ADMET Scoring Models for Real-World Drug Design

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1. Introduction

The optimization of absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiles is critical for clinical viability, yet remains a primary bottleneck in drug development. While artificial intelligence has advanced in silico ADMET prediction [1][2], current predictive architectures exhibit limited translational utility. Specifically, existing methodologies predominantly rely on precompiled databases (e.g., MoleculeNet [3]) that inadequately represent real-world molecular optimization trajectories. The indiscriminate aggregation of such heterogeneous data introduces severe systematic batch effects[4]. Furthermore, conventional evaluation metrics (e.g., mean squared error) fail to accurately reflect a model's practical predictive efficacy in pharmaceutical workflows.

To bridge these translational gaps, we propose a comprehensive, end-to-end ADMET prediction framework. First, we deploy an automated natural language processing pipeline to mine authentic drug optimization data directly from primary medicinal chemistry literature. Second, to mitigate systemic inter-study batch effects, we integrate meta-learning and pairwise ranking methodologies. By treating discrete studies as independent domains, our framework isolates the intrinsic molecular determinants of ADMET properties from confounding experimental variances. Finally, we introduce an adjusted evaluation metric to assess predictive ranking efficacy under real-world lead optimization constraints.

2. Method

2.1 Data collection

We utilized automated extraction techniques to process a large corpus of research articles and patents, curating a proprietary, real-world ADMET dataset. Following rigorous cleaning, the data—encompassing multiple distinct pharmacokinetic endpoints—was chronologically partitioned for training and evaluation, ensuring a realistic representation of the chemical space optimization process.

2.2 Models

We propose a novel few-shot molecular property prediction framework that synergizes gradient-based meta-learning with a contrastive pairwise ranking objective. To resolve the incompatibility of disparate assay metrics (e.g., IC50, Ki) without manual normalization, the model optimizes the relative ordering of bioactivity rather than absolute values. This induces scale-invariance, allowing the aggregation of gradients from tasks with vastly different dynamic ranges. Furthermore, to enable rapid adaptation across diverse assays, we employ a parameter-efficient meta-learning paradigm. Rather than fully fine-tuning a pre-trained backbone, we optimize low-rank parameter injections via a bi-level regime, maximizing transferability to unseen tasks while requiring minimal support data.

2.3 Metrics

To rigorously evaluate the prioritization of bioactive compounds, we introduce Adjusted-NDCG (aNDCG). Traditional metrics or raw NDCG scores can be misleading due to varying active compound distributions ("hit rates") across assays. aNDCG corrects for this baseline bias by normalizing the absolute gain over expected random-chance performance. This provides a robust, scale-independent measure of true ranking capability across heterogeneous assays.

3. Results

Preliminary evaluations demonstrate that our proposed framework consistently outperforms traditional baselines (e.g., XGBoost) and domain-specific platforms (e.g., ADMET Lab 3.0 [5]) across a wide range of pharmacokinetic endpoints. In zero-shot settings, the model establishes a robust prior, effectively avoiding the sub-random ranking frequently exhibited by conventional machine learning approaches on complex ADMET tasks.

The core efficacy of our framework is most pronounced in few-shot scenarios. Task-specific

meta-adaptation using minimal data points yields consistent, monotonic improvements across all evaluated endpoints, driving dramatic performance gains on notoriously complex pharmacokinetic parameters (e.g., half-life and clearance). These findings rigorously validate the framework's exceptional capacity to rapidly extract critical structure-activity relationships from sparse real-world data, underscoring its significant potential for accelerating practical drug optimization workflows.

References

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