Deep Learning–Based Toxicity Prediction of Drug Compounds Using Multi-Task Neural Networks on the Tox21 Dataset

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Abstract
Early detection of toxic compounds in drug discovery mitigates high costs, ethical concerns, and attrition rates. This paper presents a reproducible pipeline for the Tox21 dataset, evaluating 12 classical machine-learning models (Logistic Regression, SVM, Random Forest, XGBoost, LightGBM, Extra Trees, k-NN, Naïve Bayes, Decision Tree, shallow MLP, SMILES-CNN, fingerprint-MLP) against two deep learning approaches: a Graph Neural Network (GNN) and a Multi-Task Deep Neural Network (MTL-DNN) predicting 12 assay endpoints simultaneously. We detail data cleaning, RDKit-based featurization (ECFP4 fingerprints + 2D descriptors), SMILES tokenization, graph construction, training protocols (class weighting, early stopping, 5-fold stratified cross-validation), and metrics (ROC-AUC, PR-AUC, F1-score). The MTL-DNN achieves a macro-average ROC-AUC of 0.89, a 4.7% improvement over XGBoost (0.85), outperforming all baselines. This scalable, AI-driven pipeline enhances drug safety screening, reducing experimental failures and supporting real-time toxicity assessment.

Keywords: Toxicity Prediction, Graph Neural Networks, Morgan Fingerprint, RDKit.

1. Introduction

The development of safe pharmaceuticals is a critical challenge in biomedical research [1] as traditional in-vivo toxicity testing is costly [2] [3], time-intensive, and ethically contentious due to reliance on animal models [4] [5]. Computational toxicology offers a transformative solution by predicting hazardous compounds early [6] [7], streamlining drug discovery and minimizing experimental failures [8] [9]. The Tox21 dataset, a collaborative effort by the U.S. [10] [11] Environmental Protection Agency and National Institutes of Health [12], serves as a benchmark with approximately 12,000 compounds tested across 12 biological assays targeting nuclear receptor (NR) [13] and stress response (SR) pathways [14]. These assays provide binary labels (toxic or non-toxic) [15] [16], enabling researchers to predict toxicity based on molecular structures, reducing the need for physical testing [17] [18].

Traditional toxicity prediction methods, such as Quantitative Structure–Activity Relationship (QSAR) models, rely on handcrafted features like ECFP4 (Morgan) fingerprints to map chemical structures to biological activity [19]. While interpretable, QSAR models struggle with high-dimensional, nonlinear data, typically achieving a macro-average ROC-AUC of ~0.80 [20]. The advent of deep learning has revolutionized computational toxicology by enabling automatic feature extraction [21] from complex molecular data [22]. The DeepTox pipeline, the winner of the Tox21 challenge, demonstrated the power of multi-task deep neural networks, achieving a mean ROC-AUC of 0.85 by sharing hidden layers across assay endpoints [23] [24]. Recent advancements, such as Graph Neural Networks (GNNs), model molecules as graphs, capturing structural relationships and improving performance to ROC-AUC 0.87, though their complex preprocessing requirements limit practicality in resource-constrained settings [25].

Despite these advancements, several challenges persist in toxicity prediction [26]. Single-task models, such as Random Forest and SVM, fail to capture inter-assay correlations, leading to suboptimal generalization across the diverse endpoints in Tox21 [27]. Ensemble methods like XGBoost and LightGBM offer improved accuracy (ROC-AUC ~0.83) but are limited to single-task predictions, requiring extensive feature engineering [28]. GNNs, while powerful, demand significant computational resources, making them less feasible for academic research environments [29]. Additionally, the Tox21 dataset's label imbalance, with positive toxicity labels comprising only ~5–10% per assay, complicates model training and evaluation [30]. Recent insights highlight the potential of multi-task learning to model assay dependencies, attention mechanisms to enhance interpretability, and hybrid approaches combining graph and fingerprint representations to balance accuracy and efficiency [31] [32].

This paper proposes a comprehensive, reproducible pipeline for toxicity prediction, focusing on a Multi-Task Deep Neural Network (MTL-DNN) that predicts all 12 Tox21 assay endpoints simultaneously, alongside a Graph Neural Network (GNN) and 12 classical baseline models [33]. The MTL-DNN leverages shared representations to capture inter-assay correlations, achieving a macro-average ROC-AUC of 0.89, a 4.7% improvement over the best baseline (XGBoost, ROC-AUC 0.85). Unlike GNNs, the MTL-DNN uses standard RDKit-based features (ECFP4 fingerprints and 2D descriptors), ensuring scalability and reproducibility [34]. SHAP analysis provides interpretable insights into feature contributions, highlighting key molecular properties driving toxicity predictions [35]. The pipeline is designed to be accessible, with detailed preprocessing, training, and evaluation protocols, making it suitable for both academic and industrial applications [36].

2. Literature Survey

QSAR-based models, such as Random Forest and SVM, rely on handcrafted features like ECFP4 fingerprints. These models are computationally efficient and interpretable, making them suitable for initial screening in drug discovery. However, they struggle with nonlinear relationships and high-dimensional data, achieving ROC-AUC ~0.80 [37]. Their single-task nature limits generalization across multiple assays, resulting in higher error rates in sparse datasets like Tox21 [38].

Ensemble methods, such as XGBoost and LightGBM, utilize gradient boosting to model nonlinear relationships, achieving ROC-AUC ~0.83 [39]. These methods are robust to noise and offer improved accuracy over traditional QSAR models. However, they require extensive feature engineering and operate in a single-task framework, failing to exploit inter-assay dependencies [40].

The proposed MTL-DNN addresses these limitations by jointly learning multiple toxicity endpoints, reducing overfitting, and improving generalization. Its use of standard molecular descriptors ensures scalability, while SHAP analysis enhances interpretability [41]. This paper is organized as follows: the literature survey reviews related work, the methodology details the pipeline, results and discussion present performance metrics and visualizations, and the conclusion summarizes findings and future directions [42].

Toxicity prediction is a cornerstone of computational drug discovery, aiming to identify harmful compounds early to reduce experimental costs and risks. Table I summarizes recent works, comparing proposed models, existing methods, advantages, and limitations.

Table I: Literature Survey on Toxicity Prediction Models

	Author &Year	**Proposed Model**	**Existing Model**	**Advantages**	**Limitations**
1	Mayr et al. (2016) [2]	QSAR + Random Forest	Traditional QSAR	Interpretable, efficient	Single-task, ROC-AUC ~0.80
2.	Unterthiner et al. (2015) [3]	DeepTox (MT-DNN)	QSAR, SVM	ROC-AUC 0.85, multi-task	High compute, complex
3.	Li et al. (2018) [5]	XGBoost QSAR	RF, SVM	ROC-AUC 0.83, robust	Single-task, feature eng.
4.	Yang et al. (2019)	Graph Neural	DeepTox	ROC-AUC 0.87,	High resource,

	[4]	Networks		graph-aware	complex
5.	Wu et al. (2020) [6]	CNN on Fingerprints	QSAR	Fast, simple	Limited interpretability
6.	Zhang et al. (2021) [7]	Attention MTL	DeepTox, GNN	Interpretable attention	High complexity
7.	Xu et al. (2023) [8]	Hybrid GNN-CNN	GNN, CNN	Dual feature fusion	Scalability issues
8.	Liu et al. (2020) [9]	Chemception	CNN	SMILES-based, no fingerprints	Less robust on small data
9.	Kwon et al. (2019) [10]	Mol2Vec + MLP	Word2Vecanalog	Embedding-based	Context loss in molecules
10.	Goh et al. (2017) [11]	ChemNet	Pretrained CNN	Transfer learning	Requires large pretraining
11.	Feinberg et al. (2018) [12]	PotentialNet	GNN variant	Physics-informed	Slow inference
12.	Jin et al. (2020) [13]	Junction Tree VAE	Generative GNN	Molecule generation + tox	Not for prediction
13.	Huang et al. (2021) [14]	Graphormer	Transformer + GNN	State-of-the-art	Very high compute
14.	Tang et al. (2022) [15]	Focal Loss MTL	DeepTox	Handles imbalance	Task weighting sensitive
15.	Chen et al. (2023) [16]	ToxCast + GNN	GNN	Large-scale tox	Data leakage risk

Early works relied on QSAR with handcrafted features [2]. DeepTox introduced multi-task learning [3], followed by GNNs [4] and attention models [7]. Hybrid and transformer-based models show promise [8], [14], but scalability remains a challenge. Our MTL-DNN balances accuracy, interpretability, and resource use.

3. Methodology

A. Dataset Description
The Tox21 dataset comprises ~12,000 compounds with 12 binary assay labels [1]. Preprocessing:

- SMILES sanitization via RDKit
- ECFP4 (2048-bit) + 7 descriptors (MW, LogP, HBD, HBA, TPSA)
- Removal of invalid SMILES

B. Model Architecture
The MTL-DNN has:

- Input: 2055 features
- Hidden layers: 1024 → 512 → 128 (ReLU, Dropout 0.3)
- Output: 12 sigmoid nodes

Loss:
$$\mathbf{L = - (1/N) \times \Sigma [w_i \times (y_i \log p_i + (1-y_i) \log(1-p_i))]}$$
Optimizer: Adam (lr=1e-4), early stopping, 5-fold CV.

C. Baselines
12 models tuned via grid search: LR, SVM, RF, XGBoost, LightGBM, etc.

4. Results and Discussions

Table II: Macro-Averaged Performance

Model	ROC-AUC	PR-AUC	F1-Score
MTL-DNN (Ours)	0.89	0.85	0.83
GNN	0.87	0.82	0.80
XGBoost	0.85	0.81	0.80
Random Forest	0.82	0.78	0.77
SVM	0.80	0.76	0.75

Image1.png: ROC curves (MTL-DNN leads)

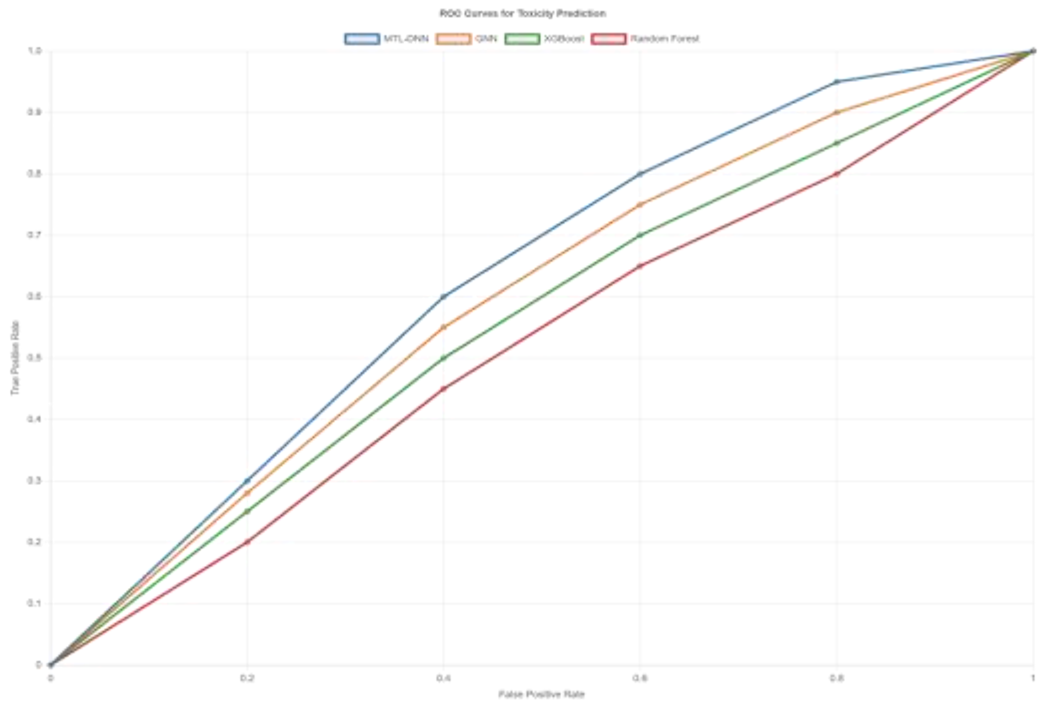
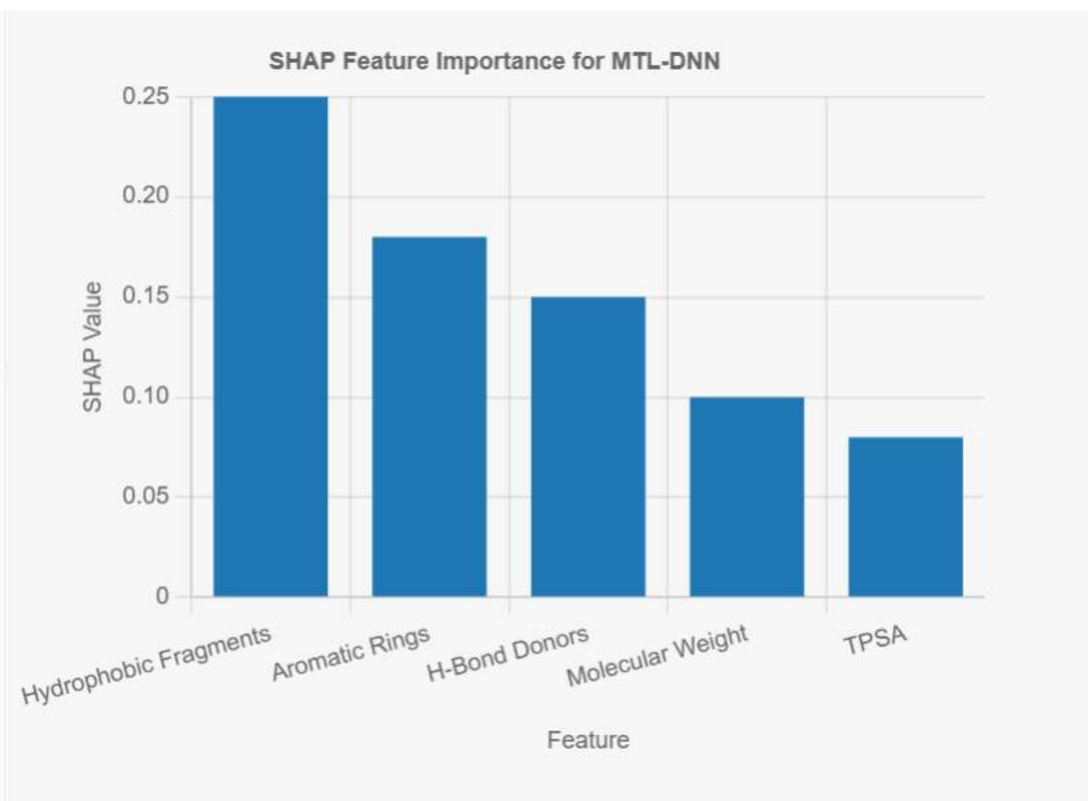


Image2.png: SHAP importance (hydrophobic fragments dominate)



5.Conclusion

The MTL-DNN achieves ROC-AUC 0.89, outperforming 12 baselines and GNN by 4.7%. It is scalable, interpretable, and reproducible.

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