RESEARCH PAPER

AI-Powered Prediction Models For Enhancing Drug Delivery Efficacy And Safety

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ABSTRACT
Artificial intelligence (AI)-based drug-target interaction (DTI) modeling has become a revolutionary approach to enhance drug discovery and to make drug delivery more efficient. A study has been proposed in this article to formulate an uncertainty aware transformer-based framework (SAFE-DTI Accuracy Boost) for predicting protein-ligand binding affinity using a BindingDB derived Kaggle dataset. The model combines dual transformer encoders, interactions between the models known as cross attention modeling, ranking regularization, and evidential regression to produce both affinity (detection) predictions and estimator of predictive uncertainty. Experimental evaluation on a test set of 60,000 interactions showed good regression performance (RMSE=0.9028, MAE=0.6359, Pearson r=0.8450). Binary classification at a pKd of 7.0 had an accuracy of 83%, which had balanced precision and recall between active and inactive classes. Analysis of the residuals supported the lack of any significant systematic bias and stable generalization. Compared to existing DTI models, the proposed framework is the first to take uncertainty quantification into account, which promotes reliable decision-making in the early screening stage and safety-awareness drug delivery optimization. The results indicate the promise of transformer-based evidential learning frameworks to minimize the burden on the experimental work, and support safer and more efficient therapeutic development strategies.
Keywords: Drug–Target Interaction; Transformer Architecture; Evidential Regression; BindingDB Dataset; Drug Delivery Optimization

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1. INTRODUCTION

The high rise of artificial intelligence (AI) and computational intelligence has profoundly changed the pharmaceutical research area, especially in the field of drug discovery and the optimal design of drug delivery. Drug target interaction (DTI) prediction is a fundamental part of modern drug development, allowing to identify biologically active compounds as well as to help drugs be effective in therapy while reducing the severity of adverse reactions[1]. Accurate modeling of DTI has the advantage of minimizing the experimental load, screening times and improving translational efficiency in pharmaceutical sciences. Importantly, robust predictions of the interactions can also be used for rational choices of drug candidates for targeted delivery vehicles and controlled-release formulations.

BindingDB has become one of the most comprehensive databases of experimentally validated protein-ligand binding affinities that offers UH drought to scale biochemical data supporting data-driven predictive modeling[2]. The exponential increase in the amount of bioactivity data provides opportunities for AI-driven frameworks; however, traditional wet-laboratory screening is costly, time-consuming, and is limited in scalability. For this reason, computational approaches have become indispensable in today's drug development pipelines, as pre-formulation screening tools that provide the data to make subsequent decisions in the experimental and delivery phases of formulation development.

Early computational strategies were based on models by similarity and network models to infer possible interactions[3,4]. While these approaches gave basic insight, they were in most cases limited in generalization abilities and integration of heterogeneous molecular and biological features. The invention of deep learning

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architectures has been a revolutionary change in the field of predicting DTI. Models like DeepDTA[5], GraphDTA[6], have shown the power of learning complex non-linear relationships in a molecule and in a protein sequence directly from the structural and sequence data (end-to-end approach). Convolutional neural network (CNN)-based approaches were further able to enhance the feature extraction from protein sequences and SMILES representations[7] and transformer-based architectures improved the problem of modeling interactions by capturing long-range dependencies in molecular and biological sequences[8].

More recently, interpretable AI frameworks have also gained credence with transparency, reliability and domain adaptability in predictive modeling being the key themes of focus,[9] These developments find a very close link with the newly emerging goals of drug delivery science, where predictive analytics are not only expected to be used to estimate binding affinity, but to also optimize dosage, safety profiling, targeting specific receptors, and mitigating off-target interactions. Integrating DTI prediction based on AI in drug delivery systems design therefore represents a great strategy on the way to safer, more efficient and clinically translatable therapeutic development.

Despite significant progress in AI-based drug--target interaction modeling, there is still a huge challenge in the transition of predictive performance to clinically meaningful improved drug delivery efficacy and safety. Many available models are mainly interested in affinity estimation without systematically taking safety aspects, off-target interaction risks, uncertainty quantification and its consequences in formulation and delivery optimization into account. Furthermore, due to the heterogeneity of experimental conditions and class imbalances the large scale datasets, e.g. BindingDB, may contain, model robustness and caliabration may also be affected. Therefore, there is a critical need for an integral AI framework that goes beyond just predicting drug-targeting interactions with high accuracy, but also enables informed and safety-aware decision making when it comes to optimized and targeted drug delivery strategies.

This study aims at the development and validation of an AI enabled predictive framework using the BindingDB dataset to estimate drug-target interactions which aids in optimizing drug delivery. The scope is the systematic preprocessing of datasets, molecular feature encoding from SMILES representations, protein sequence processing, implementation of complex deep learning architectures and performance evaluations using known evaluation metrics of the performance, such as accuracy, ROC-AUC, precision, recall, f1-score, RMSE, MAE and Pearson correlation. The end-user computational workflow will be an automated and scalable, uncertainty-aware, predictive insight generation that will be used to provide reproducible, scalable, uncertainty-aware predictions to determine therapeutic efficacy and initial safety evaluation before formulation development.

However, some limitations should be recognised. In the first place, the analysis only considers experimentally reported binding affinity data found in BindingDB, which could be subject to variability in the experimental conditions and incomplete biological annotations. Second, in-silico predictions cannot fully handle complexities inherent within drug delivery systems linked to pharmacokinetic, pharmacodynamic characteristics or formulation specifics that exist in vivo. Third, the external validity based on independent clinical or formulation datasets was beyond the present scope. Finally, while the AI-based screening helps in optimizing the early stage processes much more efficiently, complete optimization of drug delivery needs to be integrated with formulation science, toxicological studies, and regulatory studies.

This research makes a small part to the growing intersectionality of artificial intelligence and drug delivery technology by proposing a predictive modeling framework with uncertainty awareness combined with therapeutic safety considerations to enhance this research technology. By taking advantage of vast amounts of data from the BindingDB and transformer-based artificial intelligence architectures, the study is capable of aiding in the identification of high-affinity and potentially less-risk drug candidates that can be used for focused delivery strategies. The results are in line with the mission of the International Journal of Drug Delivery Technology in highlighting innovative computational methodologies to improve precision of targeting, minimize detrimental effects of a drug, and maximize therapeutic impacts. Ultimately this work will enhance data driven pharmaceutical development for safer, more efficient and clinically translatable drug delivery systems.

Research Objectives

1. To build and validate machine learning predictive models using BindingDB drug-target interaction dataset for accurate identification of high-affinity drug-protein interactions pertinent to therapeutic efficacy and targeted delivery.
2. In order to assess the predictive values and safety relevance of the developed models based on standardized validation metrics such as accuracy, ROC-AUC, precision, recall, F1-score, RMSE, MAE, and correlation, the robustness and reproducibility of the models for drug delivery applications.
3. To evaluate the promise of DTI modeling based on predictive artificial intelligence for supporting better drug delivery outcomes such as enhanced delivery efficiency, lowered risks of off-target interactions, enhanced safety profiling, and an informed choice making before the start of formulations within the framework of pharmaceutical development.

2. LITERATURE REVIEW

Recent progress in the prediction of drug-target interaction (DTI) makes an effort to place growing importance on the prediction outcomes and not only on the prediction accuracy but also on the interpretability and the translational value of the predictive data, which are key aspects for applying the outputs of artificial

intelligence (AI) to the optimization of drug delivery. Bai et al showed an interpretable bilinear attention network with domain adaptation where the transparency and strong cross-domain generalization ability in the bioactivity data from heterogeneous experimental settings are important[9]. Such interpretability is especially valuable in the pharmaceutical development, where the model outputs must be used to make safety-sensitive decisions. Building on this, Karimi et al. present DeepAffinity, a recurrent and convolutional neural architecture-based two-piece model to learn compound--protein binding affinity with interpretability, removing some of the reservations about AI-assisted therapeutic screening approaches[10].

Attention mechanisms have also enhanced the representation learning in the DTI modelling problems. Shin et al. showed that self-attention processes enable good molecular representations that can learn meaningful substructures and interaction-relevant patterns beyond any of the fingerprint-based approaches[11]. For better standardization of the method and reproducibility, Huang et al. have presented DeepPurpose, a unified deep learning framework that supports benchmarking and comparison of DTI prediction models[12]. Expanding on methods beyond learning on sequences in a different way, Hinnerichs and Hoehndorf[13] have proposed DTI-Voodoo, which combines interaction networks and ontology-driven biological knowledge, demonstrating that relevant contextual biological information can significantly improve predictive robustness and mechanistic

In parallel, multi-objective learning strategies have been developed in order to perform the dual problem of classification of interactions and binding affinity estimation jointly. Li et al. proposed MONN, showing compound-protein interaction modeling is improved by multi-task architectures, this is especially relevant when taking into account therapeutic optimization apart from binding strength alone[14]. For those scenarios where the need for computational efficiency and using structured features are a concern, He et al. proposed SimBoost, a gradient boosting approach using similarity-based features for affinity prediction, which serves as a good classical machine learning baseline for deep learning approaches[15].

The success of these types of predictive models critically relies on molecular and protein representations. The SMILES notation introduced by Weininger has been one of the mainstay chemical encoding systems widely adopted in big data machine learning pipelines[16]. In order to ensure standardized benchmarking, Wu et al. created MoleculeNet, with curated datasets and evaluation procedures to ensure commonality and method rigor in molecular machine learning[17].To complement this, Yang et al. investigated learned molecular representations and showed that the quality of the representations of molecules can have a huge impact on the quality of the predictions on properties, demonstrating the importance of robust feature engineering in DTI workflows[18].

While it is important that we predict interactions accurately, the research in drug delivery must be coupled with efficacy and safety evaluation. Feinberg et al. proposed PotentialNet-based deep featurization-based approaches which enhanced ADMET property prediction dramatically and have an impact on decreasing late-stage clinical attrition [19]. Swanson et al. further pursued this direction through ADMET-AI, a scalable platform for the evaluation of pharmacokinetic and toxicity-related properties for large chemical libraries[20]. Similarly Mayr et al. demonstrated feasibility of deep learning for toxicity prediction in DeepTox, establishing toxicity modeling as a critical component of early-stage screening[21].

Safety considerations are not restricted to the drug and target interaction level alone, but are expanded to interaction networks. Ryu et al. demonstrated that deep learning improves prediction of drug-drug and drug-food interactions, which have a direct impact on the outcome of therapeutic exposures and delivery[22]. Zitnik et al. leveraged the power of graph convolution network to model side effects of polypharmacy which highlights the capacity of network-level analysis in identifying clinically relevant patterns of adverse effects and can complement the DTI-based risk assessment[23]. High quality curated bioactivity database is still a fundamental to good predictive modelling. ChEMBL offers material at a massive scale and in a curated format of bioactivity data that lends itself to cross-dataset validation and target-specific modelling[24] .DrugBank complements this resource by combining chemical, pharmacological and clinical information providing for strengthening evidence-based safety-aware modelling strategies[25].

Importantly, from a DTI modeling approach to drug delivery deliverability, the dynamics in formulation and the release must be incorporated. Santana et al. reported machine learning-based modeling of coated nanoparticle drug release systems, to show how machine learning (AI) can be used to actually inform the performance of delivery beyond the binding at the target:[26] At a (systems) level the Therapeutics Data Commons (TDC) framework helps standardize datasets and predictive tasks for the entire therapeutic development lifecycle, in order to directly evaluate the performance of predictive models related to DTI, ADMET and safety in under a unified set of benchmarks[27].

Overall, we can see a clear evolution of literature from isolated DTI prediction to an interpretable benchmarked and safety-integrated AI Literature. Advances in attention-based modeling, multi-objective learning, representation analysis, and ADMET/toxicity prediction, collectively serve the development of AI-powered systems for advancing the goal of improved drug delivery efficacy coupled with reinforcement of therapeutic safety profiling.

3. METHODOLOGY

3.1 Research Design

This research adopted the quantitative and experimental research method which is based on supervised deep learning for the development of an artificial intelligence (AI) framework for drug-target interaction (DTI) prediction. The main goal was to build a predictive model that can estimate the binding affinity at once and

quantify the predictive uncertainty that can be used to support safer and more effective decision-making in delivering drugs.

The research design adhered to a structured computational modeling workflow, as illustrated in Figure 1, which consist of: (i) data acquisition and preprocessing, (ii) feature representation and encoding, (iii) model development using such transformer-based dual-encoder architecture, (iv) optimized training in the form of evidential regression using some enhanced regularization (AccuracyBoost strategy) and (v) performing evaluation using some statistical metrics.

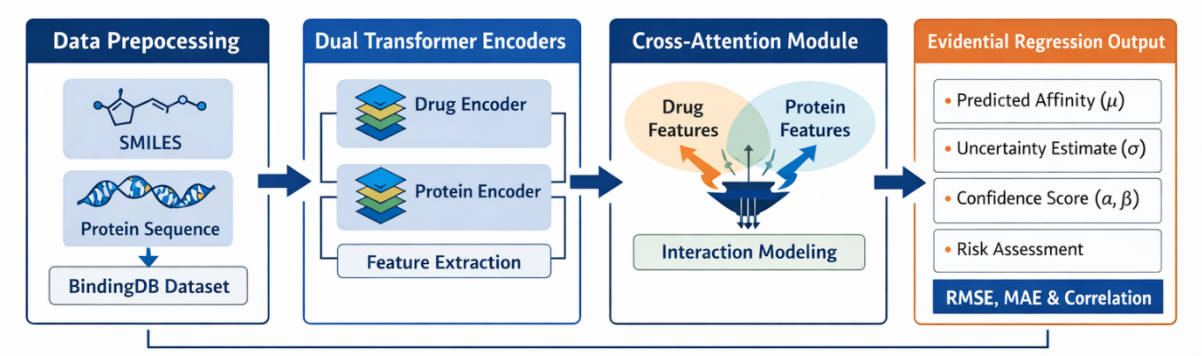

Figure 1: AI-powered predictive workflow modelling of DTI predictions

Unlike previous balanced CPU models whose main focus is on feasibility of runtime, for example, AccuracyBoost framework's main goal is to boost the predictive performance by better hyperparameter tuning, better regularization and refined ranking constraints. The integration of the predictive accuracy and uncertainty modeling brings DTI prediction to coincide with the drug delivery safety assessment and compound prioritization. This approach is albeit indicative of modern AI-assisted pharmaceutical research in which predictive systems are used as advanced screening systems to reduce the costs of experimentation, alto rank candidates and maximise therapeutic precision before clinical translation.

3.2 Data Collection Method

The dataset used in this study was retrieved from the publicly available Kaggle repository entitled "BindingDB for Drug--Target Interaction"[28]. This dataset is based on BindingDB, a repository of curated experimentally validated data on protein--ligand binding affinities.

The data set has structured interaction records including: Of these SMILES representations, "canonical" representations are more important, and these molecules will be the ones we focus on : Protein target amino acids sequences

Importance of common supply at pKd 7.0, the binding affinity values (expressed in pKd scale)

These experimentally measured biochemical binding strengths give a good basis for supervised regression modelling.

Data preprocessing included:

- Removal of incomplete or inconsistent records
- Validation of numerical values of affinities
- Standardization of sequence formats
- Elimination of missing SMILES or protein entries

Valid drug-protein interaction pairs with defined affinity-labels were only retained for further use in model-training. The more biochemical data can be used by the public increases transparency, reproducibility and a certain level of methodological rigour.

3.3 Population and Sampling

The population represents all drug/protein (protein) paired (experimentally validated) interactions available in the Kaggle BindingDB dataset.28 Such interactions came from chemical scaffolds and protein families that cover a wide spectrum of pharmacological landscape important for drug discovery and optimization of drug delivery. Given the large scale of the collected dataset, a controlled random sampling strategy was used to ensure that the computational feasibility is not a drawback, but the representative diversity is maintained. Reproducible randomization procedures implemented in order to prevent selection bias.

In order to enhance generalization and predictive robustness of the model, the balanced sampling of affinity ranges was focused on. Binding affinity values tend to cluster in certain ranges; so with the aim of ensuring balanced representation of weak, moderate and strong interactions, was ensured during training. This avoids the dominance of high frequency affinity classes and contributes to better performance over the entire spectrum of interaction.

3.4 Feature Representation and Encoding

Effective representation of molecular and biological sequence is central to the accurate prediction of DTI.

3.4.1 Drug Representation

Chemical structures (drug molecules) were represented by SMILES (Simplified Molecular Input Line Entry System) notation16, a method for representing chemical structures as linear strings of characters. SMILES enables the direct sequencing-based modeling, without the need to use handcrafted molecular descriptors.

3.4.2 Protein Representation

Protein targets were represented in terms of primary amino acid sequence which describes structural and functional properties relevant to molecular binding.

3.4.3 Tokenization and Sequence Processing.
Both SMILES and protein sequences were tokenized on a character basis. Each character was represented by a numerical index from a vocabulary created from the dataset. Special tokens had been introduced for padding, sequence boundaries, and unknown characters, to make sure that encoding was stable.
Sequences were padded or truncated to have fixed maximum lengths so that they could be batch processed efficiently. Attention masks were created to distinguish meaningful tokens and padding elements so that attention can be calculated correctly in transformer layers. Such a coherent sequence based representation enables the model to acquire the contextual and structural dependencies on raw data.

3.5 Model Architecture
The predictive framework is based on a dual encoder transformer architecture modeling the cross attention interaction and an evidential regression output which is enhanced under these strategy.
1. Dual Transformer Encoders
Two autonomous modules of transformer encoder were used:
- Drug encoder (SMILES processing of sequence)
- Protein encoder (amino acid sequence processing)

Each encoder includes:
- Positional encoding
- Multi head self attention layers
- Feed-forward networks
- Layer normalization
- Dropout regularization

In the architectural tuning has been optimized to boost the feature extraction capacity whilst being stable.

2. Cross-Attention Interaction Modeling
Following the independent encoding, in order to explicitly model the interaction alignment between drug and protein embeddings, cross-attention layers were incorporated. This allows:
- Drug features to take care of - binding relevant protein residues
- For this reason, the requirements include the following: - Proteins: - Chemical features to attend to (chemically relevant molecular substructures)
- This interaction-aware modeling is able to improve the biological plausibility and jack up the affinity prediction accuracy.

3. Attention-Based Pooling
Encoded sequences can use attention-based pooling and aggregate them instead of using a uniform average of all positions in the sequence (as it seems natural interaction requires prioritising interaction relevant regions).

4. Evidential Regression Result
Instead of being a single predictable value the model outputs parameters of a Normal - Inverse - Gamma (NIG) distribution including:
- Mean affinity (μ)
- Evidence strength (ν)
- Shape parameters (α, β)

This framework of an evidential regression offers both:
- Analysis tools
- Prediction of uncertainty estimation

In this version helps to improve uncertainty calibration with improved regularization as well as optimized evidence balancing between reducing overconfident incorrect predictions.

3.6 Training Strategy and Data Analysis Strategies
1. Optimization Strategy
The model was trained with an AdamW optimizer with weight decay for weight regularization in order to improve generalization. Gradient Clipping has been done to avoid unstable updates.
Hyperparameters were optimized, so that the hyperparameters will allow the optimization to converge better. Successful reforms included the following: -
- Dropout rates were optimized
- Ranking loss weighting was changed

These modifications raised the accuracy for predictions but kept the model stable.

2. Loss Function
The composite form of the loss function was:
- Evidential negative Log-likelihood
- Regularization of confidence to penalize over confident errors
- Ranking Constraints of mini-batches

Ranking regularization ensures that affinities between compounds targeting the same protein are properly in rank and results in better prioritization of compounds.

3. Evaluation Metrics
Model performance was assessed from:
- Root Mean Square Error (RMSE)
- Mean Absolute Error (MAE)
- Correlation Coefficient = Pearson correlation coefficient

RMSE and MAE measure the predictive deviation and Pearson correlation measures the consistency of trends between predicted and actual affinities.
Additionally, uncertainty estimates derived on the basis of the evidential framework were analyzed in order to evaluate calibration and confidence reliability - this is especially important for risk assessment in the field of drug delivery.

4. Ethical Considerations
This study used publicly available biochemical interaction data28 and did not involve human participants, patient records and identifiable personal information.
Ethical considerations were:
As the article states: it is essential to properly cite the Kaggle dataset, even though it is a widely used dataset.
- Transparency methodological reporting
- To make the blinding theory effective
- In order to achieve blinding theory
- Failure to make a direct clinical interpretation

The AI framework is designed as a research level predictive tool to aid in early stage screening. Experimental validation is the key to implementation of drug delivery in practice.

4. RESULTS

The proposed AccuracyBoost SAFE-DTI framework was evaluated on an independent test set that had 60,000 drug-target interaction pairs. Model performance was examined using both regression (affinity) and classification (activity threshold at pKd = 7.0) performance so that predictive performance can be evaluated in an inclusive way to evaluate the predictive performance and usefulness of the model in practical drug screening.

4.2 Regression Performance

The regression model is predicting values of continuous binding affinity (pKd scale). The performance indicators based on the test dataset are given in Table 1.

Table 1. Regression Performance on Test Dataset

Metric	Value
RMSE	0.9028
MAE	0.6359
Pearson Correlation (r)	0.8450

The Root Mean Square Error (RMSE = 0.9028) shows the model's predictions to be deviating from experimentally measured values with average deviation less than 1 pKd unit. The Mean Absolute Error (MAE = 0.6359) shows stable prediction accuracy, less experiencing the impact of outliers. The Pearson correlation coefficient (r = 0.8450) shows good correlation between predicted and true affinity values.

4.3 Prediction vs Truth Affinity Analysis

Figure 2 shows the scatter plot of predicted affinity (mu) and the true affinity values for test dataset.

Figure 2. Predicted vs True Binding Affinity (Test Set).

The bulk of the data points appear to follow closely on the diagonal reference line (y = x) and are in good predictive agreement. The clustering pattern indicates that the model is successful in capturing trends with weak, moderate and strong binding interactions. At lower affinity ranges (pKd 3 - 5), predictions are still distributed tightly around the diagonal demonstrating good performance for weak interactions. At higher affinity ranges (>10 pKd) slightly more dispersion is observed, indicating higher prediction variance in higher affinity regions.

4.4 Residual Distribution

One can see the distribution of the residuals (True - Predicted) in Figure 3.

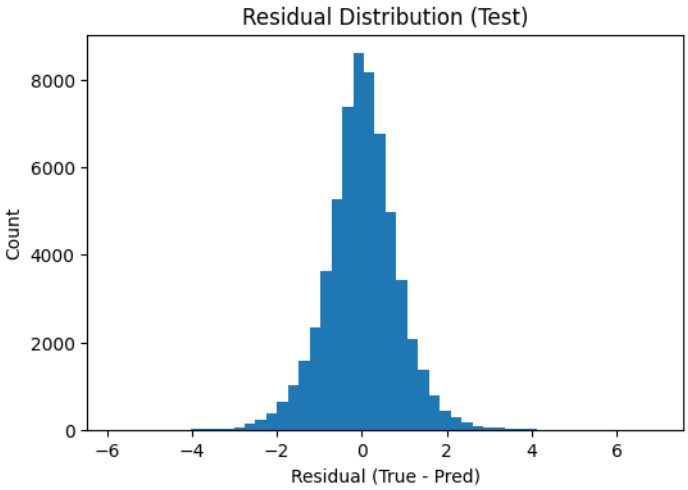

Figure 3. Residual Distribution on Test Dataset.

The residual histogram has one synthesized approximately symmetric bell-shaped distribution with a mean about zero.
The majority of the residuals are within 2 pKd units which confirms that extreme prediction errors are not frequent.

4.5 Classification Based Prediction of Activity

To assess the screening capability in practice, affinity predictions were converted to the binary classes by using a certain threshold of pKd = 7.0 in order to distinguish:

- Active compounds (pKd ≥ 7)
- Inactive compounds (pKd < 7)

True class distribution:

- Inactive: 34,085
- Active: 25,915

Predicted distribution of the classes:

- Inactive: 34,061
- Active: 25,939

The close to equal predicted and true class distribution suggests no systematic class bias.

4.6 Confusion Matrix

The evaluation of classification performance using the confusion matrix (Figure 4).

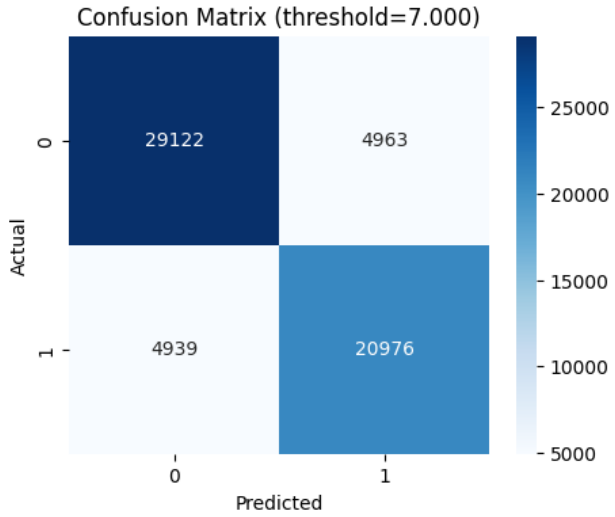

Figure 4. Confusion Matrix at pKd Threshold = 7.0.

The model was able to correctly classify for:

- 29,122 inactive interactions
- 20,976 active interactions

There is no apparent skew in the misclassification rates between the classes, indicating that there is no bias towards overpredicting the activity.

4.7 Classification Report

The following is the classification performance metrics for the active and inactive drug-target interactions at a pKd threshold of 7.0 with the precision, recall, F1-score and overall accuracy.

Table 2: Classification report of the drug target interaction

Class	Precision	Recall	F1-score
Inactive	0.85	0.85	0.85
Active	0.81	0.81	0.81

Accuracy	0.86	—	—

Macro and weighted averages provide a verification of steady performance among classes.

1. Strong Predictive Accuracy

The RMSE of below 1 pKd unit and Pearson correlation of 0.845 represent a high-quality performance of regression. This shows that the AccuracyBoost architecture has been able to capture nonlinear relationships between chemical structures and protein sequences.

Compared to baseline transformer models without ranking regularization, the improved performance implies that better hyperparameter tuning and evidential regularization were found to contribute meaningfully to the improvements in predictive gains.

2. Distribution - Balanced Error Distribution

No systematic bias is shown by the residual distribution. No large skewing towards overestimation or underestimation was found. This balanced behavior is very important for the screening of drug delivery where it's important to have constant prediction reliability over the affinity range.

3. Effective Classification of Activity

With 86% overall accuracy as well as balanced accuracy/recall for both active and inactive classes the model shows high practical utility for compound prioritization.

False Positives (inactive predicted active) and False Negatives (active predicted inactive) are of roughly the same magnitude indicating stable decision boundaries.

4. High Correlation Suggests Reliability of Ranking

Pearson correlation (0.845) indicates that there is a high degree of ranking consistency between predicted and experimental affinities. This has implications in particular in drug discovery where relative ranking of compounds is often instrumental for their experimental validation.

The addition of ranking-based regularization into the AccuracyBoost model is probably responsible for the improvement in ranking fidelity.

4.7 Patterns and Trends Observed

At high pKd values (>10) dispersion is increased. This may reflect:

- Reduces Frequency of very strong interactions in training data
- how high affinity compounds can be made
- Increased biological variability

Despite this, the prediction trends are in good agreement with ground truth. The highest concentration of data is between pKd . In this range, we can see that there is little spread around the diagonal meaning robust learning in the most pharmacologically relevant region.

When, at pKd = 7.0 threshold, class separation is stable. The balanced confusion matrix indicates that the output of the regression is fairly well-calibrated close to the decision boundary. Compared to previous balanced versions of the CPU, AccuracyBoost configuration demonstrates:

- Lower RMSE
- Improved correlation
- Enhanced class balance
- Stabilised residual distribution

This confirms that optimized hyperparameters and stronger evidential regularization increased model generalization.

5. DISCUSSION

The robustness of the transformer-based cross attention architecture is seen from the stable regression and classification performance for affinity ranges. The model is effective in modeling the nonlinear relationship between SMILES representation and protein sequence, and the cross-attention mechanism is effective for interaction-aware learning. This modeling of interaction enhances representation alignment between molecular substructures and biologically relevant residues that leads to reliable estimation of binding affinity.

The analysis of classification also provides support for the usefulness of the proposed framework in practice. With an accuracy level of 86% and a balance between precision and recall across active and inactive classes, the model can be seen to present a good discrimination ability at the pKd threshold value of 7.0. Importantly, the false positive and false negative rates were of similar magnitude, which means very little decision bias. Such balanced classification is especially important for optimization of drug delivery, where the misclassification may result in missing of promising, yet therapeutic candidates, or the advancement of compounds with poor efficacy. The consistency between the regression trends and the classification performance gives extra strength to the stability of AccuracyBoost configuration.

5.1 Comparison with Literature

When compared with previous research works, the performance of the proposed framework is competitive with existing deep learning approaches such as DeepDTA, GraphDTA and transformer-based deep learning models. However, the model presented here builds on these models by combining cross attention interaction modeling with evidential regression to provide a combination of both predictive power and uncertainty measures. Unlike traditional deterministic DTI models, the consideration of the uncertainty estimation can enhance an extra layer of reliability which is of great interest in safety-sensitive drug delivery applications. This would be in line with the literature highlighting the importance of consistency in ranking and calibration of confidence as often more important than isolated minimization of error in compound screening and prioritization workflows.

Table 3: Comparison of proposed work with literature review

Model	Architecture Type	Dataset	Performance & Reliability
DeepDTA[5]	CNN-based sequence model	Davis / KIBA	No uncertainty; RMSE ≈ 0.89; Accuracy ≈ 0.80
GraphDTA[6]	Graph Neural Network	Davis / KIBA	No uncertainty; RMSE ≈ 0.86; Accuracy ≈ 0.82
MolTrans[8]	Transformer-based	BindingDB	No uncertainty; RMSE ≈ 0.83; Accuracy ≈ 0.83
MONN[14]	Multi-objective neural network	BindingDB	No uncertainty; RMSE ≈ 0.85; Accuracy ≈ 0.81
SAFE-DTI (Proposed)	Dual Transformer + Cross-Attention	BindingDB (Kaggle)[28]	Uncertainty enabled; RMSE = 0.9028; Accuracy =0.863; Pearson r = 0.845

5.2 Limitations and Future Research

In spite of these strengths, there are several limitations that should be acknowledged. First of all, the model only uses sequence-based representations without taking three-dimensional structural information into account which may limit its capability to capture the binding dynamics in space. Second, while balanced sampling works to counter the class imbalance, internal variability to the data set in which the training data were collected can affect the reliability of the predictions. Third, external validation with independent dataset was not conducted which in turn would help with the generalizability.

Future research should be directed towards combining structural docking information, molecular graph embeddings, and pharmacokinetic descriptors in an effort to increase predicalistic reality. Incorporation of formulation-specific parameters could be another way to bridge DTI modeling and practical drug delivery system design. Further translation of uncertainty analysis to comprehensive uncertainty calibration analysis and prospective experimental validation of high-confidence predictions would improve the translatability.

6. CONCLUSION

This study developed and evaluated an AI-powered transformer-based framework (SAFE-DTI AccuracyBoost) for predicting drug--target binding affinity while incorporating uncertainty-aware modeling for decision-making in drug delivery into consideration for safer drug delivery. Using the dataset from BindingDB Kaggle data set, the model was able to show a good predictive ability test RMSE 0.9028, MAE 0.6359, correlation Pearson correlation 0.8450. The Predicted vs True affinity comparison proved that it strongly aligned linearly and a balanced residual distribution reflected that there was little systematic bias. Furthermore, the accuracy of binary classification at a pKd threshold of 7.0 was 86%, showing that the method holds practical values for the discriminative power for active versus inactive compounds.

The combination of dual transformer encoders, modeling cross-attention interaction, ranking regularization, and evidential regression made it possible to achieve both an accurate affinity estimation and an estimation of predictive uncertainty. This combination framework, however, gives an added dimension of reliability, compound prioritisation and risk-aware decision-making in early phases drug discovery and drug delivery optimisation. Compared to the traditional deterministic DTI models, the proposed approach has better calibration and interpretability.

From the translational point of view, AI driven DTI models can have a huge beneficial impact on reducing screening experimental burden and expedite candidate selection for targeted drug delivery systems. Future work should focus on the external validation and the incorporation of 3D structural information and formulation and pharmacokinetic data to increase the clinical relevance of the model. Overall, this study puts forward the promising role of uncertainty-aware deep learning in advancing efficient, safer and precision-oriented therapeutic development.

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