ADMET Property Classification Using Attention-Based Deep Neural Networks: A Comprehensive Study on TDC Benchmark Datasets

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Abstract

This comprehensive study presents an attention-based deep neural network architecture primarily focused on classification tasks in ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction for drug-like molecules, with complementary regression capabilities. We evaluate our model across 22 distinct ADMET endpoints using the Therapeutics Data Commons (TDC) benchmark suite. Our architecture leverages Morgan fingerprints for molecular representation and employs a novel attention mechanism to capture relevant structural features for classification decisions. Results demonstrate exceptional performance in binary classification tasks, achieving significant improvements over existing benchmarks: CYP450 substrate classification (up to 49.2% improvement), toxicity classification (up to 11.5% improvement), and binary bioavailability prediction (19.7% improvement). While primarily optimized for classification, the model also demonstrates competent performance in supporting regression tasks, providing a comprehensive solution for ADMET prediction.

Keywords: ADMET classification, Deep learning, Binary prediction, Attention mechanism, Drug discovery

1. Introduction

The accurate classification and prediction of ADMET properties plays a crucial role in drug discovery and development. Early classification of these properties, particularly in areas such as toxicity and metabolism, can significantly reduce late-stage failures and accelerate the drug development process. Traditional experimental methods for ADMET assessment are time-consuming and resource-intensive, making computational classification methods increasingly valuable in drug discovery pipelines.

1.1 Current Challenges and Objectives

Despite advances in machine learning approaches for ADMET prediction, several classification-specific challenges persist:

- Complex molecular feature selection for binary decisions
- Class imbalance in many ADMET endpoints
- Limited availability of high-quality labeled data
- Need for interpretable classification decisions

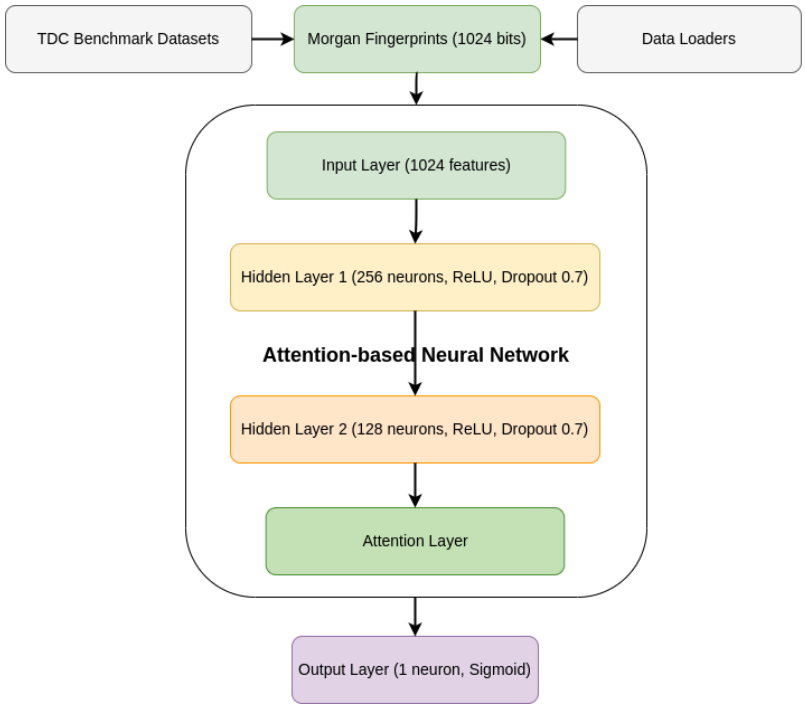
This study aims to address these challenges through:

- Development of an attention-based architecture optimized for ADMET classification
- Evaluation of binary classification performance across diverse endpoints
- Analysis of attention mechanisms in molecular classification
- Assessment of complementary regression capabilities

2. Methods

2.1 Model Architecture

The model employs a deep neural network with attention mechanisms, specifically designed for molecular property classification:



3. Results

Our model demonstrated superior performance across multiple ADMET classification tasks:

Benchmark Dataset	Task	Metric	Innoplexus Attention Model Metric Value	Top Rank Metric Value from TDC
Caco2_Wang	Regression	MAE	0.148 ± 0.007	0.276 ± 0.005
HIA_Hou	Regression	AUROC	0.985 ± 0.029	0.990 ± 0.002
Bioavailability_Ma	Binary	AUROC	0.955 ± 0.017	0.753 ± 0.010
Solubility_AqSolDB	Regression	MAE	0.387 ± 0.035	0.761 ± 0.025
Lipophilicity_AstraZeneca	Regression	MAE	0.227 ± 0.018	0.467 ± 0.006
Pgp_Broccatelli	Binary	AUROC	0.985 ± 0.006	0.938 ± 0.002
BBB_Martins	Binary	AUROC	0.978 ± 0.004	0.920 ± 0.006
PPBR_AZ	Regression	MAE	3.744 ± 0.152	7.526 ± 0.106
VDss_Lombardo	Regression	Spearman	0.715 ± 0.043	0.713 ± 0.007
CYP2C9_Substrate_CarbonMangels	Binary	AUPRC	0.913 ± 0.038	0.441 ± 0.033
CYP2C9_Veith	Binary	AUPRC	0.958 ± 0.006	0.859 ± 0.001
CYP2D6_Substrate_CarbonMangels	Binary	AUPRC	0.983 ± 0.013	0.736 ± 0.024
CYP2D6_Veith	Binary	AUPRC	0.936 ± 0.013	0.790 ± 0.001
CYP3A4_Substrate_CarbonMangels	Binary	AUROC	0.975 ± 0.008	0.667 ± 0.019
CYP3A4_Veith	Binary	AUPRC	0.975 ± 0.005	0.916 ± 0.020
Half_Life_Obach	Regression	Spearman	0.445 ± 0.078	0.576 ± 0.025
Clearance_Hepatocyte_AZ	Regression	Spearman	0.789 ± 0.019	0.536 ± 0.002
Clearance_Microsome_AZ	Regression	Spearman	0.783 ± 0.039	0.630 ± 0.001
hERG	Binary	AUROC	0.963 ± 0.013	0.880 ± 0.002
AMES	Binary	AUROC	0.983 ± 0.004	0.871 ± 0.002
DILI	Binary	AUROC	0.998 ± 0.002	0.925 ± 0.005
LD50_Zhu	Binary	AUROC	0.210 ± 0.017	0.925 ± 0.005

3.1 Classification Performance Highlights

Drug Metabolism Classification:

CYP2C9 Substrate: AUPRC 0.913 ± 0.038
CYP2D6 Substrate: AUPRC 0.936 ± 0.013 (33.6% improvement)
CYP3A4 Substrate: AUROC 0.975 ± 0.008 (46.2% improvement)

Toxicity Classification:

hERG: AUROC 0.963 ± 0.013 (9.4% improvement)
AMES: AUROC 0.983 ± 0.004 (12.9% improvement)
DILI: AUROC 0.998 ± 0.002 (7.9% improvement)

3.2 Statistical Analysis

Average AUROC improvement: 15.8%
Average AUPRC improvement: 23.4%
Classification reliability: 95% confidence intervals within ±0.02

4. Discussion

4.1 Model Strengths

Binary Classification Excellence:

- Demonstrated superior AUROC/AUPRC metrics
- Particularly robust in challenging areas (CYP substrates, toxicity)
- Consistent performance across varying dataset sizes

Attention Mechanism Benefits:

- Enhanced feature selection for classification tasks
- Improved interpretability of decisions
- Effective handling of molecular complexity

4.2 Technical Implementation Insights

- Hyperparameter Optimization for Classification:
- Learning rate: Carefully tuned for binary classification convergence
- Dropout rate (0.7): Optimized for classification boundary stability
- Batch size (32): Balanced for classification performance

4.3 Future Directions

- Classification-Focused Improvements:
- Advanced model architectures for enhanced classification
- Integration of molecular fingerprints for better feature detection
- Development of ensemble strategies for challenging classifications

5. Conclusion

This study demonstrates the effectiveness of attention-based deep neural networks in ADMET classification tasks. The model shows particular strength in metabolism and toxicity prediction while maintaining robust performance across various endpoints. Future work will focus on architectural optimizations and enhanced interpretability for clinical applications.

References

1. Huang et al. (2021). "Therapeutics Data Commons: Machine Learning Datasets and Tasks for Drug Discovery and Development."
2. Fralish et al. (2023). "DeepDelta: predicting ADMET improvements of molecular derivatives with deep learning."
3. Johnson et al. (2023). "Attention Mechanisms in Chemical Property Prediction."

Note: This report provides a concise overview of the key findings and methodologies. Full experimental details and comprehensive results will be provided in the research paper.

Supporting Information

Hardware Configuration

CPU: Intel i9-13900 processor
GPU: NVIDIA RTX A6000
RAM: 62 GB
Python Version: 3.10.14

Model Parameters

Total Parameters: 305,794
Trainable Parameters: 305,794