Uncertainty Quantification in Compound Potency Prediction

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Why do we need uncertainty quantification?

- explainability
- understanding applicability domain and limitations
- application in multi-disciplinary settings
- use in downstream tasks, e.g., active learning

Models with uncertainty quantification

bagging

ensembles

snapshot ensembles

deep ensembles

Bayes by Backprop

MC dropout

Bayesian

VAE

Laplace's approximation

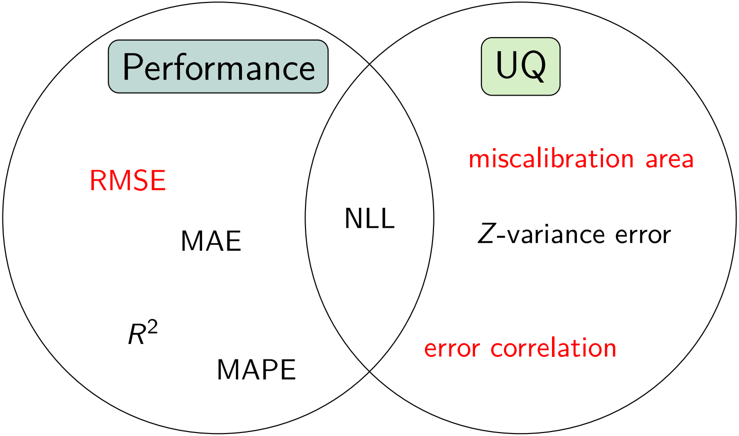
deep evidential regression

MVE

other

conformal prediction

Metrics for uncertainty quantification



Application to compound potency prediction

Data:

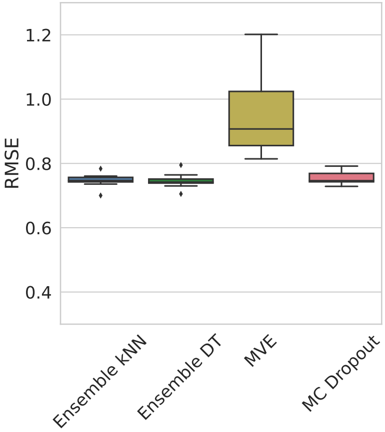
- potency of compounds in inhibition (regression)
- extracted from ChEMBL33
- extensive curation

Training pipeline:

- compounds represented using binary fingerprints
- gridsearch for hyperparameter optimization
- 10-fold cross-validation

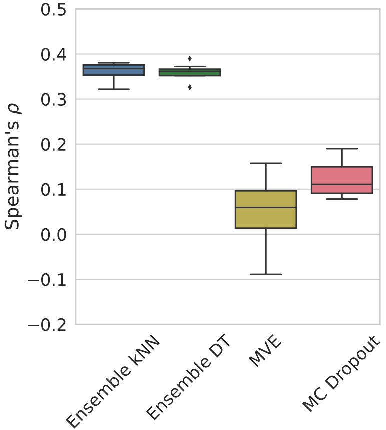
The following results are taken from:
Roth, J. P. & Bajorath, J. *Sci Rep* **14**, 6536 (2024).

Performance results



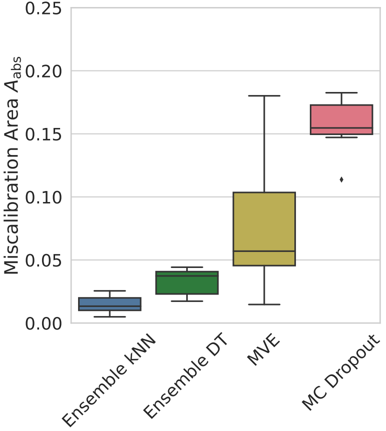
- most models exhibit overall accurate, stable, and comparable performance
- MVE model is less accurate and shows larger variance in performance
- simple ML models meet performance of neural networks

UQ results: Error correlation



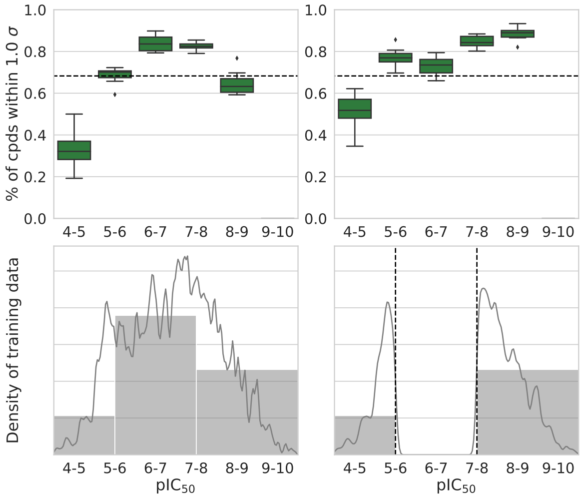
- ensemble methods show weak correlation between true error and predicted error
- NN based methods show *no* correlation and large spread

UQ results: Miscalibration area



- ensembles exhibit smallest miscalibration area
- MC Dropout model shows worse calibration compared to MVE
- MVE exhibits considerable spread in calibration quality

UQ results: Calibration across potency



Conclusion

- ensembles of conventional ML models can be used for uncertainty quantification
- NN based methods did not exhibit correlation between prediction error and uncertainty
- single metrics for the assessment and comparison of uncertainty quantification are often limited in their interpretability
- data distribution influences the quality of uncertainty quantification (model and data dependent)

Outlook

- understanding of error sources (data-based and model-based)
- combination of different approaches
  - e.g., building a separate error model
- establishing viable metrics for comparison of models with uncertainty quantification
- evaluating benchmark sets for proper comparison of models and metrics