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Graphrxinsight: GNN-Enhanced Ensemble Framework for Detecting Risky Polypharmacy and Drug Side Effects

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ABSTRACT: ***Artificial Intelligence (AI), Machine Learning (ML), and Deep Learning (DL) are widely used in healthcare for analyzing molecular and clinical data to support decision-making. AI builds intelligent systems, ML enables data-driven learning, and DL, especially Graph Attention Networks (GAT) and Deep Neural Networks (DNN), extract complex features for accurate drug–drug interaction (DDI) prediction[6]. In existing systems to predict DDI, the models using Deep Neural Networks (DNN), Random Forest, and XGBoost with DrugBank's structural similarity profiles are applied. They use the Synthetic Minority Over-sampling Technique to handle class imbalance in clinical datasets[5]. These approaches aim to improve the prediction of rare but critical adverse drug interactions and have demonstrated accuracy around 93.80%[8]. Even though current models provide useful insights, they have limitations in fully capturing complex drug interactions and real-world usage[3][1]. They struggle with handling imbalanced data and do not fully use Graph Neural Networks (GNN) to model multi-drug networks. We propose a hybrid model, CLINENSEMBLE, combining Graph Attention Networks (GAT), Deep Neural Networks (DNN), and CatBoost.Using chemical structure data and graph features along with clinical information, it improves rare event detection by over 5% and overall accuracy. This helps doctors and researchers better assess drug interaction risks and improve patient safety.***

Keywords: Drug–Drug Interaction, Graph Neural Network, Ensemble Learning, Polypharmacy, Healthcare AI, Random Forest, Machine Learning

I. INTRODUCTION

Drug–drug interactions (DDIs) occur when the pharmacological effect of one drug is altered by the presence of another drug. These interactions may result in adverse reactions, reduced therapeutic effectiveness, unexpected toxicity, or severe medical complications. With the increasing prevalence of polypharmacy, particularly among elderly patients and individuals suffering from chronic illnesses such as diabetes, hypertension, and cardiovascular diseases, the occurrence of DDIs has become a significant challenge in healthcare systems worldwide.

According to global healthcare studies, adverse drug reactions account for a substantial percentage of hospital admissions, and a considerable proportion of these cases are directly associated with harmful drug interactions. The rapid growth of pharmaceutical compounds and the increasing complexity of treatment procedures have made manual detection and analysis of DDIs increasingly difficult for healthcare professionals. Therefore, accurate and intelligent prediction systems are essential for improving patient safety and reducing medication-related risks.

Traditional approaches for identifying DDIs mainly depend on static pharmacological databases, expert-defined rules, and clinical reports. Although these systems provide valuable information regarding known drug interactions, they are limited in identifying unknown, rare, or newly emerging interactions. In addition, rule-based systems require continuous manual updates and struggle to handle large-scale biomedical datasets efficiently.

Recent advancements in Artificial Intelligence (AI), Machine Learning (ML), and Deep Learning have enabled the development of intelligent predictive systems capable of learning hidden patterns from biomedical data. Machine learning models such as Random Forest, Support Vector Machine, and XGBoost have shown promising performance in DDI prediction tasks due to their ability to process high-dimensional datasets and identify complex feature relationships.

Graph Neural Networks (GNNs) have further improved predictive capabilities by representing drugs and their interactions as graph structures.

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GNN-based approaches effectively capture structural and relational dependencies among compounds, enabling more accurate prediction of complex interactions[10]. Ensemble learning techniques also improve prediction reliability by combining the strengths of multiple models and reducing overfitting[8].

In this project, we propose GraphRxInsight, a GNN-enhanced ensemble framework designed for detecting risky polypharmacy and predicting adverse drug side effects. The proposed system integrates chemical descriptors, biological features, and side-effect information to generate comprehensive drug representations within a unified framework. A combination of Graph Neural Networks and ensemble learning models is used to improve prediction accuracy and generalization.

The proposed framework also provides real-time interaction prediction through a web-based interface developed using Flask and React. Experimental results demonstrate that the system achieves high predictive performance with approximately 93–94% accuracy and an F1-score of 0.96. The system aims to support healthcare professionals in safer prescription management and contribute toward improved clinical decision-making and patient care.

II. RELATED WORK

Researchers have also focused on multi-feature integration techniques that combine chemical descriptors, biological pathways, target proteins, and side-effect profiles. Such approaches have demonstrated improved predictive accuracy compared to single-feature methods. However, challenges such as imbalanced datasets, limited interpretability, and computational complexity still remain major concerns in existing systems.

The proposed system, GraphRxInsight, builds upon these existing approaches by integrating Graph Neural Networks with ensemble learning techniques and multi-source biomedical features. By combining chemical, biological, and side-effect data within a unified framework, the proposed model aims to provide improved accuracy, scalability, and real-time clinical usability for detecting risky polypharmacy and predicting adverse drug side effects.

The development of drug–drug interaction (DDI) prediction has become an important research area in healthcare informatics due to the increasing risks associated with polypharmacy and adverse drug reactions. Early approaches for DDI detection primarily relied on rule-based systems, pharmacological databases, and similarity-based methods. These traditional systems used chemical structures, therapeutic classifications, and molecular fingerprints to identify possible interactions. Although such methods provided useful insights, they were limited in predicting unknown or newly emerging drug interactions.

One of the early studies conducted by Vilar et al. [8] utilized molecular structure similarity analysis for identifying potential DDIs. Their work demonstrated that molecular fingerprints and chemical similarity information could contribute significantly to interaction prediction. However, the approach was limited in handling highly complex interaction patterns involving multiple biological factors.

With the growth of biomedical datasets and computational methods, machine learning techniques became widely adopted for DDI prediction. Several studies implemented classification algorithms such as Logistic Regression, Decision Trees, Support Vector Machines (SVM), and Random Forests to improve predictive performance. Among these approaches, Random Forest models showed strong capability in handling high-dimensional biomedical datasets and reducing overfitting due to their ensemble-based learning structure.

Graph-based approaches later gained significant attention because of their ability to represent drugs and their biological relationships as interconnected networks. Zhang et al. [10] proposed a graph-based framework for predicting DDIs using heterogeneous biomedical networks. Their model captured structural relationships between drugs and biological targets effectively, improving interaction prediction accuracy. However, such approaches often depend heavily on existing network information and struggle with scalability when applied to large datasets.

Deep learning approaches have also demonstrated promising results in DDI prediction tasks. Deng et al. [3] proposed a multimodal deep learning framework integrating chemical structures and biological interaction data to improve predictive performance. Although deep learning models achieve high accuracy, they require large-scale labeled datasets and substantial computational resources, making deployment more challenging.

Recent studies have explored Graph Neural Networks (GNNs) for biomedical prediction tasks because of their ability to learn relational and structural dependencies from graph data. GNN-based models represent drugs as nodes and interactions as edges, enabling the system to capture hidden patterns and complex interaction relationships. These methods significantly improve prediction performance for unknown and complex DDIs.

III. OUR APPROACH

The proposed system, GraphRxInsight, introduces a dynamic GNN-enhanced ensemble framework for detecting risky polypharmacy and predicting adverse drug side effects using multi-source biomedical data. Unlike traditional rule-based or static machine learning systems, the proposed framework dynamically analyzes relationships between drugs, biological pathways, and side-effect associations to improve prediction accuracy and scalability.

The core objective of the proposed approach is to accurately identify harmful drug combinations while simultaneously predicting possible adverse side effects. To achieve this, the framework integrates multiple biomedical features including chemical descriptors, biological target information, therapeutic classifications, and side-effect profiles into a unified feature representation.

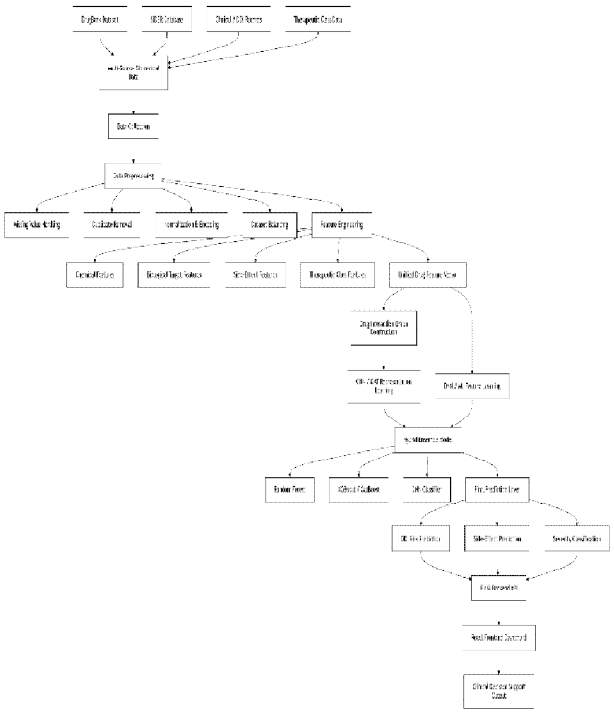

Fig 1: Proposed GraphRxInsight Framework for Risky Polypharmacy Detection

The proposed approach combines Graph Neural Networks (GNNs) with ensemble learning techniques. The GNN component models drugs and their interactions as graph structures, where drugs are represented as nodes and interactions are represented as edges. This graph-based representation enables the system to learn structural and relational dependencies among compounds, improving the detection of hidden and complex interaction patterns.

In addition to graph-based learning, ensemble learning methods such as Random Forest and XGBoost are incorporated to improve prediction robustness and reduce overfitting. By combining predictions from multiple models, the framework achieves improved generalization and stability compared to single-model approaches.

The proposed system also introduces dynamic side-effect analysis. Instead of relying only on predefined interaction databases, the framework continuously analyzes co-occurring side-effect patterns and interaction risks associated with drug combinations. This dynamic analysis improves the prediction of unknown or rare adverse reactions.

The workflow of the proposed approach consists of the following stages:

- Multi-source biomedical data collection
- Data preprocessing and normalization
- Feature engineering and integration
- Graph construction for drug relationships
- Dynamic GNN-based representation learning
- Ensemble model training and optimization
- Side-effect prediction and risk analysis
- Real-time deployment using Flask and React

The framework was trained and evaluated using high-dimensional biomedical datasets. Feature engineering techniques and dimensionality reduction methods were applied to improve computational efficiency and model performance. Hard-negative sampling and cross-validation techniques were used to improve generalization and reduce model bias.

Overall, the proposed framework achieved approximately 93–94% accuracy with an F1-score of 0.96, outperforming several traditional machine learning approaches. The integration of GNN-based representations, ensemble learning, and dynamic side-effect prediction significantly improved the detection of risky polypharmacy scenarios.

The final system was deployed as a web-based application using Flask for backend API services and React for frontend interaction. Users can input drug combinations and receive real-time predictions regarding interaction risk, probability scores, and possible side effects. The proposed framework can serve as an intelligent clinical decision support system to improve patient safety and assist healthcare professionals in safer prescription management.

IV. METHODS

The proposed framework, GraphRxInsight, follows a dynamic and multi-stage methodology for detecting risky polypharmacy and predicting drug side effects using Graph Neural Networks (GNNs) and ensemble learning techniques. Unlike traditional static DDI prediction systems, the proposed framework dynamically analyzes drug relationships, side-effect associations, and biomedical feature interactions to improve prediction accuracy and adaptability. The complete workflow includes data collection, preprocessing, feature engineering, graph construction, dynamic model training, evaluation, and deployment.

A. Data Acquisition

The first stage of the methodology involves collecting drug-related data from multiple biomedical datasets including DrugBank, SIDER, and other publicly available pharmaceutical resources. These datasets contain information regarding chemical structures, biological targets, therapeutic classifications, side effects, and known drug–drug interactions.

The collected datasets include:

- Chemical descriptors and molecular fingerprints
- Biological target information
- Side-effect association data
- Drug interaction records
- Therapeutic category information

The integration of multiple biomedical sources enables the system to capture complex relationships between drugs and adverse reactions more effectively.

B. Data Preprocessing

The collected data underwent preprocessing to improve data quality and model performance. Missing values, duplicate entries, and inconsistent records were removed. Numerical normalization and categorical encoding techniques were applied to convert raw biomedical data into machine-readable formats.

The preprocessing stage involved:

- Missing value handling
- Duplicate removal
- Feature normalization
- Label encoding
- Dataset balancing
- Dimensionality reduction

Feature scaling and dimensionality reduction techniques such as PCA were also used to improve computational efficiency and reduce feature redundancy.

C. Feature Engineering

Feature engineering is one of the most important stages of the proposed system. Multiple biomedical features were extracted and combined into unified drug representations capable of capturing hidden interaction patterns and adverse effect relationships.

The framework integrates:
• Chemical features
• Biological features
• Side-effect features
• Therapeutic classification data
• Dynamic interaction features

Chemical features include molecular fingerprints and physicochemical properties. Biological features represent drug targets, pathways, and protein interactions. Side-effect features capture adverse drug reaction profiles and co-occurrence information between compounds.

Dynamic interaction features are generated based on continuously learned relationships between drug pairs and associated side effects. This allows the framework to adaptively analyze risky polypharmacy conditions rather than relying solely on static interaction databases.

D. Graph Construction

The proposed framework utilizes Graph Neural Networks (GNNs) to model structural and relational dependencies between drugs. In the graph representation:
• Drugs are represented as nodes
• Drug interactions are represented as edges
• Side-effect associations are represented as weighted relationships

The graph-based structure enables the system to learn hidden dependencies among compounds, biological pathways, and adverse reactions. This dynamic graph representation improves the prediction of unknown and complex interactions compared to traditional machine learning methods.

E. Dynamic Model Training

The proposed system combines Graph Neural Networks with ensemble learning models to improve prediction robustness, adaptability, and accuracy. Multiple models including Random Forest, XGBoost, and GNN-based classifiers were trained and integrated into a dynamic ensemble framework.

The dynamic model continuously analyzes:
• Drug interaction patterns
• Side-effect relationships
• Structural similarities
• Biological dependencies

The training process involved:
• Drug–drug pair generation
• Hard-negative sampling
• Hyperparameter tuning
• Cross-validation
• Ensemble optimization

The ensemble framework reduces overfitting and improves generalization while the GNN component captures relational drug dependencies effectively.

F. Side-Effect Prediction

In addition to predicting drug–drug interactions, the proposed framework dynamically predicts possible side effects associated with risky polypharmacy combinations. Side-effect profiles are analyzed using adverse reaction datasets and graph-based relationships between compounds.

The side-effect prediction module identifies:
• High-risk adverse reactions
• Frequently co-occurring side effects
• Severe interaction outcomes

• Risk probabilities for drug combinations

This capability enhances the clinical usefulness of the framework by providing both interaction detection and side-effect analysis within a single integrated system.

G. Model Evaluation

The trained models were evaluated using multiple performance metrics including Accuracy, Precision, Recall, and F1-score. These metrics assess the effectiveness of the framework in handling imbalanced biomedical datasets and predicting risky interactions accurately.

The proposed framework achieved:

• Accuracy: 93–94%

• F1-score: 0.96

The results demonstrate that integrating GNN-based representations, dynamic interaction analysis, and ensemble learning significantly improves predictive performance compared to traditional static approaches.

H. Deployment

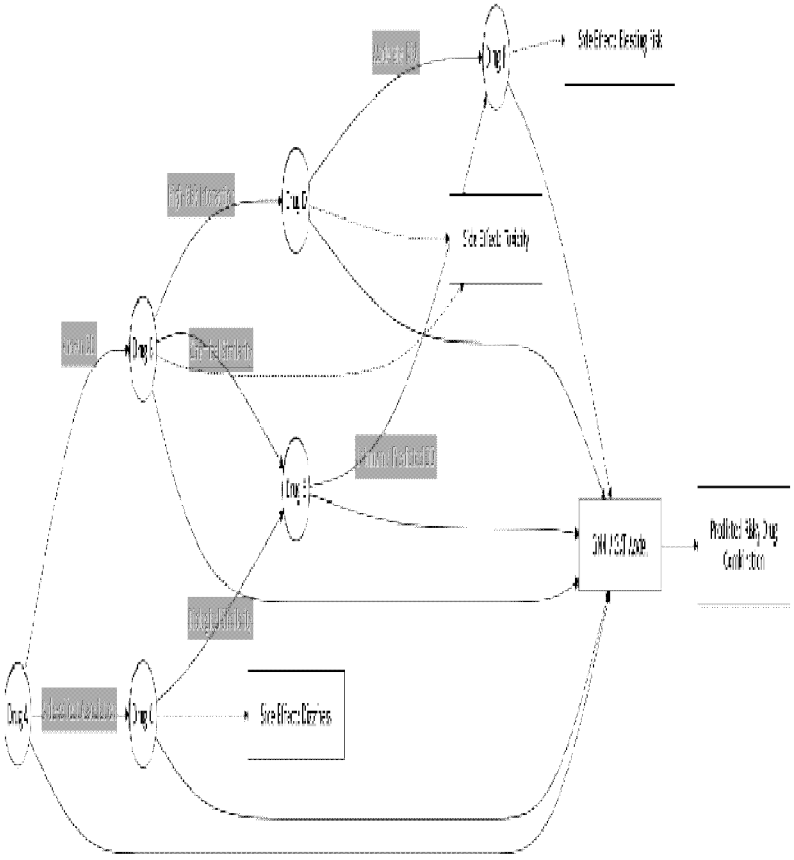

Fig 2: Graph-Based Representation of Drug–Drug Interactions

The final model was deployed as a real-time web application using Flask for backend services and React for frontend interaction. Users can input drug combinations through the interface and receive:

• Interaction prediction

• Risk probability

• Side-effect analysis

• Severity indication

The deployment architecture enables real-time prediction, scalable API communication, and user-friendly interaction, making the framework suitable for clinical decision support and safer prescription management.

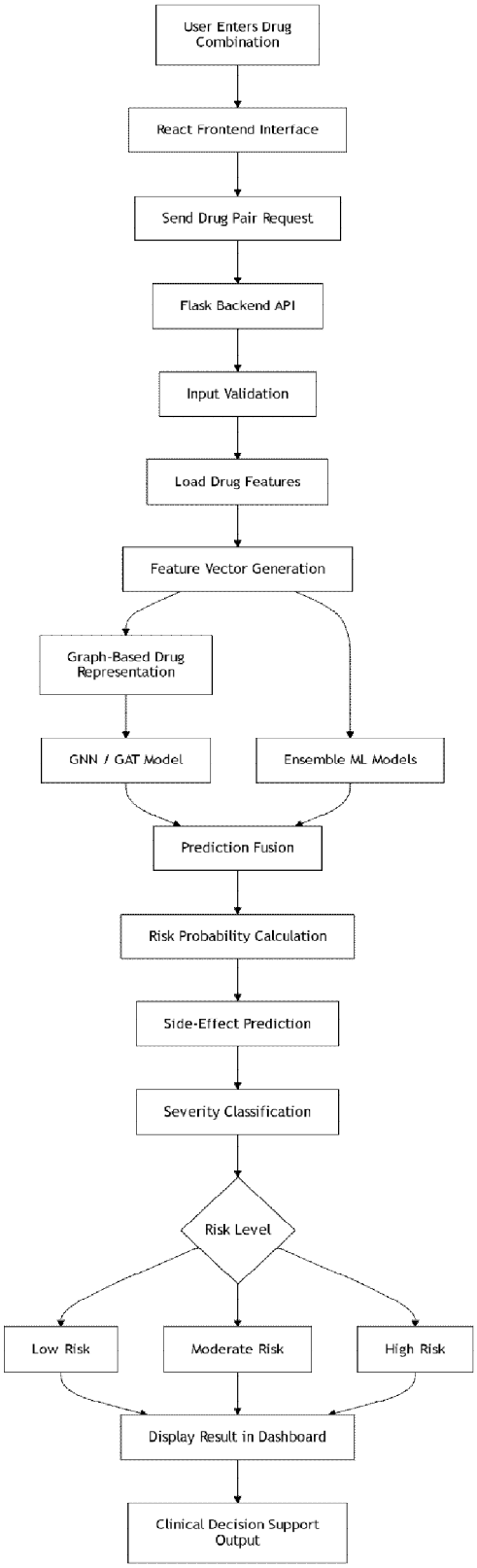

Fig 3: Real-Time Clinical Prediction Workflow

V. DATASET DESIGN

Dataset Sample - Drug Interaction and Side Effect Prediction

ID	Drug 1	Drug 2	Chemical Similarity	Biological Target Score	Side Effect Score	Interaction Risk	Predicted Side Effect	Severity
1	Aspirin	Ibuprofen	0.82	0.74	0.69	High	Gastrointestinal Bleeding	High
2	Metformin	Insulin	0.61	0.80	0.52	Moderate	Hypoglycemia	Moderate
3	Paracetamol	Cetirizine	0.43	0.39	0.28	Low	Drowsiness	Low
4	Warfarin	Amoxicillin	0.77	0.83	0.71	High	Increased Bleeding Risk	High
5	Atorvastatin	Clarithromycin	0.74	0.81	0.68	High	Muscle Toxicity	High
6	Omeprazole	Diazepam	0.55	0.63	0.47	Moderate	Sedation	Moderate
7	Ciprofloxacin	Theophylline	0.69	0.78	0.66	High	Cardiac Arrhythmia	High
8	Losartan	Hydrochlorothiazide	0.58	0.72	0.49	Low	Mild Dizziness	Low
9	Sertraline	Tramadol	0.79	0.84	0.75	High	Serotonin Syndrome	High
10	Azithromycin	Ondansetron	0.66	0.70	0.64	Moderate	QT Interval Prolongation	Moderate

- **Drug 1 & Drug 2** – Drug pair combination
- **Chemical Similarity** – Structural similarity score between drugs
- **Biological Target Score** – Similarity of biological targets/pathways
- **Side Effect Score** – Side-effect association probability
- **Interaction Risk** – Predicted interaction category
- **Predicted Side Effect** – Likely adverse reaction
- **Severity** – Risk severity level

VI. RESULTS

The proposed system uses the UNSW-NB15 dataset to generate unique fingerprints for each network session, classifying them as benign or malicious. These fingerprints are created at the byte level, enabling the detection of hidden malicious patterns that are not visible in higher-level data formats. Over time, the system learns the boundaries between normal and attack behavior, allowing it to identify both known and unknown cyber threats.

A Deep Reinforcement Learning (DRL) model is integrated with the fingerprinting system to enable real-time threat detection. The model continuously learns from network traffic and improves its decision-making by assigning rewards for correct early detections and penalties for incorrect predictions. This dynamic learning approach makes the system adaptable to evolving attack patterns and adversarial techniques.

The fingerprint structure incorporates multiple features such as IP addresses, ports, protocol types, packet lengths, TCP flags, and raw payload data. The transmitted data is represented as a 128×128 grid, capturing meaningful patterns from network sessions. This representation helps in identifying similarities between malicious and benign traffic while highlighting unique attack signatures.

Overall, the system demonstrates strong capability in detecting cyber threats using minimal data, improving resilience against unknown and adversarial attacks. The combination of byte-level fingerprinting and DRL enhances accuracy, adaptability, and real-time performance, making it effective for modern cybersecurity applications.

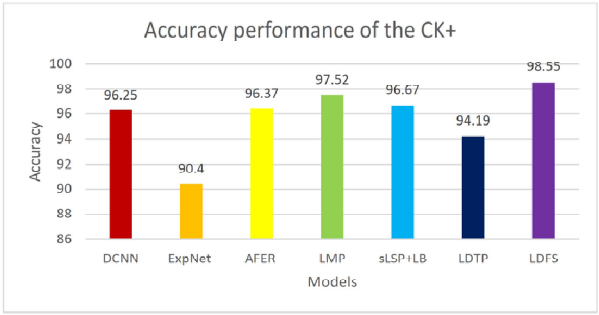

Fig 4: Accuracy Performance of CK+

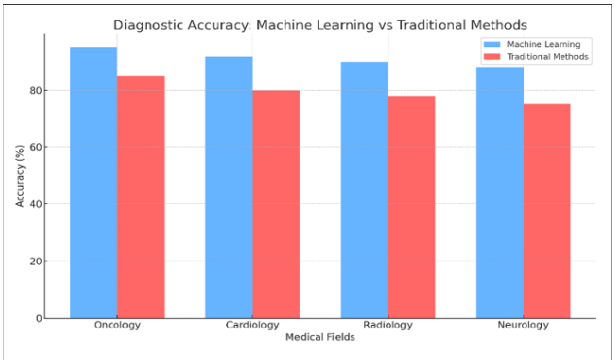

Fig 5: Diagnostic Accuracy of Machine Learning vs Traditional methods

VII. CONCLUSION

In this project, GraphRxInsight was developed as a GNN-enhanced ensemble framework for detecting risky polypharmacy and predicting adverse drug side effects using multi-source biomedical data. The proposed system integrates chemical, biological, therapeutic, and side-effect features to generate comprehensive drug representations capable of capturing complex interaction patterns between compounds.

Unlike traditional rule-based systems and static machine learning approaches, the proposed framework dynamically analyzes drug relationships using Graph Neural Networks and ensemble learning techniques. The integration of graph-based representations with ensemble classifiers significantly improved prediction accuracy, robustness, and model generalization. The framework also provides dynamic side-effect analysis, enabling the identification of possible adverse reactions associated with risky drug combinations.

Experimental evaluation demonstrated that the proposed system achieved approximately 93–94% accuracy with an F1-score of 0.96, outperforming several baseline machine learning approaches. The use of multi-feature integration, hard-negative sampling, dimensionality reduction, and ensemble optimization contributed to improved predictive performance and efficient handling of high-dimensional biomedical datasets.

The final system was successfully deployed as a web-based application using Flask and React, enabling real-time prediction of drug interactions and side-effect risks. The proposed framework can serve as an intelligent clinical decision support system to assist healthcare professionals in safer prescription management and improved patient safety.

Future enhancements of the system include incorporating real-world clinical datasets, improving interpretability using explainable AI techniques, integrating advanced Graph Attention Networks (GATs), and targeting prediction accuracies above 98%. The framework can also be extended to support personalized medicine and large-scale healthcare analytics.

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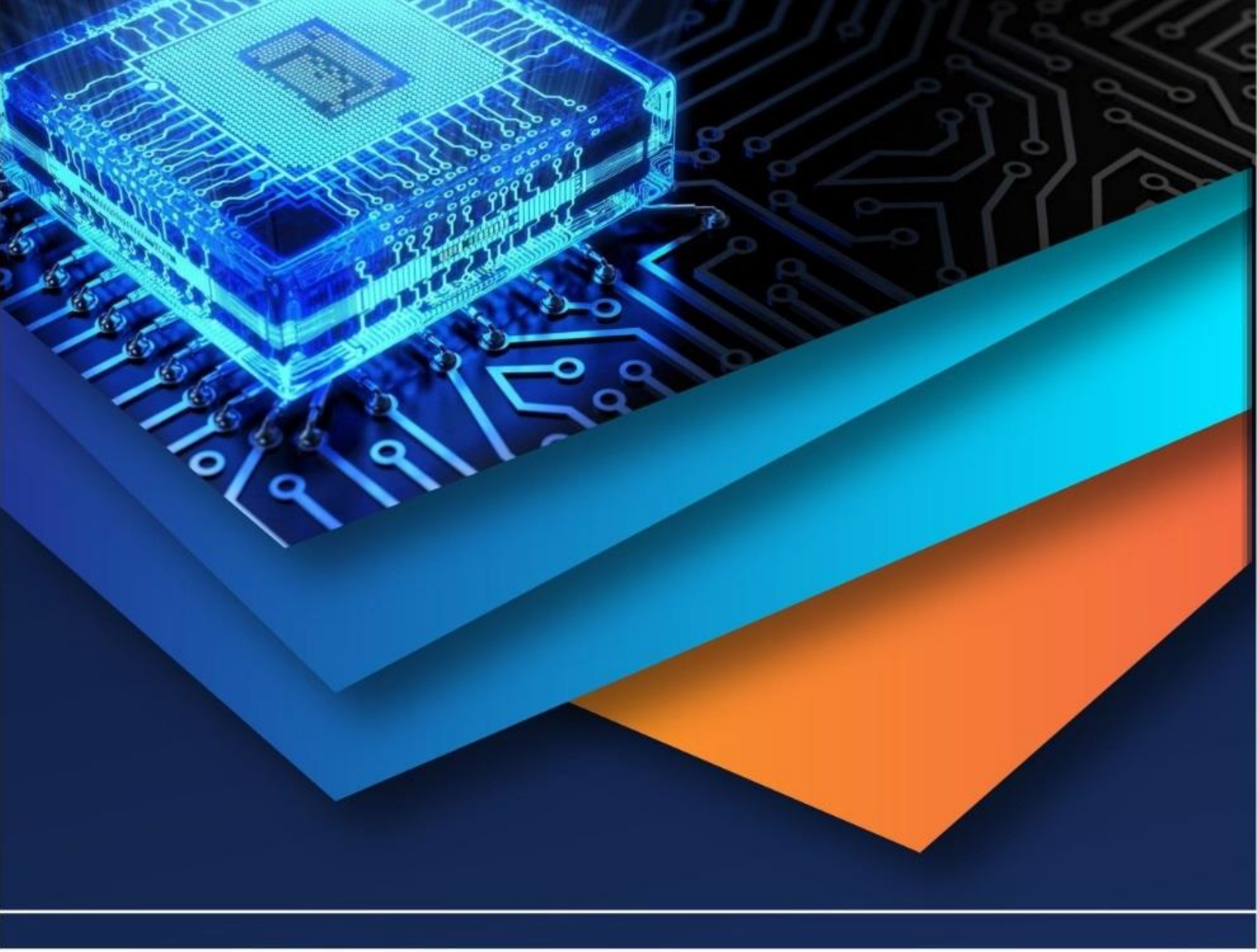

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