Advancing ADMET Prediction: A Hybrid Machine Learning Framework (ADMETrix) for Enhanced In Silico Drug Discovery

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This document outlines the development and implementation of a hybrid machine learning framework for improved prediction of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties in the drug discovery process. The prediction of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) properties is a critical bottleneck in the pharmaceutical industry, significantly impacting drug development timelines and costs. Early and accurate in-silico ADMET assessment can de-risk candidates and streamline the discovery pipeline. This report details the performance of a sophisticated, hybrid machine learning (ML) framework Partex ADMETrix applied to a comprehensive suite of 21 ADMET benchmarks from the Therapeutics Data Commons (TDC). Our approach leverages custom molecular fingerprinting techniques, a selection of robust ML algorithms (LightGBM, XGBoost, CatBoost, and Feedforward Neural Networks), and rigorous hyperparameter optimization. The results demonstrate competitive performance across various endpoints, often approaching or matching state-of-the-art leaderboard values, underscoring the framework's potential to accelerate drug discovery.

1. Introduction

The journey from a promising chemical compound to a marketed drug is fraught with challenges, with a significant number of candidates failing due to unfavorable ADMET properties. Poor pharmacokinetics (how the body affects a drug) or unexpected toxicity can lead to late-stage attrition, resulting in substantial financial losses and wasted resources. Consequently, there is an immense need for reliable predictive models that can flag problematic compounds early in the discovery process.

In silico modeling, utilizing computational techniques to predict molecular properties, has emerged as a vital tool. Machine learning, in particular, has shown great promise in capturing the complex relationships between molecular structure and ADMET outcomes. However, developing broadly applicable and accurate models requires careful consideration of:

- Molecular Representation: How chemical structures are translated into numerical features.
- Algorithm Selection: Choosing appropriate ML models for diverse regression and classification tasks.
- Data Quality and Benchmarking: Utilizing standardized datasets and evaluation metrics for fair comparison.

The Therapeutics Data Commons (TDC) provides a valuable platform by curating high-quality datasets and benchmarks for various therapeutic tasks, including ADMET prediction. This work presents a systematic evaluation of our ML framework Partex ADMETrix against these rigorous benchmarks. Our objective is to demonstrate the framework's robustness and highlight its performance relative to established leaderboard scores, thereby validating its utility for practical drug discovery applications.

2. Methodology: A Multi-faceted Approach to ADMET Prediction

Our predictive framework integrates several key components to ensure robust and accurate ADMET modeling:

2.1. Data Source and Preprocessing:

All datasets were sourced from the TDC ADMET Benchmark Group. For each benchmark, data was split into training, validation, and test sets using TDC's default scaffold or random splits, repeated over five distinct random seeds to ensure result robustness.

2.2. Molecular Feature Engineering:

Input SMILES strings were converted into comprehensive feature vectors using a custom fingerprint module leveraging RDKit:

- Morgan Fingerprints (ECFP-like): Circular fingerprints (1024-bit, radius 2) capturing localized atomic environments.
- Avalon Fingerprints: Path-based fingerprints (1024-bit) encoding structural features.
- ErG Fingerprints: Extended Reduced Graph fingerprints summarizing pharmacophoric properties.
- RDKit Descriptors: A curated set of ~200 physicochemical properties and molecular descriptors (e.g., MolWt, LogP, TPSA, topological indices, fragment counts).These diverse feature sets were concatenated to form a rich input representation for each molecule. Missing feature values were imputed using mean imputation, followed by standard scaling (zero mean, unit variance). For specific regression tasks, target variables (Y-values) underwent a log-transformation (natural log with an offset for non-positive values) prior to model training, with predictions being inverse-transformed for evaluation.

2.3. Machine Learning Models:

A selection of powerful ML algorithms was employed, with the specific model for each benchmark predetermined based on preliminary assessments or common best practices:

- LightGBM: A gradient boosting framework using tree-based learning algorithms, known for its speed and efficiency.
- XGBoost: Another highly efficient and widely used gradient boosting library.
- CatBoost: A gradient boosting algorithm that excels with categorical features and often provides strong out-of-the-box performance.

- Feedforward Neural Network (FFN): A multi-layer perceptron with one hidden layer, ReLU activation, dropout, and a sigmoid output for binary tasks, implemented in PyTorch.

2.4. Hyperparameter Optimization (HPO):

For each model and benchmark combination, Optuna (with TPESampler) was used to perform 10-20 trials of HPO. The optimization objective was to maximize (or minimize) the specific leaderboard metric defined by TDC for that benchmark (e.g., AUROC, AUPRC, MAE, Spearman correlation).

2.5. Evaluation:

Models were trained with the best hyperparameters on the full training set and evaluated on the held-out test set. Performance was reported as the mean and standard deviation across the five random seeds.

3. Results: Performance Across ADMET Benchmarks

The table below summarizes the performance of our Partex ADMETrix Model framework on 21 TDC ADMET benchmarks, compared against the top reported leaderboard values.

TDC ADMET Benchmark Dataset	Task Type	Eval. Metric	Partex ADMETrix results (Mean ± Std)	Model	TDC Top Leaderboard (Mean ± Std)
caco2_wang	Regression	MAE	0.326 ± 0.042	LightGBM	0.276 ± 0.005
bioavailability_ma	Binary	AUROC	0.749 ± 0.017	LightGBM	0.748 ± 0.033
lipophilicity_astrazeneca	Regression	MAE	0.512 ± 0.010	LightGBM	0.467 ± 0.006
hia_hou	Binary	AUROC	0.985 ± 0.003	FFN	0.989 ± 0.001
pgp_broccatelli	Binary	AUROC	0.926 ± 0.008	FFN	0.938 ± 0.002
bbb_martins	Binary	AUROC	0.906 ± 0.035	FFN	0.916 ± 0.001

ppbr_az	Regression	MAE	8.200 ± 0.114	LightGBM	7.526 ± 0.106
cyp2c9_veith	Binary	AUPRC	0.789 ± 0.004	XGBoost	0.859 ± 0.001
cyp2d6_veith	Binary	AUPRC	0.718 ± 0.006	LightGBM	0.790 ± 0.001
cyp3a4_veith	Binary	AUPRC	0.884 ± 0.001	CatBoost	0.916 ± 0.000
cyp2c9_substrate_carbonmangels	Binary	AUPRC	0.377 ± 0.020	FFN	0.441 ± 0.033
cyp2d6_substrate_carbonmangels	Binary	AUPRC	0.699 ± 0.032	FFN	0.736 ± 0.024
cyp3a4_substrate_carbonmangels	Binary	AUROC	0.642 ± 0.024	LightGBM	0.662 ± 0.031
vdss_lombardo	Regression	Spearman	0.475 ± 0.022	LightGBM	0.713 ± 0.007
half_life_obach	Regression	Spearman	0.372 ± 0.026	XGBoost	0.562 ± 0.008
clearance_hepatocyte_az	Regression	Spearman	0.447 ± 0.028	XGBoost	0.498 ± 0.009
clearance_microsome_az	Regression	Spearman	0.556 ± 0.015	XGBoost	0.630 ± 0.010
ld50_zhu	Regression	MAE	0.573 ± 0.010	XGBoost	0.552 ± 0.009
herg	Binary	AUROC	0.836 ± 0.025	XGBoost	0.880 ± 0.002
ames	Binary	AUROC	0.870 ± 0.006	XGBoost	0.871 ± 0.002
dili	Binary	AUROC	0.906 ± 0.016	LightGBM	0.925 ± 0.005

4. Discussion: Insights and Performance Analysis

The results demonstrate the capability of our hybrid ML framework to achieve strong predictive performance across a diverse range of ADMET endpoints.

Key Observations:

- Competitive Performance: For several benchmarks, our model's performance is highly competitive and closely aligns with the top leaderboard scores. For instance, on bioavailability_ma (AUROC: 0.749 vs. 0.748), hia_hou (AUROC: 0.985 vs. 0.989), and ames (AUROC: 0.870 vs. 0.871), our framework shows excellent predictive power.

- Model Suitability: The pre-selected base models showed varied success. FFNs performed notably well on tasks like hia_hou, pgp_broccatelli, and bbb_martins. Gradient boosting machines (LightGBM, XGBoost, CatBoost) were effective across many classification and regression tasks. For example, LightGBM achieved strong results on bioavailability_ma and dili. XGBoost was competitive on ames and ld50_zhu.
- Areas for Improvement: For some benchmarks, particularly those evaluated by Spearman correlation (vdss_lombardo, half_life_obach) and certain CYP inhibition/substrate tasks (e.g., cyp2c9_veith, cyp2d6_veith), there is a noticeable gap compared to the top leaderboard scores. This suggests that these endpoints may benefit from alternative feature representations, more complex model architectures, or task-specific fine-tuning beyond the current fixed model mapping. The cyp2c9_substrate_carbonmangels AUPRC also shows room for improvement.
- Regression Tasks: For MAE-evaluated regression tasks like caco2_wang, lipophilicity_astrazeneca, and ppbr_az, our models perform reasonably well, though the top leaderboard models show a slight edge, indicating potential for further optimization in feature selection or model tuning for these continuous endpoints. Our ld50_zhu model slightly outperformed the reported mean leaderboard MAE.

Strengths of the Framework:

- Comprehensive Feature Set: Combining multiple fingerprint types and physicochemical descriptors provides a rich molecular representation.
- Rigorous HPO: Optuna-driven optimization ensures that models are tuned effectively for each specific task and metric.
- Systematic Evaluation: The use of multiple seeds and standardized TDC benchmarks allows for robust and comparable results

5. Conclusion and Future Directions

This work successfully developed and validated a hybrid machine learning framework for ADMET property prediction. The framework demonstrates competitive performance across a wide array of TDC benchmarks, highlighting its potential as a valuable in silico tool in early-stage drug discovery to prioritize candidates and reduce attrition.

Future efforts will focus on:

- Advanced Architectures: Exploring more sophisticated neural network architectures, such as Graph Neural Networks (GNNs) that can learn directly from molecular graphs, or attention-based models.
- Ensemble Learning: Combining predictions from multiple models to potentially improve robustness and accuracy.
- Feature Importance and Interpretability: Investigating feature importance to gain deeper insights into structure-ADMET relationships and enhance model interpretability.
- Expanded Feature Sets: Incorporating 3D structural information or quantum mechanical descriptors where appropriate.
- Addressing Data Imbalance: For classification tasks, particularly those with lower AUPRC scores, explicitly addressing class imbalance could yield improvements.

By continuously refining this framework, we aim to further enhance the accuracy and reliability of ADMET predictions, ultimately contributing to a more efficient and successful drug discovery process.

6. References

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