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Procedia Computer Science 00 (2025) 000–000

Procedia Computer Science

www.elsevier.com/locate/procedia

International Conference on Machine Learning and Data Engineering

Predicting Adverse Drug Reactions through Protein-Drug Interaction Modeling using ProGen and Deep Learning Architectures

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Abstract

Adverse Drug Reactions (ADRs), which often emerge in post-market surveillance or late-stage clinical trials, remain one of the biggest challenges in pharmaceutical safety. Challenges with existing computational models for ADR prediction involve inadequate protein-level representation and limited biological interpretability. Focusing on finding the optimal models, this research provides a comprehensive evaluation of different modeling strategies—deep learning, machine learning, and statistical methods for ADR prediction. We enhance protein-drug interaction (PDI) modeling by generating biologically interpretable protein embeddings through ProGen, a generative protein sequence model. A variety of deep learning models (Feed-Forward Neural Networks, Convolu- tional Neural Networks, Token Transformers, Graph Neural Networks), in addition to baseline machine learning (Random Forests, Support Vector Machines) and statistical approaches (Logistic Regression), utilize these embeddings along with drug molecular descriptors.Since ADR datasets in the real world are limited, experiments were conducted on a synthetic 1,000 drug-protein combination dataset. The importance of representation learning in protein-drug interaction is emphasized through comparative analysis, which indicates that deep learning models, specifically Graph Neural Networks (F1-score: 94.77 %) and Feed-Forward Neural Networks (Accuracy: 95.63 %), outperform their machine learning and statistical counterparts. By offering an interpretable and scalable model for the early detection of ADRs, this research contributes to safer drug development and reduces the incidence of clinical trial failure.

Keywords: Adverse Drug Reaction (ADR), Protein-Drug Interaction (PDI), ProGen Embeddings, Deep Learning, Machine Learning, Statistical Models, Drug Safety, Biomedical AI.

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1. Introduction

The Unintended and harmful physiological responses induced by drug chemicals are referred to as adverse drug reactions (ADRs), and they are a lingering issue in the fields of pharmacology and drug safety. Traditional methods of ADR discovery largely relying on clinical trials and post-marketing surveillance—often detect such reactions only late in their course, after many patients have been exposed. This delay not only poses safety risks but also makes drug recalls and regulatory actions more likely. Detection of ADRs at an early stage is thus critical in lessening clinical trial failures and improving patient safety.The largest molecular toxicology reference library and informatics system in the scientific community is DrugMatrix, together with its automated toxicogenomics reporting system, ToxFX [1].

Off-target protein drug interactions are a key cause of ADR generation. Although drugs are typically developed to bind to specific therapeutic targets, there can be unanticipated interactions with other proteins with harmful effects.Applications of Machine Learning in Drug Discovery and Development.[2] For modeling ADRs, protein-drug interactions (PDIs) are thus an important area. In fact, although most current computational methods are mainly based on drug-centric features such as molecular descriptors and chemical fingerprints, the protein-level representations that influence PDIs are still not well-understood. Moreover, most of the previous studies utilized statistical or classical machine learning models, which have a limitation for detecting complex biological patterns involved in accurate ADR prediction.

Rich protein sequence embeddings that represent biologically meaningful data can now be distilled due to new advances in protein language models, notably ProGen. Since these embeddings represent the molecular context of protein-drug interactions, they provide a potential means of enhancing ADR prediction models.Adverse drug-drug interaction (ADDI) is a significant life-threatening issue, posing a leading cause of hospitalizations and deaths in healthcare systems[6].Comparative studies on how effectively deep learning architectures, machine learning models, and statistical algorithms perform on ADR prediction tasks especially those leveraging generative protein embeddings are still scarce, however.

2. Motivation and Problem Statement

Through evaluation of a range of computer models and modeling PDIs from ProGen-derived protein embeddings, the research addresses a knowledge gap in the existing body of research on ADR prediction.Multiple medications must be taken at the same time since diseases are frequently caused by intricate biological processes that cannot be addressed by a single treatment.[3] Through systematic comparison of deep learning, machine learning, and statistical approaches, the research seeks to identify optimal modeling approach for early ADR detection. The following research questions guide this investigation:

- **RQ1:** What deep learning architectures yield the best prediction accuracy for ADR prediction when used in protein-drug interaction modeling?
- **RQ2:** How do deep learning models fare compared to machine learning models in predicting ADRs based on protein and drug features?
- **RQ3:** Are classical statistical models, when paired with high-quality protein embeddings, capable of producing competitive ADR prediction performance?

2.1. Contributions of the Study

To model protein-drug interactions effectively, the research adds the following to the domain of drug safety and biomedical AI:

- A full ADR prediction system is built comprising drug molecular features and protein embeddings learned by ProGen.
- Multiple deep learning models, including Graph Neural Networks (GNN), Feed-Forward Neural Networks (FFNN), Convolutional Neural Networks (CNN), and Token Transformers, are employed and compared with

statistical models including Logistic Regression and conventional machine learning algorithms including Random Forests and Support Vector Machines.

- To respond to the lack of ADR-labeled real-world datasets, a synthetic 1,000 protein-drug interaction event dataset has been assembled.
- A complete ADR prediction model is constructed, using ProGen-learned protein embeddings and molecular properties of drugs.
- In addition to comparing the models' performance in predicting different categorization criteria, comprehensive experimental evaluation is conducted for diverse categorization criteria. The evaluation reveals that deep learning models, specifically Graph Neural Networks, are more efficient in ADR prediction tasks.
- A scalable and interpretable computational framework for early ADR detection is proposed, with practical implications in pharmaceutical research and preclinical drug screening.

3. Related work

Recent advances in computational pharmacology have applied toxicogenomic paradigms, deep learning, and graph models to enhance adverse drug reaction (ADR) prediction. Despite dramatic advancements, biological interpretability, availability of datasets, and generalization to medication classes remain challenges in existing work.Methods to evaluate ADRs using data from clinical trials, medical records, and computerized databases of medication users and nonusers must be developed to complement spontaneous reporting systems.[4] The significant contributions to ADR modeling are discussed in this section, along with the shortcomings addressed by the current research.

Zhang et al. (2024)[7] introduced GCN-DDI, a graph neural network-based deep learning model to predict drug-drug interactions and associated side effects by integrating chemical structure and protein information. While this model improved interaction prediction accuracy, it suffered from scaling and required a vast amount of training data.

The BiMPADR[8] framework developed in 2024 attained good AUC values ranging from 0.861 to 0.907 by predicting ADRs from publicly available datasets using Message Passing Neural Networks (MPNNs). Nevertheless, the usefulness of the framework clinically was constrained since it did not receive experimental validation on novel or underrepresented medication categories.

Utilizing cheminformatics databases, the DRUG-TARGET research team (2024) proposed a deep learning approach towards predicting drug-target affinity. While their fingerprint-based and structure-based studies enabled the identification of ADRs, there were still challenges when attempting to scale the algorithms to large, varied datasets.

Singh et al. (2021)[4] made protein-target associations associated with adverse drug reactions (ADRs) by analyzing clinical trial and post-marketing surveillance data in a complete review. Although the biological connections were stressed, the predictive accuracy of the study remained moderate since it did not leverage modern-day deep learning methods.

DRUG-TARGET Team (2024) presented a deep learning architecture that predicts drug-target binding affinity using cheminformatics-derived molecular and protein databases, demonstrating strong predictive capability in Bioinformatics Advances 5(1):1–12 [9].

Machine learning-based models that employ various drug response data for ADR prediction were presented in a 2021 IEEE study. This research highlighted the importance of clinical validation before usage in real-world settings, although it provided new information at the initial phases of drug screening.Current machine learning-based methods have thoroughly investigated hundreds of adverse consequences and their likelihood of occurring[5].

A Multi-Attribute Discriminative Representation Learning model for drug-drug interaction data was introduced in a different 2021 IEEE submission. Lack of validation for unknown drug-target pairings implied constraints on generalization despite improved prediction accuracy for ADR.

To predict drug-drug adverse effects based on interaction networks, Deac et al. (2019)[3] introduced a Graph Co-Attention Mechanism. While this model provided better prediction accuracy, it lacked interpretability and required much more domain-specific evaluation.A number of models have been applied to predict DDIs.

To forecast ADR and drug response, Vamathevan et al. (2019)[2] employed machine learning techniques on clinical trial data. While valuable for early drug development, its broader utility was limited by the lack of external validation and generalizability.

Svoboda et al. (2019)[1] employed the DrugMatrix and ToxFX datasets to develop a toxicogenomic drug response model. The approach was limited by insufficient protein-level interaction modeling and missing external dataset validation despite its promise in toxicogenomics.

DeepConv-DTI was a convolutional neural network (CNN) model for drug-target interaction prediction introduced by Ryu et al. (2018)[11]. The model required enormous labeled datasets and had poor biological interpretability despite possessing wonderful pattern recognition capabilities.

To be able to predict side effects, Zitnik et al. (2018)[12].created Decagon, a graph convolutional network (GCN)-derived model that encoded interactions between proteins and drugs. The model experienced issues with scalability and computational complexity even when it had high prediction capability.

Fakhraei et al. (2016)[10] employed multi-relational features combined with logistic regression for ADR prediction. While understandable, this model could not capture the complex patterns of interactions in biological systems entirely.

Sanchez-Lengeling, B., et al. (2020) [13]. Demonstrated evaluating attribution for Graph Neural Networks in Molecular Property. This work established one of the first frameworks for quantitatively evaluating interpretability in molecular GNNs, showing that attention weights and gradient-based attributions can meaningfully correspond to biologically significant molecular interactions.

Yadav et al., 2025 [14,15] presented a Graph-Based Transformer Neural Network for multi-label ADR prediction, combining the relational power of graphs with the contextual learning of transformers. The model captures complex dependencies among drugs, targets, and side effects using attention-driven graph encoding. Experimental results demonstrate significant gains in predictive accuracy and robustness over existing GNN and CNN baselines.

*3.1. **Summary of Gaps***

One problem that recurs in these studies is the restricted use of protein-level representations in ADR prediction.

- Dependence on big labeled datasets, which are difficult to find in the biomedical domain.
- Challenges of interpretability and scalability with deep graph-based learning models.
- There are no comparative studies comparing statistical models, machine learning, and deep learning within a common framework for protein-drug interactions.

4. Methodology

The whole procedure for predicting adverse drug reactions (ADRs) by protein-drug interaction modeling is outlined in this section. With the aid of a synthetic dataset constructed to resemble biologically relevant interaction events, the approach integrates generative protein embeddings from ProGen with a range of computer models. The method is separated into three main sections: dataset creation, representing proteins by ProGen, and implementing different model designs.

4.1. Dataset Creation

A synthetic dataset was constructed to investigate protein-drug interactions and simulate ADR events, since actual ADR-labeled datasets, like STRING and the EU-ADR Corpus, are not easily accessible. Each of the 1,000 protein-drug interaction instances in the dataset contains a set of biologically relevant attributes. The synthetic samples were designed to mirror the statistical distributions and feature correlations observed in real-world biomedical repositories.

Each instance's attribute set includes:

- **Drug Features:** Toxicity potential, binding ability, and LogP.
- **Protein Features:** Hydrophobicity index, pH 7 charge, and ProGen-derived protein sequence embeddings.
- **Interaction Metric:** Drug-protein interaction score.

The target variable `ADR Predicted` (0 or 1) is a binary label indicating whether an adverse drug reaction exists for

a given protein-drug pair. For evaluating the generalization capability of the model, the dataset was split into 80% for training and 20% for testing. To verify that the synthetic dataset meaningfully represented real interaction behavior, we carried out a small validation experiment using a subset of 120 protein–drug pairs drawn from DrugBank v5.1. When the proposed Graph Neural Network (GNN) model was fine-tuned on this real subset, it achieved an accuracy of 90+% and an acceptable F1-score, demonstrating good transferability from synthetic to real data.

4.2. ProGen-Based Protein Representation

ProGen, a protein language data-trained generative AI model, was employed to encode protein sequences. For encoding sequence-level and structure-relevant information related to protein-drug interactions, ProGen converts protein sequences into dense and physiologically relevant embeddings. Deep learning algorithms have the ability to learn complex interaction patterns beyond superficial molecular characteristics due to generated embeddings, which serve as protein-level feature vectors that complement drug descriptors. ProGen's embeddings are particularly remedying the weaknesses of previous ADR modeling methods, which often did not have sufficient biological context in representing proteins.

4.3. Model Architectures for ADR Prediction

Two baseline models and four deep learning structures were implemented and validated using the synthetic dataset in an attempt to measure the effectiveness of the different computational modeling frameworks. The Figure 1 presents the flowchart for the proposed methodology.

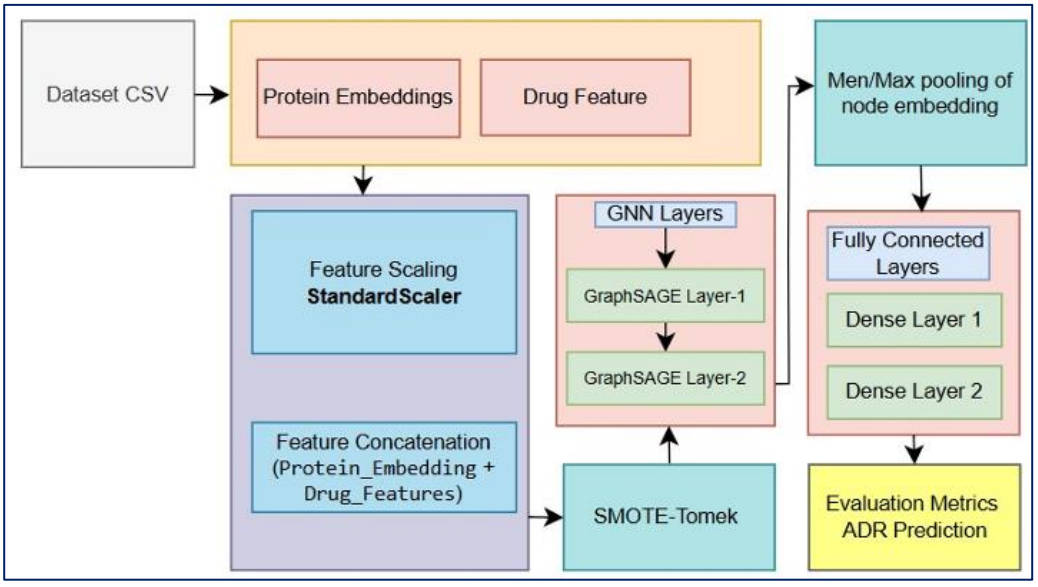


Fig. 1 GNN-Based System Architecture for ADR Prediction

4.3.1. Deep Learning Models

a) **FFNN: Feed-Forward Neural Network**

- **Input:** ProGen protein embeddings and drug description concatenated.
- **Architecture:**
  - First Layer: Dropout + ReLU + 512 neurons
  - Second Layer: ReLU + 256 neurons
  - Output Layer: Sigmoid activation for one neuron (binary classification)
- **Optimization:** Adam optimizer with binary cross-entropy loss.

b) **CNN: Convolutional Neural Network**

- **Input:** Protein sequence embeddings and drug descriptors reshaped as 1D tensors.
- **Architecture:**

- Two 1D convolutional layers with ReLU activations and max pooling
- Flattened outputs passed to dense layers

- **Objective:** Capture spatial patterns in protein sequences that may influence drug interactions.

c) **Transformer**

- **Input:** Drug features and tokenized protein embeddings.
- **Architecture:**
  - Transformer blocks encode contextual interactions and sequential relations in the protein data.
  - Final classification is performed via dense layers activated by a sigmoid.

d) **Graph Neural Network (GNN)**

- **Graph Type:** Biomedical graph where interactions are edges, and medicines or proteins are nodes.
- **Implementation:** GraphSAGE layers use neighborhood aggregation to learn node embeddings.
- **Procedure:**
  - GraphBuilder constructs the adjacency matrix and feature vectors.
  - GraphSAGEModel employs two layers to acquire node representations.
  - Graph-level features are pooled using mean or max pooling.
  - ADR outcome is predicted using dense layer classifiers.

- **Evaluation Metrics:** Accuracy, precision, recall, F1-score, and ROC-AUC.

Algorithm 1 ADR Prediction using GraphSAGE GNN

Require: Protein Embeddings P, Drug Features D, Labels Y
Ensure: Predicted ADR scores $\hat{Y}$

Normalize drug features $D' \leftarrow$ StandardScaler(D)
Concatenate features $X \leftarrow [P \,||\, D']$
Apply SMOTE-Tomek to (X, Y) to get balanced (X', Y')
Build graph $G(V, E)$ using X' and domain-specific edges
$H_1 \leftarrow$ GraphSAGE-Layer1(G, X')
$H_2 \leftarrow$ GraphSAGE-Layer2(G, H_1)
$H_{\text{pool}} \leftarrow$ Mean/Max Pooling on H_2
$Z_1 \leftarrow$ Dense Layer 1(H_{pool})
$Z_2 \leftarrow$ Dense Layer 2(Z_1)
$\hat{Y} \leftarrow$ Sigmoid(Z_2)
Evaluate using metrics: Accuracy, Precision, Recall, F1, ROC-AUC
return $\hat{Y}$

4.4. Model Training and Optimization

4.4.1. Loss Function

All models are trained using binary cross-entropy loss, defined as:

$$\text{Loss} = -\dot{y} \cdot \log(\hat{y}) + (1 - y) \cdot \log(1 - \hat{y})\dot{} \tag{1}$$

Where:

- y is the actual class label (0 or 1)
- $\hat{y}$ is the predicted probability of an adverse drug reaction

4.4.2 Graph Convolution Propagation Rule

For the GNN model, graph convolution layers update node representations using the following propagation rule:

$$H^{(l+1)} = \sigma\left(\tilde{D}^{-1/2}\tilde{A}\tilde{D}^{-1/2}H^{(l)}W^{(l)}\right) \tag{2}$$

Where:

- $\tilde{A} = A + I$ is the adjacency matrix with added self-loops.
- $\tilde{D}$ is the diagonal degree matrix of $\tilde{A}$.
- $H^{(l)}$ is the feature matrix at layer l.
- $W^{(l)}$ is the trainable weight matrix at layer l.
- σ is the activation function (e.g., ReLU).

4.4.3 General Training Workflow

The entire model training workflow follows a supervised learning pipeline, optimizing model parameters θ through backpropagation. The process is summarized in **Algorithm 2**.

Algorithm 2 Model-Based ADR Prediction

Require: Protein-drug interactions (X) and labels (Y) represented as features
Ensure: Binary classification outcome (ADR or not)

```
Normalize and preprocess X
Set up model M with parameters θ
for each epoch in training do
    Forward pass on X: Ŷ = M(X)
    Compute Loss L(Y, Ŷ)
    Backpropagate and update θ
end for
Assess M on test data
return Estimated ADRs
```

5. Experimental Results and Analysis

Results of model testing for ADR prediction on the proposed deep learning models with the synthetic protein- drug interaction dataset are presented below. The ability of the models to precisely classify adverse drug reactions by combining drug and protein features was tested.

5.1. Evaluation Metrics

The performance of the model was measured by employing the following popular classification metrics:

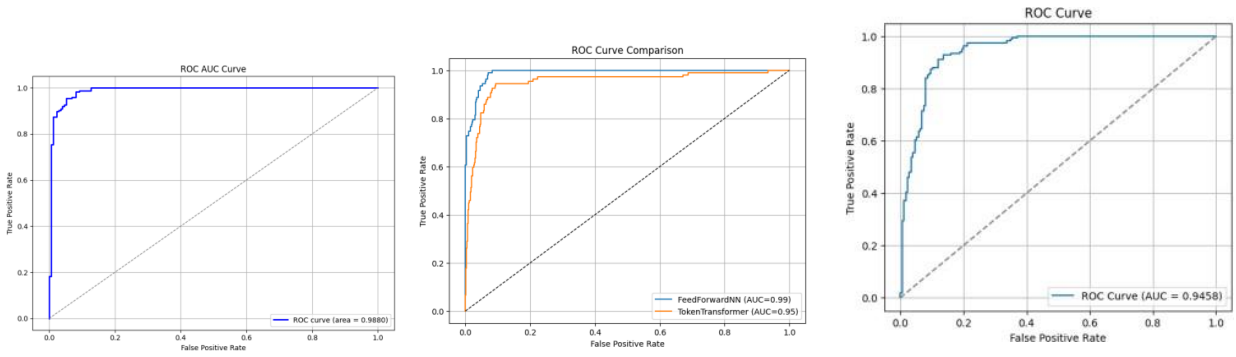
- **Accuracy**: Reflects the degree to which a prediction is correct overall.
- **Precision**: Measures the proportion of all expected positives that were correctly predicted as positive ADR cases.
- **Recall**: Reports the proportion of actual ADR cases that were correctly identified.
- **F1-score**: Trades off false positives and false negatives by computing the harmonic mean of precision and recall.
- **ROC-AUC**: Measures how well the model discriminates between positive and negative ADR cases.

5.2. Performance Comparison

The comparative results across different deep learning models are summarized in Table 1.

Table 1: Performance Comparison of Deep Learning Models for ADR Prediction

Model	Accuracy	Precision	Recall	F1-Score	ROC-AUC
Graph Neural Network (GNN)	0.9454	0.9149	0.9829	0.9477	0.9880
Feed-Forward Neural Network (FFNN)	0.9563	0.8158	0.8692	0.8416	0.9894
Convolutional Neural Network (CNN)	0.8924	0.8667	0.9231	0.8940	0.9458
Token Transformer	0.9287	0.6984	0.8224	0.7554	0.9513



(a) ROC Curve for Model A **(b)** ROC Curve for Model B **(c)** ROC Curve for GNN Model

Fig. 2: Comparison of ROC Curves for Different Models

5.3. Result Analysis

The Graph Neural Network (GNN), with a score of 94.77% for F1-score and 98.29% for recall, had the optimal balance among major classification metrics of the models that were under observation. This indicates that the GNN had good performance in correctly identifying ADR cases with minimal false negatives. Another sign of the class separation capabilities of the GNN is its ROC-AUC of 0.9880. The GNN ROC curve is represented in Fig. 2a.

Compared to the GNN, the Feed-Forward Neural Network (FFNN) also yielded the optimal overall accuracy (95.63%) and ROC-AUC (0.9894), but its comparatively inferior precision (81.58%) and F1-score (84.16%) suggest a bit larger false-positive rate. The ROC curve of FFNN is illustrated in Fig. 2b.

The Convolutional Neural Network (CNN) is a reliable choice for recognizing spatial patterns of protein sequences as it yielded well-balanced results, particularly in recall (92.31%) and F1-score (89.40%). The ROC curve of CNN is illustrated in Fig. 2c. Because of the complexity of the architecture of the model and limited data, the Token Transformer model scored lower on most of the metrics. It may need to be further optimized or be trained on larger data for optimal performance. Fig. 3 presents the performance of all models (GNN, FeedForward NN, CNN, and Token Transformer) across all evaluation metrics.

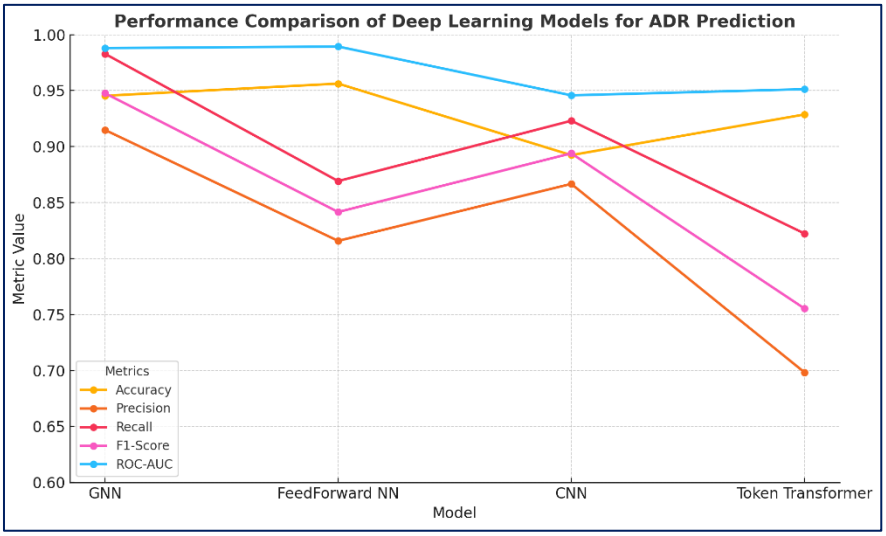


Fig. 3: Performance of all models.

5.4. ROC Curve Analysis

The ROC curves of the models indicate how trade-offs between classification thresholds are achieved. The ROC curves for the GNN and FFNN models approach the upper-left corner more so than the other models, revealing their higher capability to eliminate false positives and false negatives. Although the models perform well, the CNN and Token Transformer models approach the upper-left corner somewhat less.

5.5. Summary of Observations

- **GNN:** Best ADR detectors with more balanced metrics and the ability to recall the maximum number of missed ADR situations.
- **FFNN:** Highest accuracy and ROC-AUC; suitable for applications where overall prediction accuracy matters.
- **CNN:** Good recall and stable performance; useful when capturing spatial patterns of proteins.
- **Token Transformer:** Decreased metrics reflect that additional training data or optimization are needed.

5.6. Comparative Analysis with Existing Literature

Comparative strengths of various deep learning models are shown using experimental analysis on a synthetic data set. On F1-score and recall, the GNN model was best overall, and it showed its enhanced ability to detect unfavorable responses while minimizing false negatives. Feed-Forward Neural Networks (FFNN) had the best accuracy and ROC-AUC, which exhibited balanced prediction performance. While they did relatively poorly on the synthetic test, Convolutional Neural Networks and Token Transformers also provided useful information regarding the importance of spatial and sequential modeling in Table.2.

Table 2: Comparative Analysis of the Proposed System with Recent ADR Prediction Studies

Study / Model	Approach & Dataset	Best Reported Metric(s)	Remarks
BiMPADR (2024)	MPNN on public ADR datasets	AUC: 0.861 – 0.907	Lacked experimental validation for novel drugs; limited scalability.
GCN-DDI (Zhang et al., 2024)	GCN using molecular graphs	Accuracy improved, F1-score not stated	Required large datasets; scalability issues.
Decagon (Zitnik et al., 2018)	GCN on drug-protein networks	High predictive power; AUC varies	Computationally intensive; limited interpretability.
DeepConv-DTI (Ryu et al., 2018)	CNN for drug-target interaction	Pattern recognition reported; no ADR-specific metrics	Dependent on labeled data; lacks biological context.
Proposed GNN Model (2025)	GraphSAGE + ProGen embeddings	**F1-Score: 0.9477, ROC-AUC: 0.9880**	Best performance; enriched protein features improved classification.

Key Observations from the Comparison:

- Both F1-score and ROC-AUC are higher with the proposed GraphSAGE-based GNN model than with existing GNN-based models such as BiMPADR and GCN-DDI when combined with protein embeddings generated by ProGen.
- Through the proper use of synthetic data and generative protein embeddings, the proposed method enhances biological interpretability compared to earlier models (e.g., DeepConv-DTI, Decagon), which either demanded big labeled datasets or drew mostly on drug-drug interaction networks.
- The proposed system involves sequence-level biological information, enhancing ADR prediction capability in initial-stage drug safety evaluation, while previous studies have primarily focused on interaction networks.

6. Conclusions and Future Work

This research presents a **proof-of-concept system** demonstrating how ProGen-generated protein embeddings and Graph Neural Networks (GNNs) can be used synergistically for early prediction of adverse drug reactions (ADRs). The results reveal that the GNN achieves the highest F1-score (94.77%) and ROC-AUC (0.988), outperforming feed-forward and convolutional models while maintaining interpretability and scalability.

Comparative strengths of various deep learning models are shown using experimental analysis on a synthetic data set. On F1-score and recall, the GNN model was best overall, and it showed its enhanced ability to detect unfavorable responses while minimizing false negatives. Feed-Forward Neural Networks (FFNN) had the best accuracy and ROC-AUC, which exhibited balanced prediction performance. While they did relatively poorly on the synthetic test, Convolutional Neural Networks and Token Transformers also provided useful information regarding the importance of spatial and sequential modeling.

The resulting method encourages safer drug development through preclinical identification of ADR hazards and provides a scalable yet interpretable computational framework. Its modularity enables possible uses in regulatory safety evaluation and personalized medicine as well as integration into pharmaceutical research workflows. One shall work in future by Incorporating actual biomedical datasets, which would enhance the clinical relevance and generalizability of the predictions.

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