Mixture-of-Experts Approach for Enhanced Drug-Target Interaction Prediction and Confidence Assessment

Yijingxiu Lu[1], Sangseon Lee[1], Soosung Kang[2], Sun Kim[1]
1 Seoul National University
2 Ewha Womans University

Outline

- **Background**
- Motivation
- Method
- Experiments
- Summary

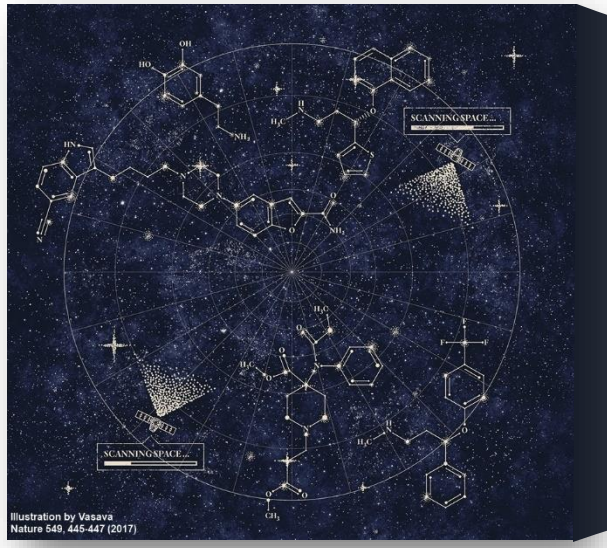
Background | Drug-Target Interaction Task

1. Drug candidate space is too vast for SBDD methods alone.

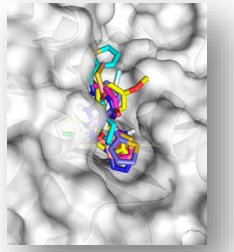
- Computer-Aided Drug Discovery (CADD) has become essential for accelerating drug development, with a primary focus on accurately identifying complex drug-target interactions (DTIs).

- Structure-Based Drug Design (SBDD) models have revolutionized the field. However, **limited availability**, **high computational costs**, and **lengthy inference times** still present significant challenges for researchers seeking to screen large libraries of drug candidates.

Large space of drug candidates



Structure-Based Drug Design



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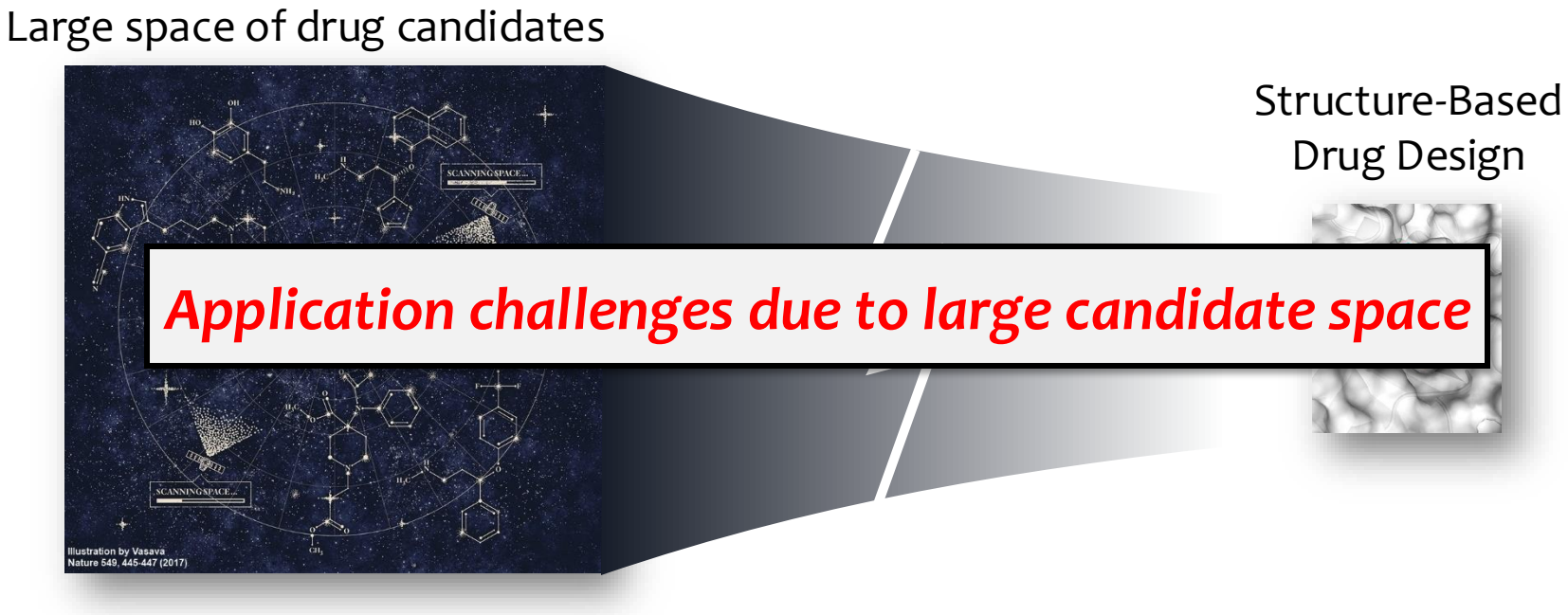
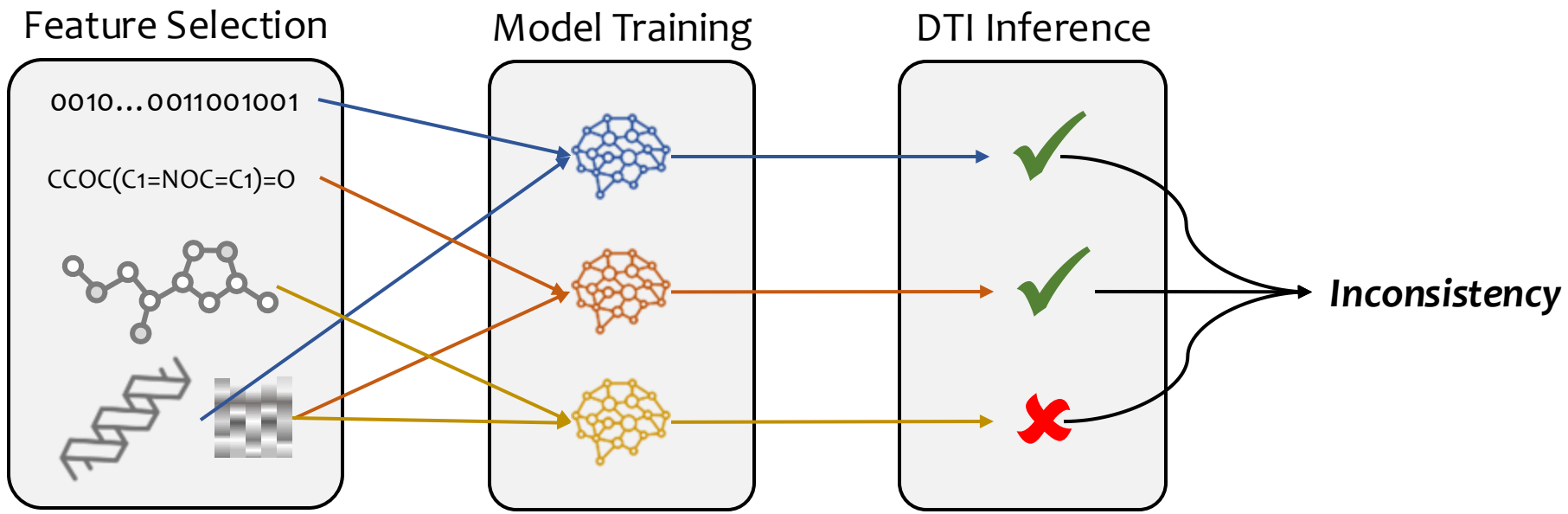


Background | Inconsistency in DTI prediction

2. LBDD methods are not yet suitable for preliminary drug candidate screening.

- Current Ligand Based Drug Design (LBDD) models for Drug-Target Interaction (DTI) prediction show a **lack of consensus**, often producing divergent outcomes for the same test samples.

- Moreover, the **performance of these models can vary significantly** across different datasets, highlighting their inconsistency and limited reliability for early-stage drug screening.



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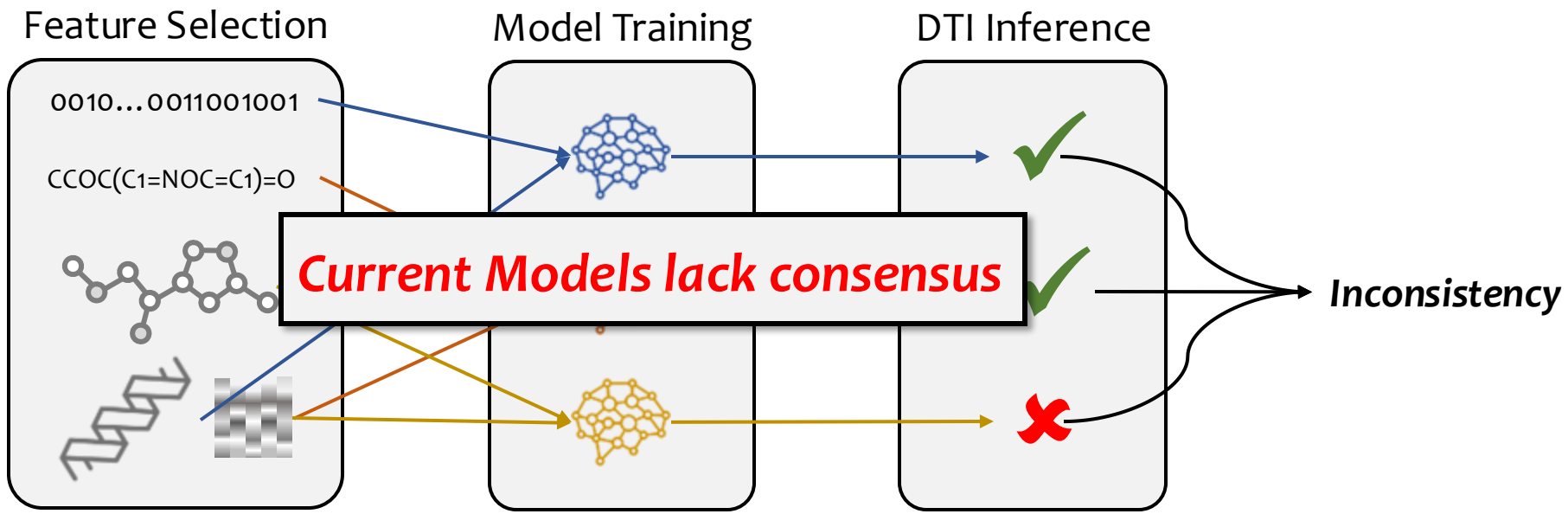

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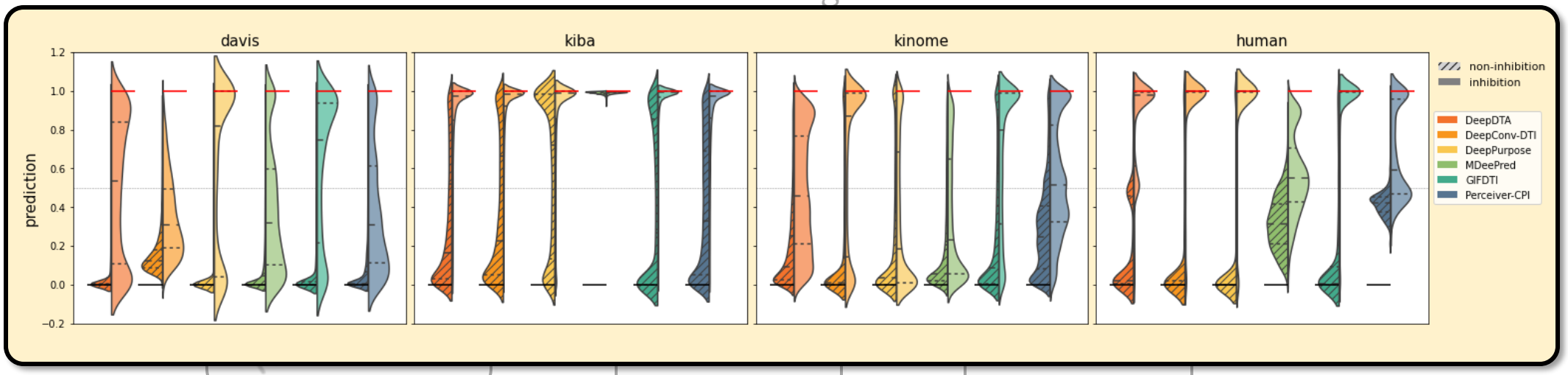
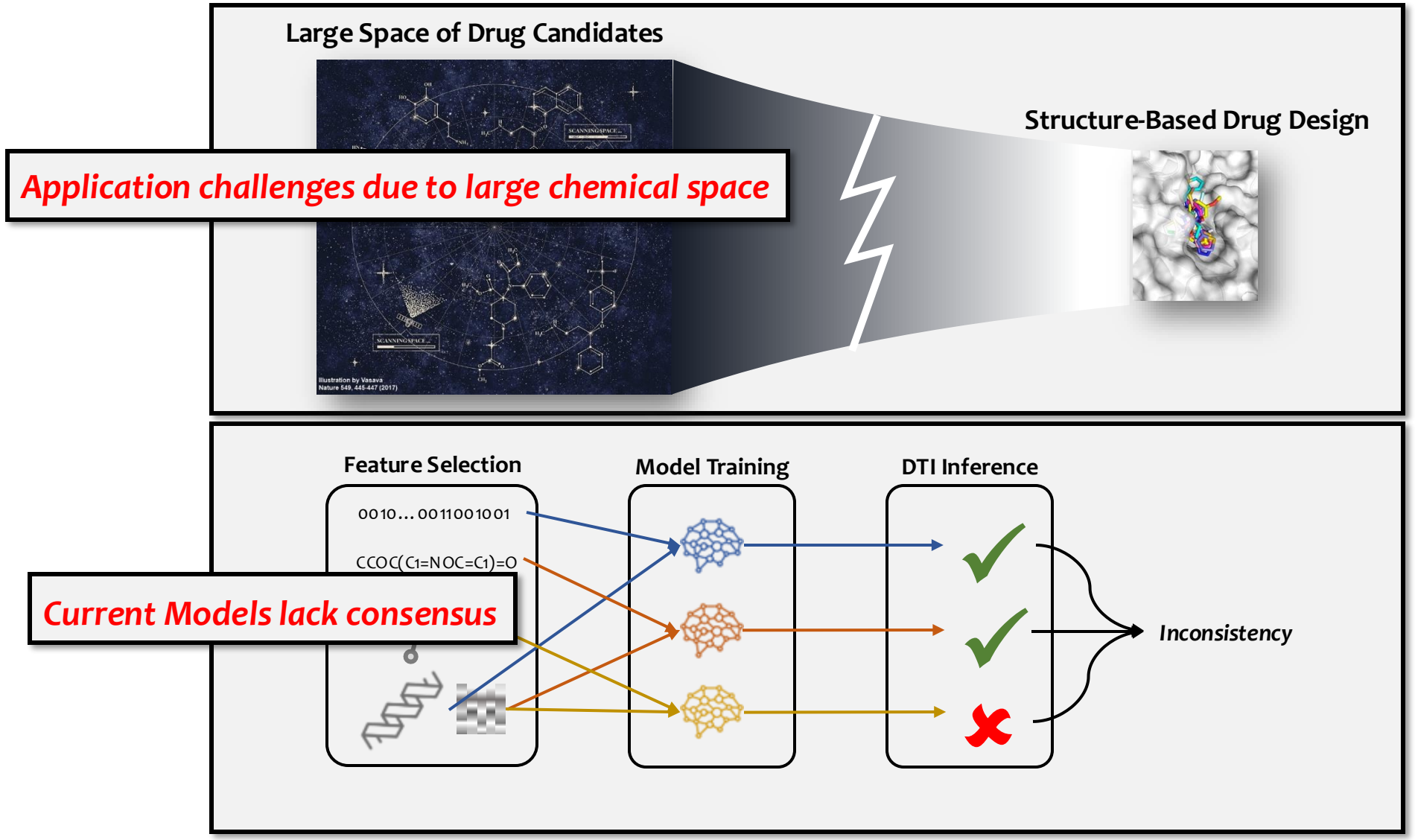
Feature Selection Model Training DTI Inference



Motivation | Consistent Screening Method with Ranking



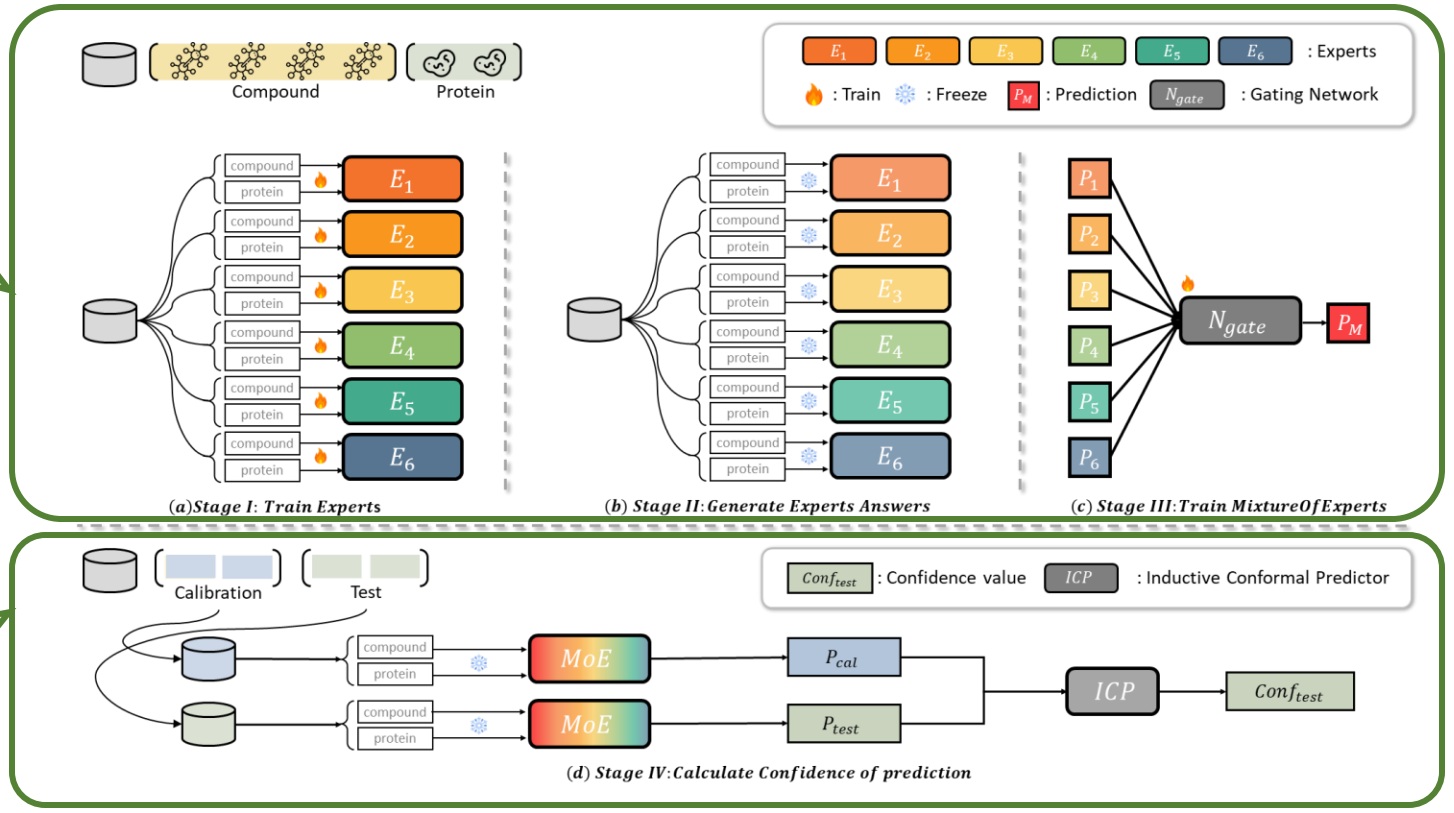
Method

Model Architecture

*We propose a Mixture-of-Experts (MoE) approach designed to enhance the prediction **accuracy** and **reliability** of existing expert models across diverse data distributions. Additionally, we apply an Inductive Conformal Predictor (ICP) to **generate a ranked list** that prioritizes candidates for screening.*

- ***MoE*** effectively captures **various aspects of the data**, leading to improved performance and **ensuring consistency**.

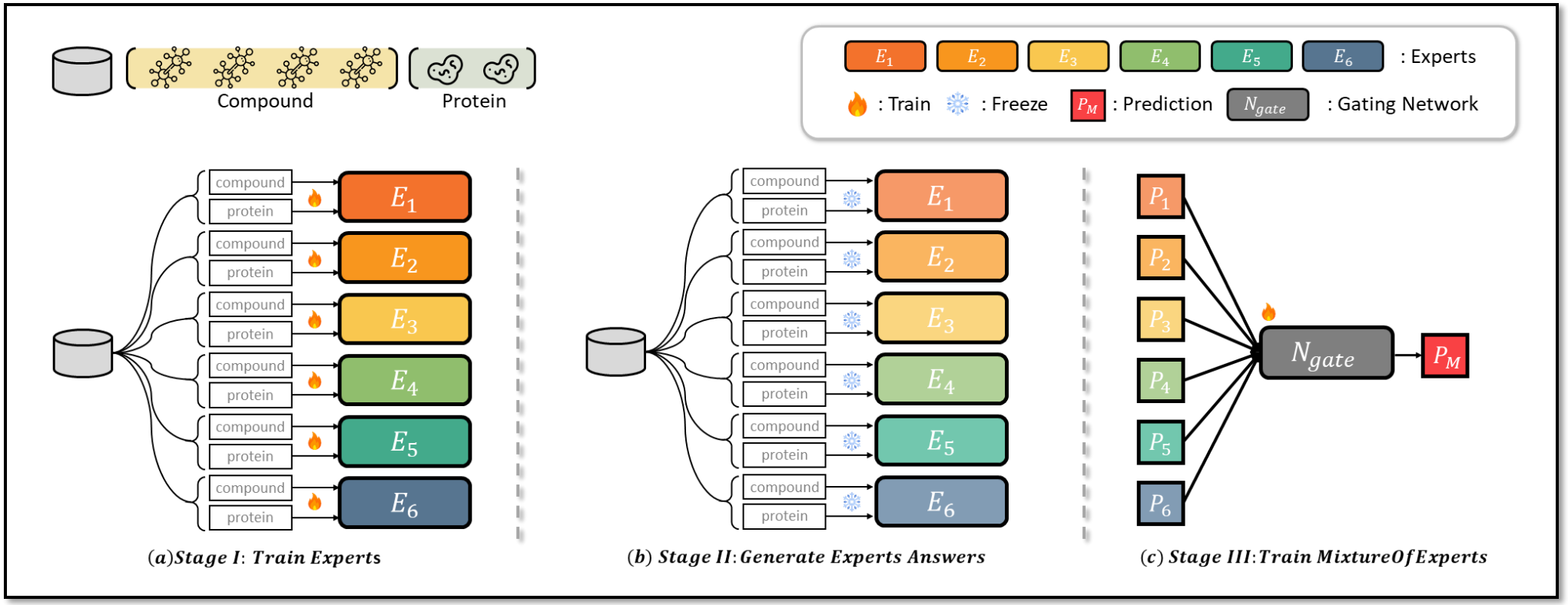
- ***ICP*** provides a confidence measure for the final prediction, further assisting researchers in identifying small molecules that are likely to bind to target proteins.



Method | Mixture-of-Experts

- Mixture of experts (MOE) is a powerful machine learning technique that leverages multiple specialized models to enhance overall prediction accuracy and robustness.

$$\text{MoE}(d, p) = \text{MLP}\left([\, f_1(d, p), f_2\,(d, p), \ldots, f_6\,(d, p)\,]\right)$$



Method

Inductive Conformal Predictor

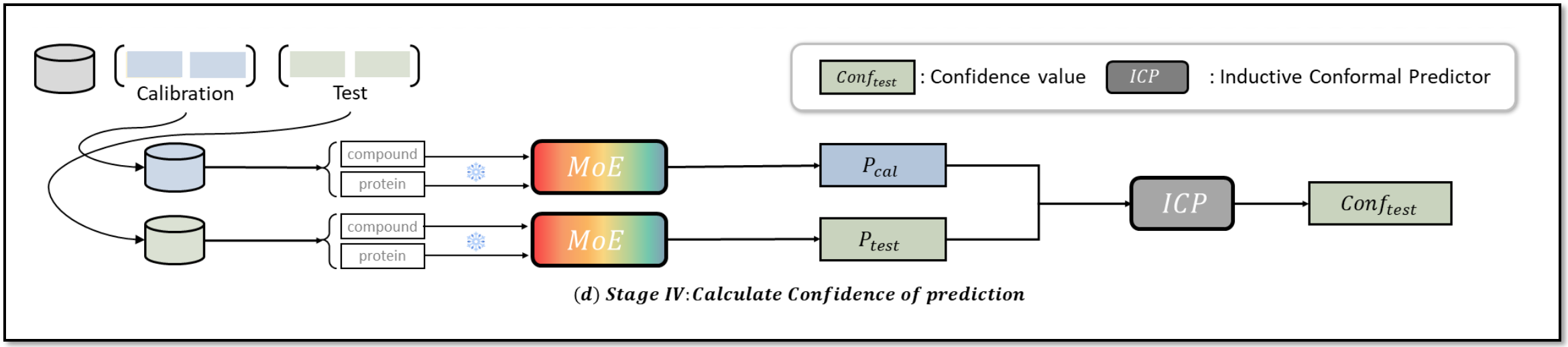
- The inductive conformal predictor (ICP) framework independently assesses the credibility of model predictions by estimating confidence levels for each sample.

- Non-conformity score measures the confidence level:

$$\alpha_i = 0.5 - \frac{\hat{p}(y_i|x_i) - \max_{y \neq y_i} \hat{p}(y|x_i)}{\#\ of\ class}$$

- Ranking with p-value:

$$p(y|x) = \frac{\sum_{x_i \in calib} \mathbb{I}(\alpha_i > \alpha)}{|X_{calib}|}$$



(d) Stage IV: Calculate Confidence of prediction

Results

Overall Performance

- we evaluate our approach using four benchmark datasets (*each derived from distinct experimental settings*).
  - *Davis, Kiba, Kinome, and Human*
- EnsDTI demonstrates **significant improvements in performance** compared to existing DTI models across these varied databases.
- By leveraging the Mixture-of-Experts (MoE) approach, EnsDTI **effectively balances the expertise from multiple models**, delivering stable and robust predictions across diverse data distributions.

Model	davis			kiba			kinome			human		
	ACC	AUROC	AUPRC	ACC	AUROC	AUPRC	ACC	AUROC	AUPRC	ACC	AUROC	AUPRC
DeepDTA	0.938	0.901	0.603	0.875	0.915	0.955	0.730	0.802	0.716	0.893	0.888	0.921
DeepConv-DTI	0.924	0.828	0.440	0.890	0.909	0.953	0.767	0.821	0.757	0.906	0.905	0.938
DeepPurpose	0.939	0.923	0.636	0.773	0.715	0.910	0.610	0.602	0.550	0.908	0.910	0.943
MDeePred	0.929	0.869	0.500	0.790	0.599	0.895	0.670	0.696	0.627	0.763	0.773	0.859
GIFDTI	0.927	0.912	0.604	0.886	0.914	0.944	0.742	0.802	**0.857**	0.905	**0.970**	0.976
CPI-Perceiver	0.928	0.863	0.488	0.877	0.901	0.946	0.714	0.762	0.826	0.825	0.904	0.920
EnsDTI	**0.949**	**0.929**	**0.670**	**0.906**	**0.942**	**0.958**	**0.795**	**0.866**	0.790	**0.959**	0.958	**0.977**

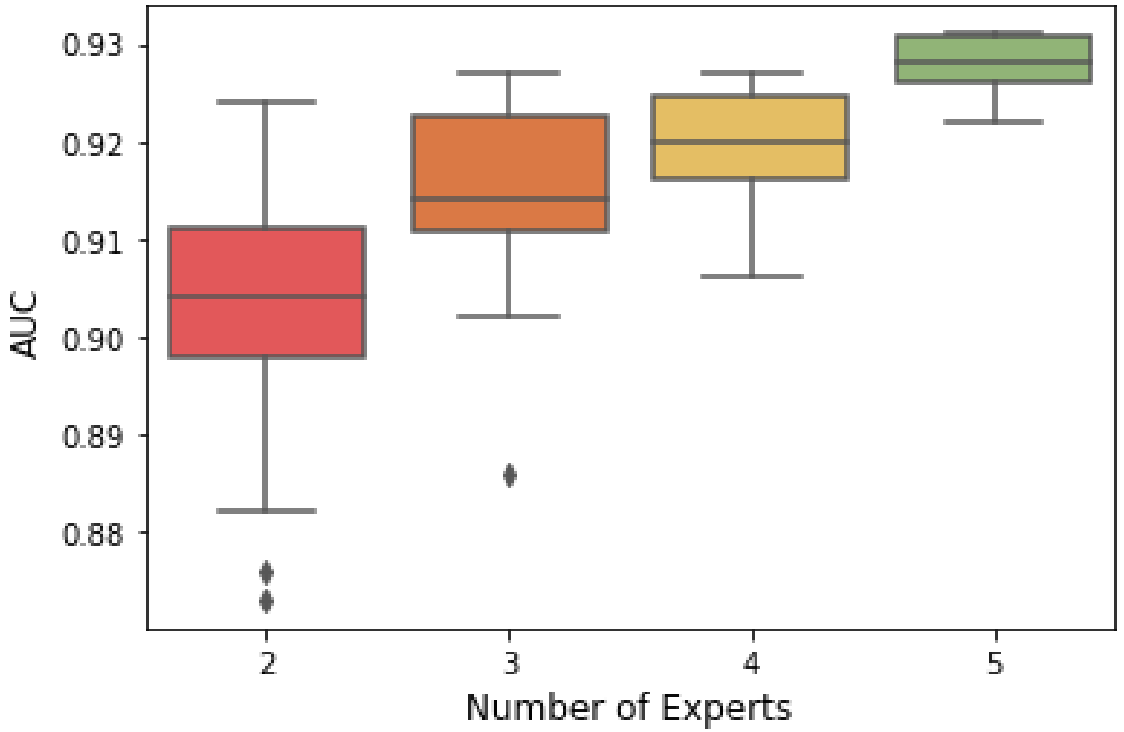
Results

Consensus Achieved with EnsDTI

- As the number of expert models increases, EnsDTI achieves improved performance and **reduced bias**.

-> Potential:

State-of-the-art models can be seamlessly integrated into EnsDTI. Thus, EnsDTI has the potential to function as a plug-and-play, up-to-date, and reliable public tool for candidate screening.

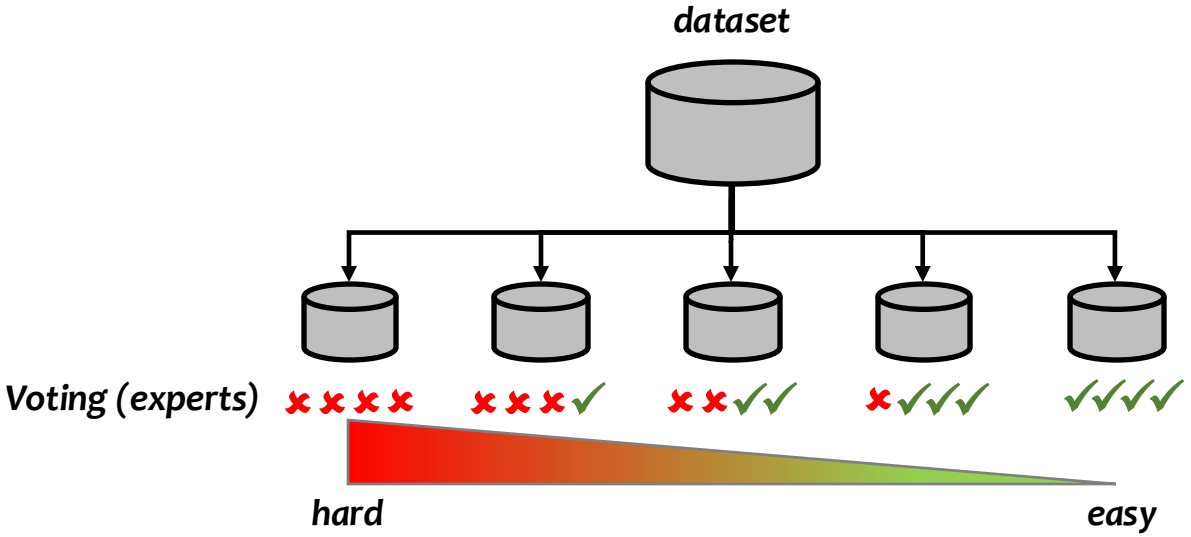


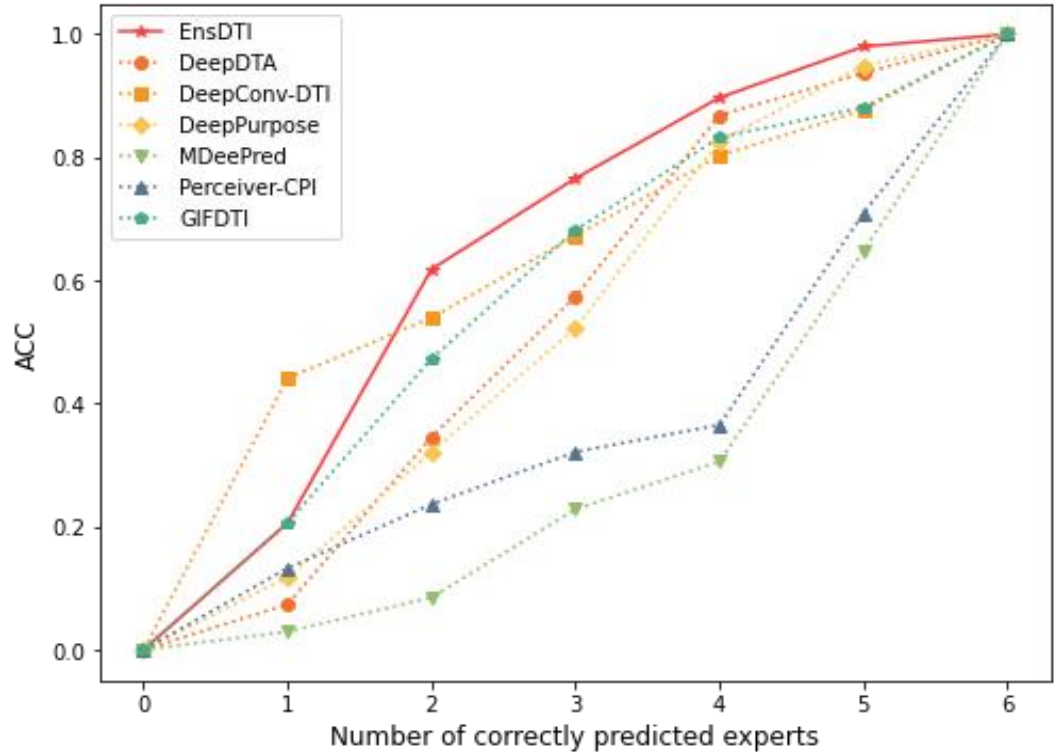
Results

Effectiveness of EnsDTI (MoE)

EnsDTI outperforms traditional DTI expert models on data where experts exhibit uncertainty

- Overall, EnsDTI demonstrates greater reliability compared to other models, especially on high-difficulty datasets.



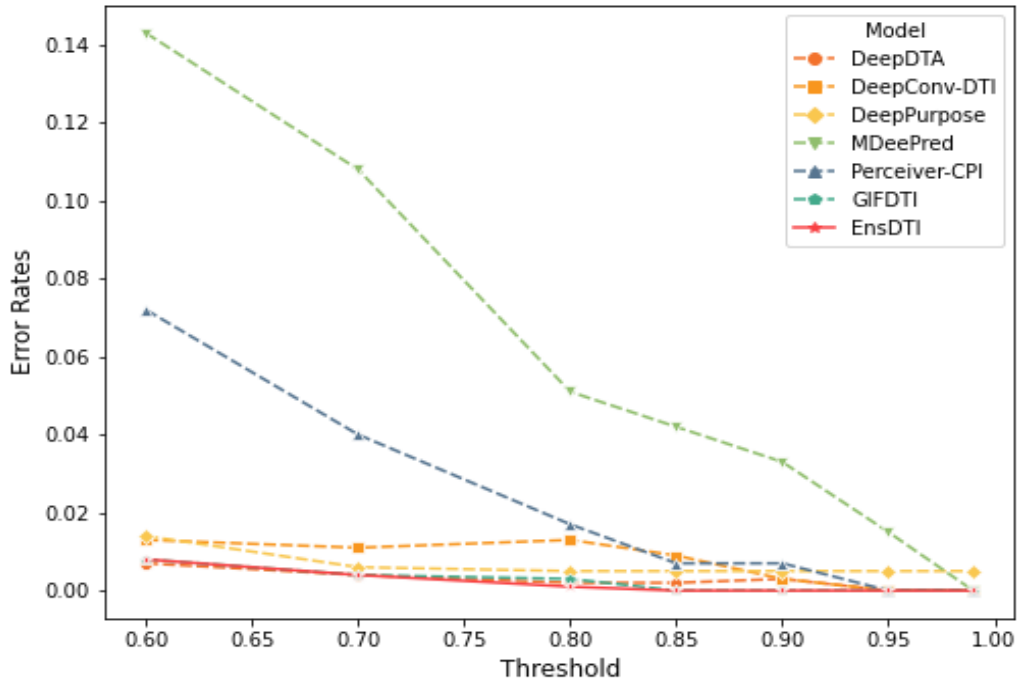


Results

Effectiveness of EnsDTI (ICP)

EnsDTI Predicts DTIs with High Confidence

- We use inductive conformal prediction to evaluate the confidence of each prediction.
- **<u>Compared to baselines:</u>**
  - At the same confidence threshold, EnsDTI demonstrates lower error rates.
- **<u>Under various confidence thresholds:</u>**
  - EnsDTI consistently delivers robust performance, maintaining significantly lower error rates compared to its promised confidence threshold.



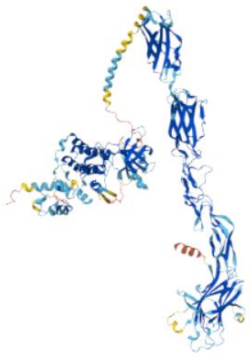
Results | Case Study

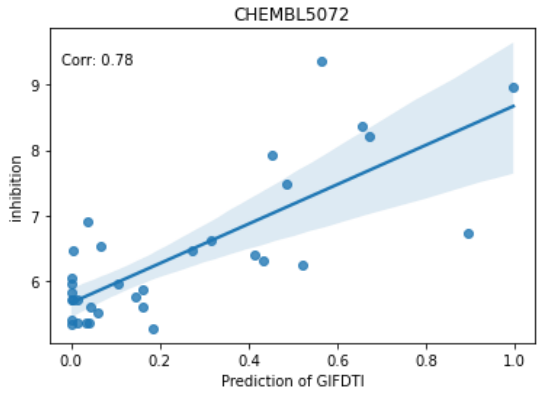
EnsDTI shows promise in inferring target bioactivities

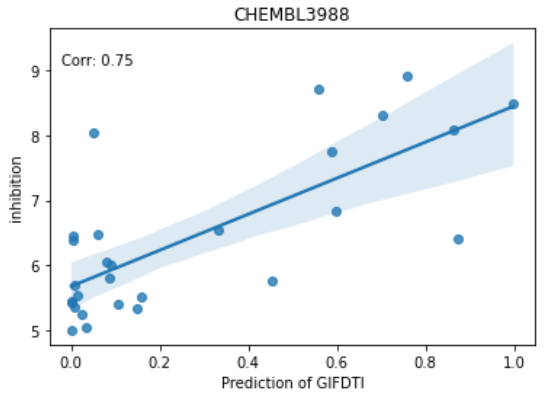
Models trained on binarized labels implicitly reflect the likelihood of how effectively a small molecule can interact with a specific protein.

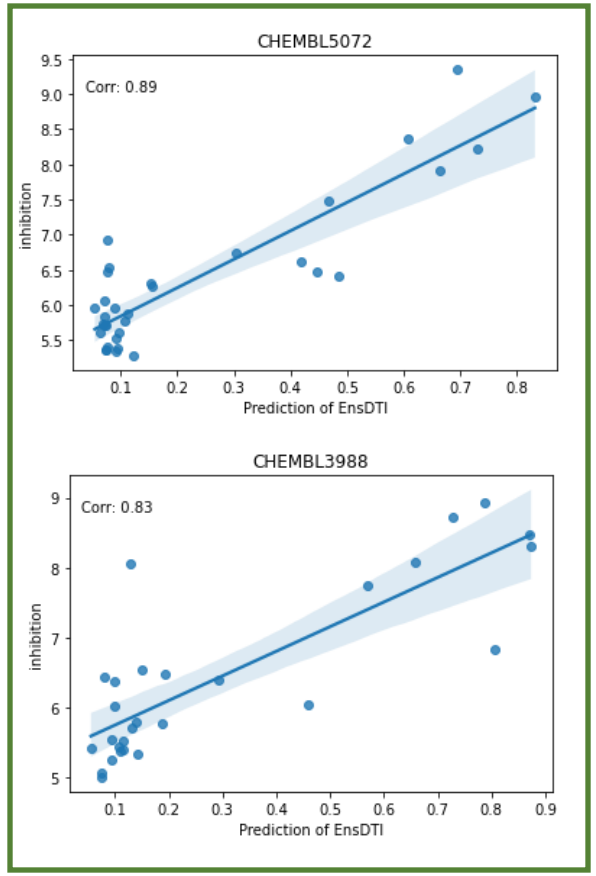
For example, when comparing two functionally similar proteins, Ephrin type-B receptor 1 (CHEMBL5072) and Ephrin type-A receptor 4 (CHEMBL3988):

- prediction probabilities provided by EnsDTI for potential candidate drugs exhibit the highest correlation with experimental assay results.









Summary

- In this work, we introduce EnsDTI, to the best of our knowledge, the first mixture-of-experts architecture designed for drug-target interaction (DTI) prediction.

Our key contributions are:

- **Robust Predictions**: By leveraging the mixture-of-experts mechanism, EnsDTI delivers accurate and reliable predictions across diverse data distributions.

- **Confidence Estimation**: The integration of the inductive conformal predictor further enhances the model's predictions with confidence values, facilitating easier and more reliable application in real-world tasks.

- **Versatility and Integration**: EnsDTI demonstrates strong potential for incorporating state-of-the-art models, offering a user-friendly tool for drug development scientists.

Thank you for listening!