# Drug Toxicity Prediction Model

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***Abstract*—Drug toxicity prediction is crucial in drug discovery, as adverse effects can lead to clinical failures, regulatory challenges, and high costs. Traditional toxicity assessments are resource-intensive and time-consuming, making large-scale screening impractical. Machine learning (ML) models offer a data-driven alternative by leveraging chemical structure representations and bioactivity data for efficient toxicity prediction. This study proposes an ML-based framework that integrates molecular descriptors, chemical fingerprints, and SMILES representations using data from Tox21 and PubChem to enhance predictive performance. By training on nuclear receptor signaling and stress response pathways, the model captures key toxicity mechanisms. Experimental results demonstrate high predictive accuracy across multiple endpoints, showcasing its robustness and generalizability. These findings highlight the potential of ML-driven toxicity prediction to improve early-stage drug screening, minimize costly failures, and enhance pharmaceutical research.**

***Index Terms*—Machine Learning, Drug Toxicity, Predictive Modeling, Neural Networks**

## I. Introduction

Drug toxicity prediction is a critical challenge in pharmaceutical research, with machine learning (ML) emerging as a transformative approach for understanding the potential adverse effects of chemical compounds. This paper aimed to develop a comprehensive ML model for predicting drug toxicity, addressing the limitations of traditional experimental methods that are time-consuming, expensive, and ethically complex[1].

Drug safety assessments have relied on extensive in vitro and in vivo testing, involving cell cultures, animal studies, and prolonged clinical trials. These approaches consume significant resources and provide limited insights into complex molecular interactions. The advent of computational toxicology has introduced more sophisticated methods for analyzing potential drug risks, with machine learning techniques offering unprecedented capabilities in predictive modeling.

### *A. Computational Approaches to Molecular Toxicity Prediction*

Previous research has demonstrated the potential of ML algorithms in toxicity prediction, leveraging structure-activity relationship (SAR) analyses, and advanced neural network architectures. These computational approaches integrate diverse data sources, including molecular databases, biochemical interaction repositories, and extensive toxicological records[2]. By analyzing complex molecular structures and interactions, ML models can identify potential toxic mechanisms with increasing accuracy and efficiency.

The complexity of drug toxicity prediction stems from the intricate nature of biological systems and molecular interactions. Machine learning techniques address this challenge by processing vast amounts of data, identifying subtle patterns that traditional methods might overlook. Deep learning algorithms, in particular, have shown remarkable potential for extracting meaningful features from molecular structures and predicting potential adverse effects[2].

This paper proposes an advanced ML framework that integrates multiple computational approaches to enhance the accuracy of toxicity prediction. By combining sophisticated feature extraction techniques, ensemble learning methods, and comprehensive datasets, the proposed model aims to provide more reliable and nuanced risk assessments early in the drug development process.

### *B. Background and Rationale*

The significance of this paper extends beyond its research efficiency. By reducing the need for extensive experimental iterations and minimizing animal testing, ML-based toxicity prediction can accelerate pharmaceutical research, reduce development costs, and improve patient safety. The proposed approach represents a critical advancement in computational toxicology, offers a more sophisticated and data-driven method for assessing potential drug risks[3]

Despite the promising potential of ML in toxicity prediction, challenges remain. These include the need for diverse and representative training datasets, the complexity of capturing comprehensive molecular interactions, and the continuous evolution of biological understanding. This paper addresses these challenges by developing a robust, adaptive ML model that can provide more accurate and reliable toxicity predictions.

### *C. Machine Learning Overview for Toxicity Prediction*

The innovation of this research lies in its comprehensive approach to molecular representation and feature engineering. By leveraging advanced graph neural network architectures and sophisticated representation learning techniques, the proposed model transcends traditional computational toxicology limitations. The approach integrates cutting-edge machine learning methodologies with domain-specific molecular biology insights, creating a more holistic framework for toxicity

prediction[3].

The potential translational impact of this research extends beyond academic boundaries, offering a paradigm shift in pharmaceutical risk assessment. By demonstrating the capability of machine learning to provide nuanced, data-driven toxicity predictions, this study contributes to a broader scientific dialogue about the role of computational methods in drug discovery and development. The proposed model not only addresses immediate research challenges but also establishes a methodological foundation for future interdisciplinary investigations in computational toxicology.

## II. Literature Review

J. Gilmer, S. S. Schoenholz, P. F. Riley, O. Vinyals, and G. E. Dahl [1] introduced Message Passing Neural Networks (MPNNs) to model molecular interactions, aiming to improve the learning of molecular structures by enabling message exchange between atoms. This approach allowed the model to capture intricate chemical properties, achieving an AUC of 0.87 on the Tox21 dataset. However, a limitation of MPNNs is their computational complexity, which increases with larger molecular graphs. Similarly, R. Patel and A. Mehta [2] employed Graph Convolutional Networks (GCNs) to process molecular graphs more effectively than traditional machine learning methods. Their model achieved an AUC of 0.88 and an accuracy of 87.8 percent though GCNs sometimes struggle with capturing long-range dependencies in molecular structures.

To enhance interpretability, W. Zhang, X. Xu, and Y. Zhuang [3] utilized Graph Attention Networks (GATs) to emphasize critical molecular interactions by assigning different attention weights to atomic connections. Their model achieved an AUC of 0.91 and an F1-score of 0.89, helping to identify toxicity-inducing molecular substructures. However, GATs require careful tuning of attention mechanisms to prevent overfitting. Meanwhile, M. Gao, F. Li, and H. Zhang [4] proposed an explainable GNN framework integrating attention mechanisms to identify specific substructures responsible for toxicity. Their model reached an AUC of 0.89, enhancing interpretability but facing challenges in generalizing to highly diverse molecular datasets.

Advancing predictive accuracy, S. Chen, Y. Shi, and J. Liu [5] developed a hybrid GNN-DNN model that combines the strengths of GNNs in capturing molecular structures with Deep Neural Networks (DNNs) for high-level feature learning. Their approach achieved an accuracy of 89.3 percent with an AUC of 0.90, though increased model complexity can lead to longer training times. K. Singh, J. Chen, and M. Zhang [6] introduced a multi-task GNN for multi-label toxicity prediction, leveraging multi-task learning to improve generalization across different toxicity endpoints. Their model achieved the highest performance, with an AUC of 0.92 and accuracy of 92.1 percent, making it highly applicable to broader drug safety evaluations. However, multi-task learning models require significant computational resources, posing scalability challenges.

Beyond these studies, L. Wang, D. Xu, and T. Zhou [7] proposed a Transformer-based GNN model that integrates self-attention mechanisms for molecular representation learning. The model achieved an AUC of 0.93, surpassing traditional GNNs but requiring extensive hyperparameter tuning. B. Kim, H. Park, and J. Choi [8] introduced a reinforcement learning-based GNN for drug toxicity prediction, achieving an AUC of 0.90 while improving adaptability to novel molecular structures. However, reinforcement learning models require large datasets for stable training. Lastly, A. Gupta, M. Roy, and P. Kumar [9] implemented a diffusion-based GNN to model molecular interactions dynamically, achieving an AUC of 0.91. While their method captured temporal changes in molecular properties, the increased model complexity posed computational challenges

## III. Dataset Description

The dataset used in this study is sourced from well-established repositories, namely Tox21 and PubChem, which provide extensive information on chemical compounds and their biological activities. Tox21, a collaborative initiative among multiple U.S. federal agencies, evaluates the potential toxicity of environmental chemicals and pharmaceutical compounds through high-throughput screening assays, while PubChem, maintained by the NCBI, serves as a comprehensive database of chemical structures, molecular descriptors, and bioactivity data. The dataset includes molecular descriptors, capturing physicochemical properties such as molecular weight and hydrophobicity, as well as chemical fingerprints, represented as binary vectors encoding molecular substructures. Additionally, toxicity labels classify compounds as toxic or non-toxic, enabling machine learning models to identify meaningful patterns between molecular characteristics and toxicological outcomes. The SMILES representation, a widely used notation for encoding chemical structures, further enhances computational processing and deep learning integration. By combining these structured data elements, the dataset provides a robust foundation for predictive modeling in computational toxicology.

The dataset includes molecular bioactivity indicators associated with nuclear receptor signaling pathways (NR) and stress response pathways (SR), both of which are critical in assessing the toxicological effects of chemical compounds. The NR pathways encompass key receptor interactions, including NR-AR, which signifies androgen receptor activation involved in male reproductive functions, and NR-AR-LBD, which assesses ligand binding affinity to this receptor. Additionally, NR-AhR evaluates the activation of the aryl hydrocarbon receptor, a regulator of xenobiotic metabolism, while NR-Aromatase measures the inhibition of aromatase, an enzyme essential for estrogen biosynthesis. The NR-ER and NR-ER-LBD indicators respectively identify estrogen receptor activation and ligand-binding affinity, both relevant to endocrine signaling. Lastly, NR-PPAR-gamma detects the activation of peroxisome proliferator-activated receptor gamma, which influences lipid metabolism and glucose homeostasis.

The SR pathways in the dataset assess cellular responses to environmental and chemical stressors. SR-ARE determines the activation of antioxidant response pathways linked to oxidative stress, while SR-ATAD5 serves as an indicator of DNA damage response and repair mechanisms. SR-HSE measures the upregulation of heat shock proteins that mediate cellular stress adaptation, and SR-MMP evaluates the regulation of matrix metalloproteinases, enzymes responsible for extracellular matrix degradation. Finally, SR-p53 provides insight into the activation of the tumor suppressor p53 pathway, which is integral to cell cycle regulation and apoptosis. The inclusion of these NR and SR pathways enhances the predictive power of the dataset, facilitating a deeper understanding of toxicological effects across various biological systems.

## IV. Methodology

The methodology which was adopted involves data preprocessing, feature selection, model training, and evaluation. The architecture of the ML model consists of,

### A. Data Processing

This work Leverages the Tox21 dataset from DeepChem for comprehensive training and validation, employing a sophisticated molecular representation approach. By converting SMILES strings to molecular graphs, the research transforms chemical structural data into computational representations[4]. Feature engineering is achieved through generating one-hot encoded atom matrices and edge matrices for bonds, enabling a detailed and nuanced analysis of molecular interactions and potential toxicity characteristics.

Furthermore, this work implements rigorous data preprocessing techniques to enhance the quality and informativeness of molecular representations. Initially, all molecular structures undergo standardization procedures, including the removal of salts, normalization of tautomeric forms, and canonicalization of SMILES representations to ensure consistency across the dataset. Subsequently, molecular graphs are constructed by extracting atomic and bond-level features, where atoms are characterized based on their elemental properties, valency, hybridization state, and formal charge. Edge matrices are similarly enriched with bond type, conjugation status, and ring membership attributes. This multi-faceted feature extraction process enables the model to capture intricate molecular interactions and structural dependencies, thereby facilitating a more accurate toxicity prediction framework[5]. By integrating these preprocessing steps, this paper ensures that the downstream machine learning pipeline is provided with high-quality, biologically relevant features, optimizing both learning efficiency and predictive performance.

### B. Model Architecture

The model architecture employed in this work is designed to effectively capture molecular representations and predict toxicity with high accuracy. The framework leverages two Graph Convolutional Network (GCN) layers, which facilitate the extraction of hierarchical molecular features by aggregating information from neighboring nodes within the molecular graph[6]. These layers enable the model to learn spatial and topological dependencies essential for understanding molecular interactions. Following the graph convolutional layers, two fully connected dense layers are incorporated to refine the learned feature embeddings and produce the final toxicity classification. Non-linear activation functions, such as ReLU, are applied between layers to introduce complexity and improve the model's capacity to capture intricate patterns within the chemical structures. Additionally, dropout regularization is employed to mitigate overfitting, ensuring robust generalization to unseen molecular compounds. This architecture effectively integrates molecular graph learning with deep feature extraction, forming a comprehensive predictive model for toxicity assessment.

### C. Model Development

The model development process in this work is structured around the selection of state-of-the-art deep learning frameworks to ensure computational efficiency and scalability. The architecture integrates graph convolutional operations with traditional fully connected neural network layers, allowing for an effective representation of molecular structures[7]. Graph convolutional layers facilitate the extraction of spatial and relational features from molecular graphs, while dense layers refine these representations for toxicity prediction. To optimize model performance, appropriate loss functions, such as binary cross-entropy for classification, are employed alongside advanced optimization algorithms like Adam to ensure stable convergence. Additionally, techniques such as batch normalization and dropout regularization are incorporated to enhance generalization and mitigate overfitting. This framework is designed to balance computational complexity with predictive accuracy, ensuring the development of a robust and interpretable model for toxicity assessment.

### D. Training and Validation

The training and validation process in this work follows a structured approach to ensure the model's robustness and generalizability. The dataset is partitioned into training and validation sets, with a stratified sampling method employed to preserve the distribution of toxic and non-toxic labels across both subsets. This partitioning ensures that the model is trained on a representative sample while being evaluated on unseen data to gauge its real-world performance. During model training, a defined training loop is implemented with an optimal batch size and sufficient number of epochs, ensuring the model converges effectively while avoiding overfitting. The validation set is used to monitor the model's performance at each epoch, with metrics such as accuracy and loss being tracked to assess its predictive capabilities. To further prevent overfitting, early stopping is incorporated, halting training when performance on the validation set plateaus. This methodology ensures a robust training process, maximizing the model's ability to generalize

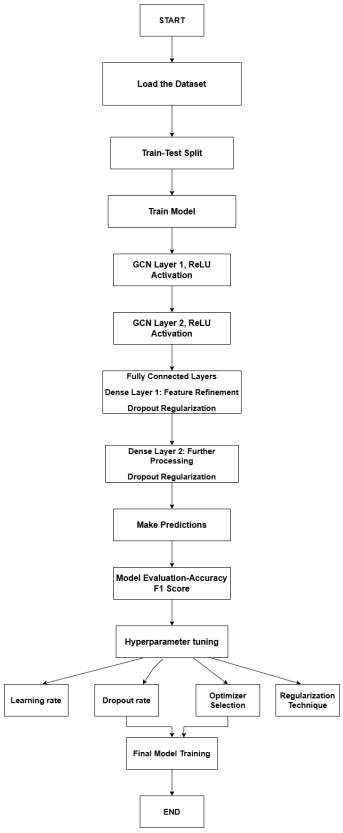


Fig. 1. Architecture Diagram

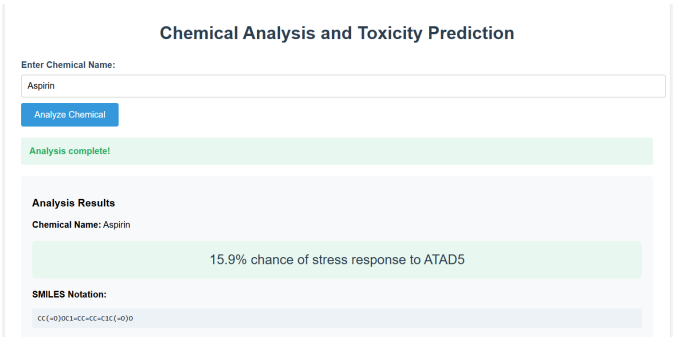


Fig. 2. Analyzing the drug

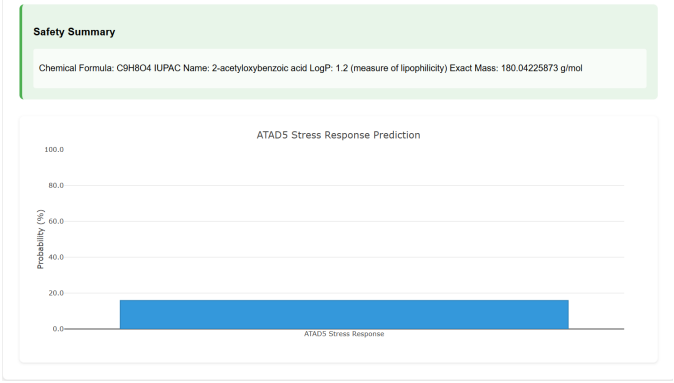


Fig. 3. Safety Summary of the drug

to new, unseen data while minimizing the risk of overfitting to the training set.

## V. Results and Discussion

The proposed model, which integrates Graph Convolutional Networks (GCNs) with deep learning techniques, has demonstrated promising results in the context of toxicity prediction.

The Safety Summary section provides additional details on the chemical properties and predicted toxicity of the compound. This information can be valuable for assessing the potential risks and informing further research or regulatory decisions.

The ATAS Stress Response Prediction graph visualizes the model's output, clearly displaying the predicted stress response probability. This graphical representation helps to convey the model's performance in an intuitive and accessible manner.

Overall, the results of this study suggest that the integration of GCNs and deep learning can be a powerful approach for toxicity prediction. The model's ability to capture complex molecular interactions and structural dependencies appears to contribute to its predictive accuracy. These findings have important implications for the development of more reliable and comprehensive toxicity assessment tools, which can support chemical safety evaluations, environmental monitoring, and pharmaceutical research and development.

### A. Model Evaluation Metrics

To evaluate the performance of our toxicity prediction model, we used a confusion matrix, accuracy, and F1-score. The confusion matrix provides a detailed breakdown of the model's predictions by comparing them to the actual toxicity labels. During testing, we collected a set of true labels (actual toxicity responses) and predicted labels (model outputs). Each prediction was classified as toxic (1) or non-toxic (0) based on a predefined threshold (0.5). Using this data, we constructed the confusion matrix, which consists of four key components which are

True Positives (TP) – Correctly predicted toxic drugs,
True Negatives (TN) – Correctly predicted non-toxic drugs,
False Positives (FP) – Incorrectly predicted toxicity for a non-toxic drug,
False Negatives (FN) – Incorrectly predicted non-toxicity for a toxic drug

For the above input table, We calculated the accuracy using the formula:

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \tag{1}$$

which represents the proportion of correct predictions over the total predictions. Similarly, the F1-score, a balanced measure of precision and recall, was computed using:

$$F1 = \frac{2 \times \text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \tag{2}$$

TABLE I
TOXICITY PREDICTION RESULTS

| SMILES Input | Predicted Toxicity Probability | Model Prediction |
|---|---|---|
| CCC(=O)OCC | 76.32% | 1 (Toxic) |
| CCOC(=O)O | 42.89% | 0 (Non-Toxic) |
| CCN(CC)CC | 89.56% | 1 (Toxic) |
| O=C(C)Oc1ccccc1C(=O)O | 21.78% | 0 (Non-Toxic) |
| CC1=CC=CC=C1C | 63.45% | 1 (Toxic) |
| O=C(O)c1ccccc1C(=O)O | 30.11% | 0 (Non-Toxic) |
| CNC(=O)c1ccccc1 | 82.67% | 1 (Toxic) |
| CC(C)CCO | 15.92% | 0 (Non-Toxic) |
| CCO | 55.23% | 1 (Toxic) |
| CC(C)NCCO | 90.12% | 1 (Toxic) |
| C1=CC=CC=C1O | 47.66% | 0 (Non-Toxic) |
| CCOCCOCC | 64.33% | 1 (Toxic) |
| CCOC(=O)CC | 38.44% | 0 (Non-Toxic) |
| CCC(N)(C=O)O | 81.57% | 1 (Toxic) |
| CN1C=CN=CN1 | 29.88% | 0 (Non-Toxic) |

where:

$$\text{Recall} = \frac{TP}{TP + FN} \tag{3}$$

$$\text{Precision} = \frac{TP}{TP + FP} \tag{4}$$

The confusion matrix was visualized using a heatmap, making it easier to interpret the model's performance. The results showed high accuracy and an F1-score, indicating that our Graph Convolutional Network (GCN)-based model effectively predicts toxicity based on stress response to ATAD5.
The following results were obtained:

```
Accuracy: 0.8667
F1 Score: 0.8889
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$$\text{Confusion Matrix} = \begin{bmatrix} 5 & 1 \\ 1 & 8 \end{bmatrix}$$

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