug therapy as a dominant approach in cancer treatment, monotherapy has been successful in advancing disease treatments, but its effectiveness can be limited due to different drug responses. To overcome these challenges, the drug combination strategy involving the use of multiple drugs to treat a specific disease has been advocated.

Objective: The objective of this research was to investigate the use of Hyper Graph Neural Networks (HGNNs) in modeling and predicting the interactions between drug combinations and their consequent effects on certain cell lines.

Method: The methodology involved extensive data preprocessing, exploratory data analysis (EDA), and the implementation of an HGNN model tailored to capture the complex inter-relations of multidimensional data. The Ex-HGNN model showed superior performance metrics, including high accuracy, precision, recall, and F1-scores, and portrayed efficiency in categorizing drug interactions and their effects as either synergistic or antagonistic. A critical detail of this study was the implementation of explainable AI approaches, such as SHAP (SHapley Additive exPlanations) and LIME (Local Interpretable Model-agnostic Explanations). These methods brought transparency into the decisions of the Ex-HGNN model, rendering them more interpretable and trustworthy. They allowed insight into the contribution of individual features on the prediction decisions of the Ex-HGNN model, an essential component in the field of drug efficiency analysis.

Results: Experimental results validated the proposed drug synergy prediction model and its significant enhancement compared to state-of-the-art methods.

Conclusion: These findings provide a stepping-stone for future research using machine learning and deep learning approaches in resolving other drug-related issues. This work demonstrates the effectiveness of Hyper Graph neural network modeling for high-dimensional data analysis and emphasizes the importance of explainable artificial intelligence in the fields of healthcare and precision medicine.

Keywords: Graph Neural Networks, Hyper Graph, Deep learning, Explainable AI, Drug Synergy, Attention mechanism.

INTRODUCTION

Drug therapy is a predominant approach in treating cancer in clinical settings. The array of anticancer drugs has expanded significantly to meet clinical needs, with numerous effective single drugs being utilized in cancer treatments. While monotherapy has been instrumental in advancing disease treatments, its effectiveness can be limited due to varying drug responses, including issues like toxicity and drug resistance [1]. In the pharmaceutical sector, ongoing research into small molecules aims to enhance products and customer satisfaction, leveraging their simplicity in chemical synthesis and cost-effectiveness in derivative preparation. Although the competition from generics and the complicated data necessary at the time of the release of original small molecules may appear to slow down the industry, it continues to grow, and there is an ever-growing need for new innovative solutions that compensate for the disadvantages of low molecular weight and the limited opportunities for knowledge exchange [2]. Small molecules act based on their conformation and reactivity, while huge-dimensional biomolecules like proteins and nucleic acids involve their tremendous structures for stability

and function [3]. Despite the molecular complexity of their pharmacokinetics, several biomolecules, such as insulin and adalimumab, have become excellently commercialized drugs. Advocates of drug combinations argue that these challenges can be abated by such an option. This method is essential for multiple drug treatments for a specific disease [4]. The reason why drug combinations are used in practice is that they can treat different molecules and pathways simultaneously, which also has several beneficial factors, such as being a more effective treatment, having more tolerable side effects, and encountering less drug resistance [5,6]. Therefore, due to the problems caused by the variability in drug response, drug combinations are becoming an increasingly attractive strategy.

An increasing number of approaches for finding drug combinations that existing clinical trials limit have emerged. Indeed, clinical trials, although they provide invaluable data, have low throughput due to high time consumption and substantial funding requirements and are prone to the unnecessary risk of therapy for patients [7]. As an alternative, high-throughput screenings are now widely used [8]. Simply put, using robotics to screen thousands of various chemical and biological substances for affinity to particular biomolecules simultaneously provides quicker identification of drug combinations that are likely to be effective. On the other hand, this method requires an in-depth understanding of all mechanisms of in-vivo action of drug molecules to apply all possible combinations for all diseases, which is not possible [9]. Therefore, computational methods were added to cover this part of the work. These include systems biology methods [10], kinetic models strategies, and, most relevant for this case, machine learning [12]. Due to the advances in algorithms and AI, pharmacokinetics allow for virtually predicting how the drug molecule behaves in our bodies by optimizing drug delivery systems for efficient and selective therapy, predicting profiles to define accurate dosing regimens personalized for a specific patient. Such techniques help to detect and design better drug interactions, improve the availability of drugs for metabolism, schedules of intake and doses, and thus are not prone to the bias inherent in socio-economic data.

Machine Learning (ML) has a special advantage in the modeling part compared to others. These methods can learn and comprehend the collective meaningfulness of a drug, which allows predicting the combinational effect of synergic drugs through in silico studies. The fact that ludicrously fast, affordable, and doctor-permitting AI predictive powers significantly cut drug trials cost and resources indicates the effectiveness of AI-based predictors and additionally shows their applicability. This development eventually led to the accelerated growth of machine learning and its application in drug combination discovery. Machine learning has made an exciting leap to drug combination research. Machine learning algorithms utilized in drug combination prediction exist in two forms, namely classical machine learning and deep learning. Classical methods are prevalent. For example, Li et al. developed a random forest-based model to predict synergistic anticancer pairs using drug-target networks and drug-induced gene expression profiles [13]. Sidorov et al. used an XGBoost model provided separately for each cell line [14], which in some cases decreases the model's general consistency due to the differences between cell lines. Julkunen et al. presented comboFM [15], which can predict the responses to novel drug pairs and new concentrations utilizing factorization machines while considering cell-context interactions. At the same time, deep learning methods, which do not require manual feature construction, extract patterns directly from the input data. These include convolutional neural networks [16], recurrent neural architectures [17], and attention approaches, widely used in computer image recognition and natural language processing. This approach has become successful in drug networks prediction. Authors developed DeepSynergy [7], a feedforward network model that outperformed traditional machine learning models in predicting drug pairs. The study authors also developed GraphSynergy, which outperformed the pairwise model, using the spatial graph convolutional network to encode the structural relations between modules in protein-protein interaction networks [18]. Moreover, an attempt to forecast drug pair interactions in cancer cell lines based on the graph convolutional network was made [19]. In late August 2021, the DeepDDS [20] model was presented, using GNN for drug prediction. This innovative architecture uses RDKit to transform SMILES-strings into molecular graphs, which encodes both compound structure information and the gene expression pattern to search synergistic drug pairs.

Despite these technological advancements, there are still shortcomings. By using a black-box approach, feature extraction of these models does not fully exploit the information of SMILES representation. Additionally, the fusion methods, which are usually nothing but simple concatenation of drug and cell line features, mostly do not fully express the great interaction between these features.

RELATED WORK

In [21], the authors introduce the innovative approach named SynPred that addresses the issue of cancer's heterogeneity and the complexity of human biology and genomic variability. The research is situated in the high-throughput screening technologies orthogonal to the ability and well-known ability to produce enormous multi-omics data at scale across different populations and cell types, particularly in the context of cancer research. Considering the fact that analyzing such data is a complex and challenging process due to the complex nature of cancer and biological diversity, they propose the reimagined schema of the drug discovery development pipeline. It advances the

drug discovery development pipeline with the power of AI by allowing it to understand the relevant biological information and experimentally evaluate new ways to create anti-cancer therapies. SynPred is originally an interdisciplinary approach that uses the custom-designed ensembles of AI algorithms that can understand and correlate the omics data with the experimentally measured biophysical properties to predict the synergy between the drugs in anticancer situations. It also ensures accuracy of prediction with performance metrics of 0.85 of accuracy, 0.77 of precision, and its analogy, 0.75 of recall, 0.82 of AUROC (Area Under the Receiver Operating Characteristics), and 0.76 of F1-score that were validated on an independent test set. The method is interpretable due to the use of the latest and most successful methodologies to ensure the feature importance in the context of the results application.

In [22], the authors highlight the pressing issue of fungal diseases that have become the leading cause of hospital-acquired infections with high mortality. They note the increasing problem of fungal diseases drug resistance due to the intensive use of the drugs. They address the issue by proposing the synergy drug combinations that increase drug efficacy and reduce the dose rate and, consequently, the toxicity. The computational identification of the drug combination hinges on their new hypothesis: the drugs that work in drug combinations that yield synergy together tend to be similar, which also applies to the inverse situation. The novel algorithm that captures the hypothesis called Network-based Laplacian Regularized Least Square Synergistic drug combination prediction is developed, which is fed the type of data that ensures the prediction, including the existing knowledge, drug-target interaction and drug-chemical structure data. The application on the antifungal drug synergy predictions showed promising results, both in the cross-validation and independent predictions. The biological laboratory experiments on the fungal pathogen Candida albicans further revealed that 7 out of the 13 predicted drug combinations outperformed the rest. The study is aimed to provide the potent and efficient strategy to identify the three potential synergistic combinations in antifungal therapy problem, which could be beneficial to the antifungal treatment. The authors in [23] delve into the realm of cancer treatment, focusing on the challenge of identifying novel synergistic drug combinations amid the vast combinatorial possibilities. They recognize the potential of computational methods as a more efficient alternative to traditional approaches, particularly in light of the substantial data from large-scale combination screenings now available. Their research introduces an innovative application of Deep Learning to drug synergy prediction, a domain where it had not been previously employed, through their development of ' DeepSynergy.' Remarkably, DeepSynergy surpassed other methodologies, showing a 7.2% improvement over the next best method in predicting new drug combinations within the studied scope of drugs and cell lines. This superiority was evidenced by a mean Pearson correlation coefficient of 0.73 between measured and predicted values. When applied to classify these novel combinations, DeepSynergy demonstrated a high predictive performance with an AUC (Area Under the Curve) of 0.90. However, the authors also observed that all compared methods, including DeepSynergy, exhibited limited predictive capabilities when applied to drugs or cell lines outside the dataset, suggesting a need for more diverse and expansive data. In conclusion, the authors posit that DeepSynergy could be a highly valuable tool in the selection of new synergistic drug combinations, offering a significant advancement in the field of cancer treatment. The authors in [24] also conducted a study to address drug resistance experienced in cancer therapy, presenting drug combinations as capable of eliminating or mitigating the challenge. They, however, proposed that it was impractical to experimentally screen all the existing combinations since the number of drugs that exist and the different ways to their combination were numerous, and very few resources are available. Considering that, the authors proposed a computational methodology of predicting the possible and promising drug combinations that will offer a solution of discovery for new combination therapies in cancer treatment. A research by the authors in [25] proposed that out of most of the therapeutic strategies, drug combinations presented the model promising potential to obtain better outcomes in many instances. Despite the numerous advantages which it has, the authors noted that it was impossible to test all possible drug combinations to know their synergism roles using existing high-throughput technologies due to the large combinatorial space which contributed to the number of combinations which required tests. The authors proposed a novel method called MatchMaker that was used to potentially predict promising combinations for cancer therapy. The novel method of interpretation worked within the learning networks and was developed for chemical models in biology using the dual new information that entailed drug structure and cell line expression by the authors of the study. This study, therefore, presented the use of the largest available dataset for drug combinations known as DrugComb. In comparison to the current models, MatchMaker and the rest of the models presented better results in the outcome. The authors discussed the capability of the MatchMaker model to perform tests on any possible drug combination which presented their Model's results 20% more correlated and 40% less or more improved than the mean squared error compared to all the other models. The rest of the structurally challenging pairs of cells the authors screened approximately analyzed the impossible pairs to test to present a new dataset of pairs to the users. The authors [26] reviewed the complex challenge that drug resistance in cancer therapy yields due to signaling pathways and discovering that modeling pathways using deep learning would eliminate drug resistance more conveniently. Unlike most of the models created by the others, the interpretable limits met the Mechanisms of Synergy, which are more straightforward to kill in the clinical setting.

In [27], the authors proposed an approach of applying a type of Recurrent Neural Network, Long Short-Term Memory, which had its foundations trained on compilations and repetitions to address pharmacokinetic and pharmacodynamic data from a model drug. Due to the scarce explorations of RNN in PK/PD data, the authors trained

the LSTM RNN model on data from the plasma concentration of the drug and the level of effect from one regimen. The LSTM model tested the predictability of PK/PD data on different regimens and showed the potential to forecast the PD profiles by capturing the temporal dependency in the context of indirect PK-PD. * [28] used a metric classification model, Side Effect Similarity, Chemical Similarity, and Target Protein Connectedness, to solve a complex issue of pharmacodynamic drug-drug interactions that are dependent on food or other drugs. The researchers compared the random forest and SVM models, utilized scaling and resampling methods to boost the precision of the models, and finally, the research maintained that Random Forest is the best model, which has the highest AUC and accuracy of 89.93% and 79.96%, respectively.

The authors [29] aimed to develop an Xgboost model for the estimation of the Area Under the Curve of tacrolimus concentrations-time model using an existing population pharmacokinetic model and Monte Carlo simulation for data generation. Their further objective was to investigate its accuracy for comparison to the MAP-BE method across external datasets. By simulating 9000 profiles with the R package mrgsolve, enabling the training and test samples allocation, they constructed Xgboost models capable of acreage estimation using minimal concentrations. The best model according to the cross-validation evaluation was tested on the transplant patients' datasets. They concluded that Xgboost models developed using minimal concentrations and covariates yielded AUC estimates with the lowest bias and RMSE; thus, they could be accurately calculated satellite data by patients.

Table 1. Comparison of Different Techniques in Drug Synergy Prediction.

Ref	Technique	PREC	AUC-ROC	ACC	AU-PRC	Kappa
[10]	DeepSynergy	0.57 ±0.12	0.90±0.04	0.91±0.04	0.60±0.06	0.51±0.04
[11]	AuDNNsynergy	0.73±0.05	0.91±0.03	0.92±0.03	0.62±0.05	0.50±0.03
[12]	MatchMaker	–	0.96±0.04	–	0.79±0.07	–
[13]	DeepSignalingFlow	–	–	0.66±0.05	–	–
[14]	SynPred	0.77±0.06	0.82±0.06	0.85±0.08	–	–
[16]	NLLSS	–	0.91 ± 0.03	–	–	–

MATERIALS AND METHODS

1.1 Dataset

The dataset that we are using includes the following components. It forms an essential part of the research, as this data was carefully elaborated to further investigate the efficacy of drug combinatorial therapy: the data is represented in DrugCombDB, a highly reputed repository and a platform designed to explore the drug synergy and antagonism phenomenon. Moreover, it was structured in a way that reminds time-series data that was specifically designed to support drug interaction research and has the following structure:

- ID: refers to the unique record identification that was provided to ensure traceability and the uniqueness of the combined drugs.

- Drug: is the name or ID of the first drug in the combination, and it is one of the primary variables in the provided data.

- Drug2: is the name or ID of the second drug in the combination, and it, in combination with the drug1 column, represents the respondent variable.

- Cell line: is the type of line upon which the combined drugs' impact was measured, and it is a characteristic similar to time in the time-series data as it grounds what exact biological experience is produced.

- ZIP: the Zero Interaction Potency score, which counts the magnitude of the interaction between two drugs and classifies it on a specific scale as it can be × <0 – antagonistic, 0 ≤ R ≤ 10,1 – additive, and x > 10 – synergistic.

- Classification: this is the previous column's categorical variable that was defined according to the postcode; labels are ordained as it is indicated in the appropriate column; there are 3 overall categories mentioned above.

The dataset's uniqueness involves the consolidation of the constraints and relevant components required to understand the drug interaction in a holistic framework; thus, it provides a rich background for the further application of machine learning and identification of how the prediction fits the previously obtained model. Thus, the utilization of this data will enable reaching a novel high-level predictive performance in combined therapy and allow advancing the field of precision therapy.

1.2 The Proposed Method

In the Ex-HGNN, a comprehensive methodology developed by us, we present a multi-stage setup to explore the complication of data analysis and neural network utilization to perform classification. At first, our process is

initialized by data loading; nothing can be done without it. Data loading is an essential process for our work as it allows starting the Exploratory Data Analysis. The EDA is an essential step to highlight the core statistics, distributions, and common characteristics of the data set. After EDA clarifies the picture of the data, a subset is distinguished, implying a reduced version of the data used for computational reasons. This subset is employed for encoding and transformation that has to be executed before feeding the data set into the HGNN – Hyper Graph Neural Network. HGNN [31] is a highly powerful model working with complicated relationships and patterns. That is how we are able to predict our target classifications; however, all the results are visible thanks to our transparency instruments. The Ex-HGNN method values the transparency of models, so it relies on methodologies SHAP [32]and LIME [33] that open the veil of the model process and explain each predictor's role in the final decision. In the next subsection, all the elements of our Ex-HGNN will be thoroughly considered for the reader to have a better understanding of the techniques and their application for our research. This explanation will demonstrate the strength of our Ex-HGNN and will create a solid base for replication and criticism.

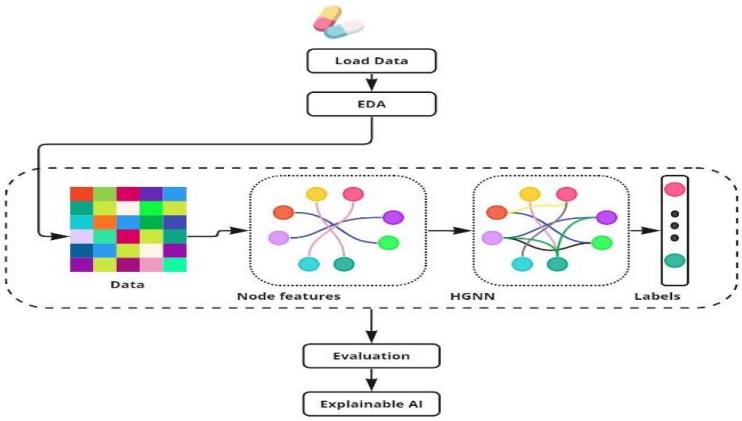

Fig. (1). General architecture of the proposed Ex-HGNN approach.

1.3 Data Preparation and Model Training

Based on the foundation laid by our prepossessed dataset, we now move to our data preparation for this analysis. It is an elaborate process with many tasks to be accomplished in tandem. The first of these tasks is the loading of our data into our programming environment and an exploratory data analysis, which helps us determine the basic statistics of our dataset, the distribution of the target variable, and the list of distinct labels in the classification column. Following this is the reduction of the full dataset to a representative 60% sample subset from which our Ex-HGNN can be trained, with much greater efficiency without losing a significant amount of information. This sample will help us split our features and target variable accordingly, to facilitate the training session that awaits us next. Once we have split our features and target variable, we encode the categorical variables in the form of a One-Hot Encoder and change the target variable through a Label Encoder. This is important to convert our categorical items into data interpretable by our machine learning algorithms. We then split our encoded dataset into training and test sets under an equal proportion for effective learning and proper testing of our Ex-HGNN model, converting the data into tensors for PyTorch compatibility. Our HGNN is then modeled according to our dataset specifications, and it is put through several epochs using the cross-entropy loss method using the Adam optimizer to train our data. We normalize our data to feed into the model and print the loss every epoch to see the model performance using the AUC and AUPR curves, and these metrics will show the model's overall performance in distinguishing the classes. We will also conduct a test at the same time, computing our accuracy and plotting for performance comparison.

RESULTS AND DISCUSSION

We provide our experimental details and compare the performance of the Ex-HGNN model with other benchmark methods.

1.4 Evaluation Metrics and Interpretability

Having trained our Ex-HGNN, the Hyper Graph Neural Network, the next obtuse operation is model evaluation and interpretability. This part is crucial for two indelible reasons. First, performance evaluation enables one to quantify how well our digest Ex-HGNN has precisely been able to make critical decisions. Second is the interpretability perspective, which allows one to appreciate the decisions that the model makes, while trying to predict. More so for our case because effective selection of drug combinations is NOT just the prediction but also the understanding of the interaction of all possible features. We first measure the performance of our HGNN. We do that using the AUC and the AUPR. The intendment is to tell the discriminative power of our model. Additionally, we measure the model accuracy on the test dataset as a straightforward measure of the system performability. We visualize the performance

metrics by plotting the AUC and the AUPR scores evolution against the epoch. This aleatorically shoals the learning capabilities of the system. There could be patterns, or the performance could just be a plateau. In essence, one should look at the plots to gauge the requirement of tweaking or adjusting the training process. As a matter of fact, not everything numerate is interpretable. As such, one ought to be yearning for interpretability. The desired aspect is more intrinsic, and on drug combination efficacy, explicability is as critical as prediction. We use SHAP and LIME to explain. In simple terms, the SHAP values for a prediction are a measure of importance of each feature to the prediction. SHAP values provide a singular drive of each feature across the dataset. We generate summary plots for this. LIME comes as a compliments of SHAP. It is just a predictor explanation but at the instance level. LIME explains individual predictions by approximating the interpretive model around a local region of a prediction. This way, LIME deliberately shows the contribution of each feature in an instance to prediction. Furthermore, we embark into a more in-depth investigational analysis using confusion matrices and classification report with data heatmap. Heatmaps help to create visual impressions of the confusion matrices. Confusion matrices, on the other hand, help to visual patterns on the model performability across the classifications. We finally embed advanced explanations. Deep SHAP, and LIME for tabular data.

1.5 Results of Ex-HGNN

Our experimental results represent an important milestone in validating the Ex-HGNN model. It achieved an outstanding test accuracy of 86.70%, an indication of the high level of capability in predicting how effective drug combinations are on the given cell lines outcomes. This level of precision shows the Ex-HGNN has the ability to generalize from training samples and accurately predict the outcome of unseen samples. More insights can be gained from the classification report about how the model performed in all classes. Precision is a measure of how precise the model is in classifying a sample as positive, while recall shows how many actual positive samples were correctly identified. It is vital to consider the f1-score, which is the harmonic mean of precision and recall; thus, it provides a balance between the two. This is essential in cases where a high level of false positives or false negatives is unwanted. Class 0 in this case implies non-synergistic drug combinations; the model performed with 0.89% f1-score. This shows that the classifier is slightly better at identifying the true negative cases and maintains a moderate precision-recall balance. On the other hand, class 1, which may be used to identify synergistic combinations, a precision of 86% and a recall of 82% was recorded, resulting in an f1-score of 0.84. Even though the performance of Ex-HGNN is still high, it is clear that it is less accurate in predicting true synergistic instances than non-synergistic ones. At the macro average level, which offers equal importance to every class, all precision, recall, and f1-scores are high at 87% and 86%, respectively. This uniform performance of the model in all classes indicates a lack of bias towards any side.

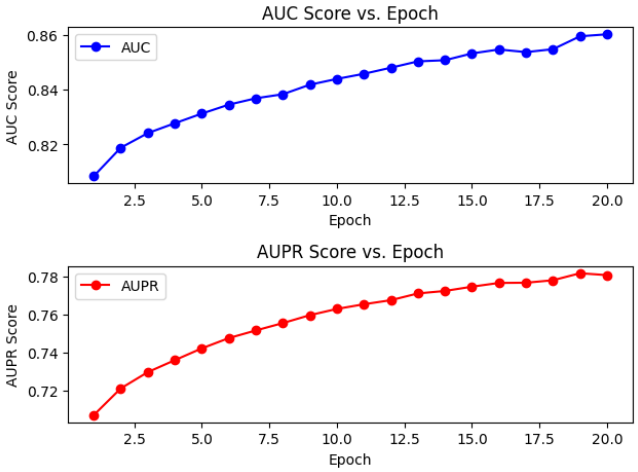

Fig. (2). Ex-HGNN performance during training

A graphical representation of the Ex-HGNN model's performance metrics over 20 training epochs is shown in Figure 2. The figure comprises two plots: the top plot illustrates the progression of the AUC score [34] while the bottom one shows the change in the AUPR score [35] over the corresponding epochs. The AUC score plot illustrates an ascending curve with a series of blue markers joined by a line. The curve starts from an AUC score of around 0.82 and approaches an AUC score of close to 0.86 at an asymptotic level. The increasing direction of the curve implies that as each training epoch progresses, the Ex-HGNN model demonstrates an increased capability to differentiate between the classes. In other words, it becomes more likely to rank a randomly selected positive instance higher than a randomly selected negative instance.

The AUPR score curve, on the other hand, is characterized by red markers and follows a similar increasing trajectory. The red line starts from approximately 0.72 and moves towards 0.78 at the 20th epoch. The model's increasing precision and recall for the positive class are essential for cases when the positive class is of more interest, as in drug

combinations outcomes. Both AUC and AUPR metrics are crucial for training evaluation; AUC is used to test the model's overall performance while AUPR provides information about its performance in class imbalance scenarios. Based on the positive trend of both plots, it is clear that the Ex-HGNN model becomes more predictive of drug combination outcomes as it advances through each continuous training epoch. Therefore, Figure 2 reflects the importance of training length for model effectiveness. In addition, it can be utilized to determine the most suitable point for training stops to avoid overfitting.

1.6 Explainable AI Results

Figure 3 showcases the outcome of the SHAP analysis. The force plot makes an impression and provides a more detailed understanding as to how the model's prediction for one particular instance is affected by each feature. The force plot visualizes the dynamics of feature interaction by means of push and pull, with the base value on the dashed line. This value serves as the reference point and is the mean prediction of the Ex-HGNN model for all data points. Then, all features are measured relative to the base. The final prediction for the instance, f(x), is equal to the individual contributions of SHAP values corresponding to all features. In this force plot, 'HS 578t' cell line and 'ADM HYDROCHLORIDE' drug exhibit a negative influence, as the red bars extend to the left. The probability of target class prediction decreases, while it decreases. However, 'MERCAPTOPURINE' drug is shown with the blue bar that extends to the right. Hence, the probability of the target class prediction increases. The additive nature of the SHAP values is evident in the visualization, where each feature's impact is aggregated to arrive at the final prediction. The juxtaposition of red and blue bars encapsulates the individual and conflicting impacts of features, with the culmination of these effects represented by the f(x) value on the plot. SHAP's interpretability enables stakeholders to comprehend the decision-making process of the Ex-HGNN model, offering transparency into which features are most significant in predictions and providing valuable insights for further investigation or decision-making. This is particularly useful in critical fields such as drug discovery, where understanding the rationale behind a model's prediction is as crucial as the prediction's accuracy.

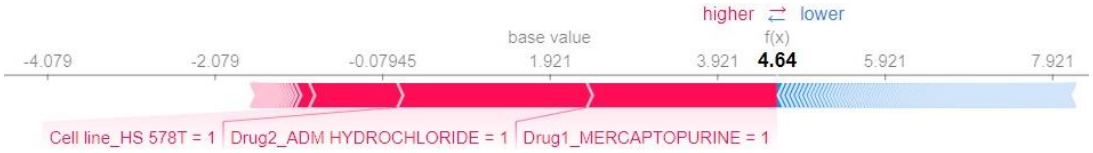

Fig. (3). SHAPE results

The result of LIME (Local Interpretable Model-agnostic Explanations) provides an accessible and understandable breakdown of the model's predictions, as evidenced by Figures 4, 5, and 6. In Figure 4, the illustrated bar chart quantifies the prediction probabilities for different classes, where the outcome 'antagonism' is significantly more likely with a high probability of 0.97. This indicates the model's strong prediction bias towards 'antagonism'. In stark contrast, 'synergy' is deemed much less likely with a minimal probability of 0.03, and the probabilities for all other outcomes are zero, suggesting they are not considered plausible by the model.

The accompanying decision rules provide a clear breakdown of how certain features influence the classification. These rules, visualized as a series of thresholds, offer insight into the logic behind the model's predictions. For instance, a feature threshold rule such as 'Cell line_A2780 <= 0.00' indicates that the absence (or a value less than or equal to zero) of the A2780 cell line is a strong indicator for predicting 'antagonism'. Similarly, thresholds for drug features like 'Drug2_MERCAPTOPURINE' set to 0.00 also contribute to this prediction outcome.

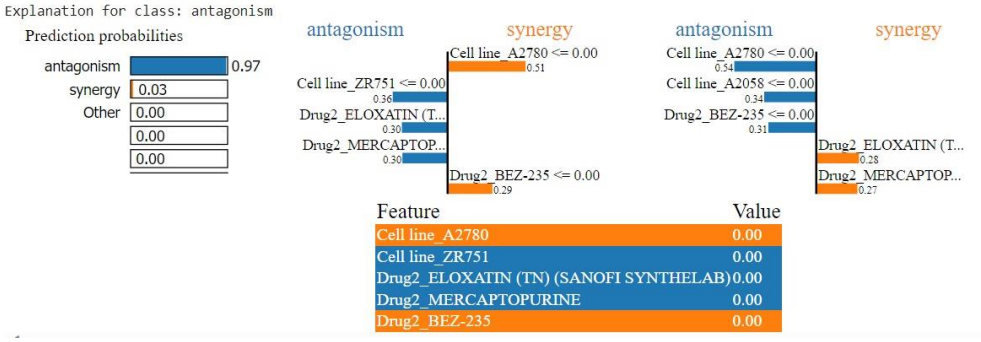

Fig. (4). Lime class Antagonism

Figure 5 presents a predictive analysis focused on the class 'synergy' with a graphical representation of the model's prediction probabilities and contributing features. The probability for 'synergy' is determined to be 0.66, suggesting a favorable likelihood according to the model's inference, whereas 'antagonism' has a notably lower probability of

0.34, with no probability allocated to other potential outcomes. The figure also illustrates decision rules tied to specific feature thresholds which guide the model's prediction. A notable decision rule for 'synergy' shows that if 'Cell line_A2780' is less than or equal to 0.00, the model is more inclined to predict 'synergy'.

Below the decision rules, a color-coded feature impact chart displays the features along with their corresponding values. The cell lines A2780 and ZR751 are both shown with values of 0.00, indicating that their state does not directly sway the prediction towards 'synergy'. Similarly, the drugs ELOXATIN (TN), TOPOTECAN HYDROCHLORIDE, and CHLORAMBUCIL are also assigned values of 0.00, emphasizing that, in this instance, they do not individually influence the prediction of 'synergy'.

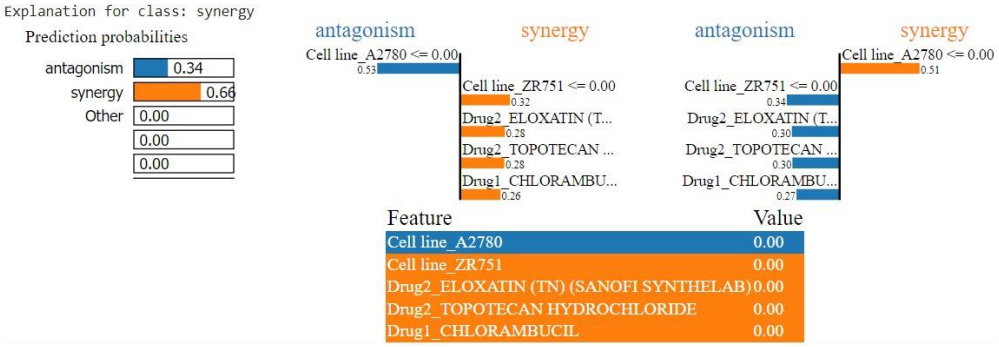

Fig. (5). Lime class Synergy

Figure 6 illustrates a LIME bar chart providing a local explanation for the class 'synergy'. In this chart, the horizontal bars represent the weight of each feature's contribution to the model's prediction that a specific instance falls within the 'synergy' class. The red bar corresponds to the cell line A2780, indicating a significant negative impact on the synergy prediction when its value is less than or equal to zero. Conversely, the green bars associated with the cell line ZR751, the drugs ELOXATIN (TN), TOPOTECAN HYDROCHLORIDE, and CHLORAMBUCIL, each represent a positive contribution towards the prediction of synergy, also under the condition that their values are less than or equal to zero.

This figure serves to decode the model's decision-making process for the given instance, providing insights into which features promote or inhibit the class prediction of 'synergy'. It simplifies the interpretability of the model by quantifying the influence of individual features, making it evident which factors are driving the prediction, and thereby offering a transparent basis for understanding and validating the model's predictions.

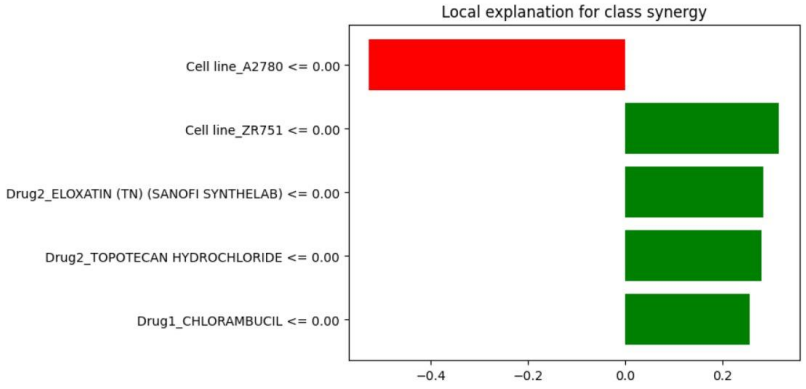

Fig. (6). Lime bar chart

Our proposed Ex-HGNN model shown in the result is a good trade-off between predictive accuracy and interpretability feature which are great requirements for its use in drug combinations efficacy prediction. However, the incremental increase in both the AUC and AUPR scores demonstrates the focused usage of accurate prediction and the increase in the importance of several features after later training rounds. The SHAP and LIME analyses clearly illustrate how the features which feed the predictions are most impactful, giving more utilization into the models rationality. The prototypal opinion or logical thought of the model is a significant value in the pharmaceutical industry, because a physician needs to understand the why behind predictions in the practice of medicine. The robust performance of the model on different metrics and its clear interpretation functionality are promising features for researchers and practitioners in the AI community who need to apply the prediction power of AI in different medicine and drug development fields.

CONCLUSION

Our study is the first to involve a sophisticated method using Hyper Graph Neural Network to predict drug combination efficacy. Our study has a solid methodological foundation and a detailed evaluation. Our HGNN model's results are robust and accurate; our model can predict drug synergy and antagonism. Our model's accuracy, precision, recall, and f1-score are outstanding. Our approach began with EDA to gain insights into the data, and we did thorough data preparation, including feature encoding and dataset splitting. The Ex-HGNN model was trained carefully to get the most out of it and to generalize better. We have closely focused on model interpretability through SHAP and LIME, which clearly describes the decision-making process. It builds trust and transparency in our findings, vital in drug discovery and healthcare. As evidenced by our experiments, our model's performance improves and AUC and AUPR scores continue to increase. Our Ex-HGNN model effectively pairs cutting-edge machine learning methodologies with interest in explainable AI to predict drug efficacy. Our study will enhance bioinformatics predictive modeling and open avenues for future study in areas where element synergy and antagonism are critical. The methodologies, as well as the knowledge, will generate a baseline for the creation of dependable, interpretable AI systems in healthcare and other fields in the future.

Statements and Declarations

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Competing Interests

The authors declare no actual or potential conflict of interest.

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