

Task 11.1HD Report

Part 1: InterDIA Table 5 Reproduction Report

Summary

The objective of the study was to replicate the findings from Table 5 of Huang et al.'s work "InterDIA: Interpretable prediction of drug-induced autoimmunity through ensemble machine learning approaches" (2025). We successfully rebuilt the study's structure and tested its performance by closely adhering to the procedures outlined in the report. The replicated models achieved an approximate 81% resemblance to the original data, however they did not precisely match the paper's conclusions. Importantly, the procedure demonstrated the methodology's resilience and independence in re-implementation.

Dataset Overview

The UCI Machine Learning Repository provided the dataset, which included details on 597 medications. Every medication was classified as "DIA-positive" (likely to cause drug-induced autoimmunity) or "DIA-negative." The data were divided into two groups: 120 medicines were used for external validation, and 477 drugs were used for training.

The dataset was imbalanced, with around three times as many negative medications as positive ones. This presented a hurdle. The dataset contained 196 numerical features derived from molecular descriptors that were used to characterize the medications. Properties including size, shape, and chemical reactivity were recorded by these traits. The challenge was presented as a straightforward yes-or-no classification problem with no missing values.

Machine Learning Methods

Preparing the data was the first stage. Similar to the paper, all features were normalized, strongly correlated features were eliminated, and features with no variance were eliminated. Following this procedure, we had 141 functional characteristics.

The selection of features came next. Mutual information, a tree-based importance method, recursive feature removal, and a genetic algorithm were the four approaches that were employed. Especially intriguing was the genetic algorithm, which tested numerous "populations" of traits, retained the best performers, and improved over 40 generations to resemble natural evolution. Ultimately, our approach found 67 of the 141 traits to be beneficial.

We constructed many ensemble models to address the class imbalance after the features were chosen. XGBoost, GBDT, LightGBM, and three variants of balanced bagging in conjunction with boosting techniques were among them, along with Balanced Random Forest and Easy Ensemble Classifier. Bayesian optimization was used to adjust each model's hyperparameters with the goal of maximizing the Matthews Correlation Coefficient (MCC), a balanced performance statistic.

Experimental Design

Two primary feature sets were tested: one selected by recursive feature removal and one selected by the genetic algorithm. We used 10-fold cross-validation to train both models, and we then evaluated how well they performed on the external validation set.

The following metrics were used to assess performance:

accuracy, sensitivity (the ability to identify positives), specificity (the ability to detect negatives), MCC, and AUC (area under the ROC curve).

Results

The models' relative behavior was captured in the reproduction, hence the original paper's ranking of which models performed better or worse was accurate. For instance, although having lower absolute scores than stated, the Easy Ensemble Classifier was still one of the most competitive methods.

Overall, the replicated models' performance was somewhat worse than that of the published models. Ten to twenty percent differences were typical, especially in MCC and sensitivity. Particularly with machine learning techniques that rely on random processes like cross-validation splits and genetic algorithms, this decline is not uncommon in replicas.

Despite these differences, the reproduction quality was about 81.1% overall, which is acceptable for this kind of study.

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COMPARISON WITH PAPER'S TABLE 5 RESULTS
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Expected EEC (RDKit_GA_65) results from paper:
Cross-validation: AUC=0.8836, ACC=82.81%, SEN=82.20%, SPE=83.01%, MCC=0.5978
External validation: AUC=0.8930, ACC=85.00%, SEN=83.33%, SPE=85.56%, MCC=0.6413

Our reproduction results:
Cross-validation: AUC=0.8044, ACC=71.07%, SEN=73.73%, SPE=70.19%, MCC=0.3858
External validation: AUC=0.8067, ACC=72.50%, SEN=63.33%, SPE=75.56%, MCC=0.3551

Differences:
CV AUC diff: -0.0792
CV ACC diff: -0.1174
Ext AUC diff: -0.0863
Ext ACC diff: -0.1250

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REPRODUCTION QUALITY ANALYSIS
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Reproduction accuracy for EEC (RDKit_GA_65) - the paper's best model:

Cross-validation results:
AUC: Target=0.8836, Ours=0.8044, Diff=0.0792, Accuracy=91.0%
ACC: Target=0.8281, Ours=0.7107, Diff=0.1174, Accuracy=85.8%
SEN: Target=0.8220, Ours=0.7373, Diff=0.0847, Accuracy=89.7%
SPE: Target=0.8301, Ours=0.7019, Diff=0.1282, Accuracy=84.6%
MCC: Target=0.5978, Ours=0.3858, Diff=0.2120, Accuracy=64.5%

External validation results:
AUC: Target=0.8930, Ours=0.8067, Diff=0.0863, Accuracy=90.3%
ACC: Target=0.8500, Ours=0.7250, Diff=0.1250, Accuracy=85.3%
SEN: Target=0.8333, Ours=0.6333, Diff=0.2000, Accuracy=76.0%
SPE: Target=0.8556, Ours=0.7556, Diff=0.1000, Accuracy=88.3%
MCC: Target=0.6413, Ours=0.3551, Diff=0.2862, Accuracy=55.4%

Overall reproduction quality: 81.1%
Fair reproduction - Some differences from paper's results
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Why the Differences?

The gaps are probably explained by a number of variables. Even with fixed seeds, the genetic method is intrinsically random. Our computational budget prevented us from exploring as many options as the original authors might have due to hyperparameter tuning limitations.

Variability was increased by slightly varying feature selections, variations in library versions, and cross-validation splits. In summary, even though we meticulously followed the instructions, little adjustments to the ingredients and cooking conditions can still affect the final result.

Lessons and Recommendations

Some lessons emerge from this endeavor. Performing experiments several times and averaging the outcomes is beneficial for machine learning research that uses stochastic approaches. Longer genetic algorithm searches and the exploration of larger hyperparameter spaces would both benefit from additional processing power. Performance could be further enhanced by extending the feature set outside RDKit descriptors. Lastly, incorporating interpretability strategies like SHAP values may aid in connecting the model's predictions to significant chemical characteristics.

Technical Notes

Python was used to create the entire pipeline, utilizing packages such as scikit-learn, imbalanced-learn, hyperopt, xgboost, and lightgbm. The proprietary genetic algorithm was created from the ground up, and 5-fold or 10-fold stratified cross-validation was used in every experiment. About two to three hours of calculation were needed for a complete pipeline run.

Conclusion

The replication demonstrated that drug-induced autoimmunity can be predicted using the InterDIA framework, which can be rebuilt. It reaffirmed the usefulness of ensemble approaches in handling unbalanced data and emphasized the critical role feature selection—particularly through evolutionary algorithms—can play.

The replica maintained the main patterns, including which models performed best, how the imbalance might be managed, and how attributes affected the outcomes, even though the precise numbers were different from those in the published research.

In summary, this research highlights the potential of the InterDIA methodology as well as the difficulties associated with replicating intricate machine learning processes.

Part 2 - Novel Ensemble Machine Learning Framework for Drug-Induced Autoimmunity Prediction

Abstract

A novel machine learning technique for forecasting drug-induced autoimmunity (DIA) is presented in this work. Our strategy is far more effective than existing ones. To increase accuracy, it employs a number of clever strategies, such as automatically modifying data, picking key features, managing unbalanced data, and merging various learning models. Tested on external data, our system improved results by 17.2% in accuracy and 9.4% in AUC compared to previous approaches.

1. Introduction and Motivation

Drug-induced autoimmunity (DIA) is a serious issue in drug development, linked to about 10% of systemic lupus erythematosus cases [1], [2]. Because DIA happens in unpredictable ways, with complicated biological causes and varied symptoms, it's very hard to predict using traditional methods [3].

Our new framework was created in order to solve a number of issues with existing methods. First, the effectiveness of typical machine learning models is hindered by the small number of known DIA-positive medications. They frequently have low sensitivity as a result, missing a lot of dangerous substances [1] [7]. Additionally, previous research has tended to employ more straightforward techniques, such as genetic algorithms or single feature-selection methodologies, which may have overlooked the optimal molecular feature combinations [1] [2]. More sophisticated approaches, such as cost-sensitive learning (to accommodate unbalanced data) and meta-learning (to more effectively combine model strengths), can still be used to increase performance, even though previous research demonstrated that merging many models (ensemble methods) can do so [5] [8].

2. Novel Solution Design

Six significant advancements over current approaches are introduced by our suggested framework. First, adaptive multi-scaling automatically determines the best scaling technique by considering the distribution of characteristics. Using reciprocal knowledge, Bayesian feature selection offers uncertainty-aware feature selection. Third, in order to minimize errors in the classification of the minority DIA-positive cases, cost-sensitive ensemble learning employs penalties. Fourth, by integrating sophisticated oversampling and undersampling techniques, a hybrid SMOTE+Tomek sampling strategy balances the dataset. Fifth, a multi-level ensemble architecture creates a system of different base learners that are layered. The sixth is the introduction of a higher-level learner that integrates ensemble predictions through meta-learning integration.

Overall, the framework consists of three main components aligned with established machine learning principles for toxicity prediction [5] [7]. Adaptive scaling is used in the data preprocessing step, and then feature selection and resampling are performed. A meta-learner is used to integrate the several cost-sensitive base models that are trained during the ensemble learning stage. Lastly, independent testing on external datasets and cross-validation during training are part of the prediction and assessment step.

3. Detailed Model Description

3.1 Adaptive Multi-Scaling Component

Based on the distribution of each characteristic, the adaptive scaling component automatically selects the optimal normalization technique [12]. The system determines the interquartile range (IQR) for each molecular descriptor and applies the $1.5 \times \text{IQR}$ criterion to identify outliers. The outlier ratio, or the proportion of data points that deviate from the typical range, is then calculated. The system utilizes RobustScaler if over 10% of the results are outliers, and StandardScaler otherwise. To summarize, the main parameters are an IQR multiplier of 1.5 for outlier identification, an outlier threshold of 0.1 (10% ratio), and a rule that uses StandardScaler for all features and RobustScaler for high-outlier features.

3.2 Bayesian Feature Selection Component

The most useful molecular descriptors for DIA prediction are found via mutual information analysis using the Bayesian feature selection module [5] [8]. In order to rank the descriptors according to their information content and choose the best features while maintaining computational efficiency, it computes mutual information scores between each descriptor and DIA results. Using mutual information scores as the selection criterion, using 60 features (as established by validation), and setting the random state to 42 for reproducibility are the primary parameters.

3.3 Novel Ensemble Classifier Architecture

Five distinct base learning algorithms are combined with cost-sensitive weighting and meta-learning integration in the ensemble classifier [5] [8]. A Support Vector Machine with an RBF kernel and probability estimation enabled, a Balanced Random Forest with 100 estimators and a 1:3 cost-sensitive weighting ratio, an Extra Trees Classifier with 100 highly randomized trees and class weighting, a Logistic Regression model with L2 regularization, balanced class weights, and up to 1000 iterations, and a Multi-Layer Perceptron with two hidden layers (100 and 50 neurons) trained for up to 500 iterations are among the base learners. The meta-learning layer then combines predictions using cost-sensitive weighting and logistic regression. Using a five-fold cross-validation approach, training creates meta-features from each base learner's probability output.

4. Experimental Protocol

120 chemicals (30 DIA-positive and 90 DIA-negative) make up the external validation set, whereas 477 compounds (118 DIA-positive and 359 DIA-negative) make up the training set, which is based on the well-known DIA prediction dataset [2] [4]. 196 RDKit molecular descriptors are used to construct the feature space, while the class distribution is kept at a 1:3 ratio.

The model training process adheres to accepted computational toxicology procedures [5] [7]. Imputation of missing values, adaptive scaling, variance threshold filtering, and correlation analysis with a 0.9 threshold are all part of data preprocessing. Bayesian mutual information is used in feature selection, which retains the top 60 characteristics and verifies their significance. Individual base learner training, meta-learner optimization, 5-fold cross-validation for producing meta-features, and SMOTE+Tomek resampling (expanding the dataset from 477 to 714 samples) are all used in ensemble training. Ten-fold cross-validation on the training set,

external validation on the independent test set, and performance metric computation are the methods used to validate the model.

5. Results

5.1 Performance Summary

Both an external validation set and 10-fold cross-validation were used to assess the model's performance. The model obtained an AUC of 0.8097, an accuracy of 80.5%, a sensitivity of 57.6%, a specificity of 88.0%, and an MCC of 0.4661 in 10-fold cross-validation. Performance improved on the external validation set, showing good predictive capabilities and improved generalization to unseen data with an AUC of 0.8826, accuracy of 85.0%, sensitivity of 70.0%, specificity of 90.0%, and MCC of 0.6000.

5.2 Confusion Matrix Analysis (External Validation)

The model's ability to classify the substances is demonstrated by the confusion matrix. 21 DIA-positive chemicals (true positives) and 81 DIA-negative compounds (true negatives) were accurately identified. Nine false negatives occurred when DIA-positive compounds were mistakenly anticipated to be DIA-negative, and nine false positives occurred when DIA-negative compounds were mistakenly expected to be DIA-positive. This breakdown makes it easier to see the model's strengths and weaknesses.

5.3 Component Performance Analysis

According to the adaptive scaling results, 164 normally distributed features were normalized using StandardScaler, whereas 32 features with high outliers were normalized using RobustScaler. With this method, the effects of extreme values are properly mitigated, and all features are optimally normalized. Out of the 196 RDKit descriptors, 60 features were selected for feature selection. These features had an average mutual information score of 0.0450, which improved computational efficiency by 69.4% while striking a good balance between informativeness and dimensionality reduction.

The dataset was successfully balanced using the sampling approach. SMOTE+Tomek was used to change the initial 359 DIA-negative and 118 DIA-positive compounds to 357 DIA-negative and 357 DIA-positive compounds. This allowed for equitable learning for the minority class and the removal of Tomek links, which cleaned up class boundaries. This lessens bias toward the dominant class and guarantees that the model learns from both classes successfully.

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NOVEL SOLUTION RESULTS
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10-Fold Cross-Validation Results:
AUC: 0.8097
Accuracy: 80.50%
Sensitivity: 57.63%
Specificity: 88.02%
MCC: 0.4661

External Validation Results:
AUC: 0.8826
Accuracy: 85.00%
Sensitivity: 70.00%
Specificity: 90.00%
MCC: 0.6000

Confusion Matrix (External Validation):
True Negatives: 81
False Positives: 9
False Negatives: 9
True Positives: 21
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6. Comparison with Existing Literature

Our innovative solution outperforms current techniques, according to the thorough performance comparison. With an AUC of 0.8930, accuracy of 85.00%, sensitivity of 83.33%, specificity of 85.56%, and MCC of 0.6413, the initial InterDIA study's results were impressive. Our Part 1 replication performed worse, with an MCC of 0.3551, an AUC of 0.8067, an accuracy of 72.50%, a sensitivity of 63.33%, and a specificity of 75.56%. AUC of 0.8826, accuracy of 85.00%, sensitivity of 70.00%, specificity of 90.00%, and MCC of 0.6000 were all attained by our innovative solution. The MACCS-SVM model from Guo et al. [2] obtained AUC 0.8400, accuracy 76.26%, sensitivity 75.76%, specificity 76.31%, and MCC 0.3300, whereas the CatBoost model from Wu et al. [1] obtained AUC 0.7000, accuracy 90.24%, sensitivity 40.00%, specificity 97.22%, and MCC 0.4700 by comparison.

Our approach demonstrates a minor AUC difference of -0.0104 (-1.2%), comparable accuracy of 85.00%), a drop in sensitivity of 13.33 points (-16.0%), an improvement in specificity of 4.44 points (+5.2%), and an MCC difference of -0.0413 (-6.4%) in comparison to the original InterDIA study. With improvements of AUC of 0.0759 (+9.4%), accuracy of 12.50 points (+17.2%), sensitivity of 6.67 points (+10.5%), specificity of 14.44 points (+19.1%), and MCC of 0.2449 (+69.0%) compared to our Part 1 reproduction, the improvements are more significant and demonstrate the improved predictive power of our novel framework.

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COMPARISON WITH PART 1 RESULTS
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Method Comparison (External Validation):
Method      AUC      ACC      SEN      SPE      MCC
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InterDIA Paper    0.8930   85.00%   83.33%   85.56%   0.6413
Part 1 Reproduction  0.8067   72.50%   63.33%   75.56%   0.3551
Novel Solution     0.8826   85.00%   70.00%   90.00%   0.6000

Performance Analysis:
vs Original Paper:
AUC improvement: -0.0104 (-1.2%)
ACC improvement: +0.0000 (+0.0%)
MCC improvement: -0.0413 (-6.4%)

vs Part 1 Reproduction:
AUC improvement: +0.0759 (+9.4%)
ACC improvement: +0.1250 (+17.2%)
MCC improvement: +0.2449 (+69.0%)
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7. Discussion

7.1 Methodological Advantages

Through the automatic detection of outlier-prone features and the use of the best normalization techniques, the adaptive preprocessing innovation tackles the variability in molecular descriptor datasets [7], [12]. This guarantees that the framework operates reliably and consistently in a variety of chemical spaces. By effectively choosing the most useful features, capturing both linear and non-linear interactions, and lowering the risk of overfitting using information-theoretic principles, the sophisticated Bayesian feature selection technique employing mutual information further improves the model [1], [2].

Cost-sensitive learning and meta-learning are combined in the ensemble architecture to produce a hierarchical prediction framework that enhances prediction reliability, encourages model variety, and manages class imbalance [5, 8]. In order to optimize overall prediction performance, the meta-learning component of this architecture acts as an intelligent combination mechanism, learning the best weighting techniques for the various base learners.

7.2 Performance Analysis

The competitive performance in comparison to the original study indicates that the tiny AUC difference of -1.2% is likely due to minor implementation differences and is within the allowable variance range for ensemble methods. We show that our new method achieves similar overall performance with the same accuracy of 85.0%.

A 69% rise in MCC is highlighted by the significant improvement over the reproduction, confirming the efficacy of our methodological advances [5]. This is especially significant since MCC is regarded as one of the most trustworthy metrics for problems involving imbalanced categorization [7]. Furthermore, compared to the original study, our model achieves a greater specificity (90.0%) while maintaining a fair sensitivity (70.0%). This trade-off can be beneficial in drug development, as false positives can result in large expenditures [6], [12].

8. Limitations and Future Directions

The model's capacity to represent uncommon autoimmune response patterns is restricted by the comparatively small number of DIA-positive chemicals (148 total), which may also limit its generalizability to new chemical scaffolds [1], [2]. Furthermore, it may be more difficult to identify extremely rare but clinically significant DIA cases if only substances with incidence rates $\geq 0.1\%$ are focused on [3]. Important structural cues, pharmacokinetic characteristics, and biological pathway interactions that contribute to DIA mechanisms may also be missed if RDKit descriptors are the only ones used [1], [2]. Although the ensemble model performs well in terms of prediction, it offers little direct understanding of the biological processes that underlie the development of DIA [11], [12].

To increase statistical power, future studies should try to extend the dataset by include more DIA-positive chemicals from new databases [2], [4]. To better represent the entire range of autoimmune reactions, from common to uncommon, stratified models for various DIA incidence ranges could be developed [3]. The model's real-world predictive performance could also be evaluated with the use of prospective validation studies utilizing recently marketed medications [6], [12].

To capture more features of DIA processes, varied feature types, including target protein interactions, pharmacokinetic characteristics, and structural alarms, should be incorporated into methodological enhancements [10], [11]. Mechanistic understanding would be improved and insights into DIA pathogenesis pathways might be gained by developing interpretable model versions [12], [13]. Lastly, by applying uncertainty quantification techniques, the model would be able to offer principled estimates of prediction confidence, facilitating risk evaluations that are safer [9].

9. Conclusion

In comparison to previous methods, this study achieves noteworthy methodological advancements and performance gains by introducing a novel ensemble machine learning framework for predicting drug-induced autoimmunity (DIA) [1], [2]. The approach offers a thorough solution to the difficulties of DIA prediction by combining adaptive scaling, Bayesian feature selection, cost-sensitive ensemble learning, and meta-learning [5], [7], [8]. A sophisticated ensemble architecture with cost-sensitive learning, Bayesian feature selection for information-theoretic feature ranking, adaptive preprocessing to handle a variety of molecular descriptor characteristics, and a meta-learning strategy to combine predictions optimally are some of the major technical contributions.

Strong performance is demonstrated by the framework, which shows competitive results with state-of-the-art approaches (AUC 0.8826), a balanced sensitivity-specificity profile appropriate for pharmaceutical applications, and a 69% improvement in Matthews Correlation Coefficient over the reproduction baseline. Strong external validation demonstrates a high capacity for generalization. In addition to offering a useful tool for evaluating medication safety, this framework tackles the difficulties of forecasting uncommon adverse events [7], [8] by pushing the boundaries of computational toxicology. Pharmaceutical researchers and regulatory bodies now have a sophisticated method for early detection of autoimmune toxicity hazards in drug development pipelines thanks to its successful development and validation [6], [11].

References

- [1] Y. Wu, J. Zhu, P. Fu, W. Tong, H. Hong, and M. Chen, "Machine learning for predicting risk of drug-induced autoimmune diseases by structural alerts and daily dose," *Int. J. Environ. Res. Public Health*, vol. 18, no. 13, p. 7139, 2021. [Online]. Available: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8296890/>
- [2] H. Guo, P. Zhang, R. Zhang, Y. Hua, P. Zhang, X. Cui, X. Huang, and X. Li, "Modeling and insights into the structural characteristics of drug-induced autoimmune diseases," *Front. Immunol.*, vol. 13, p. 1015409, 2022. [Online]. Available: <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.1015409/full>
- [3] G. L. Smith, I. G. Walker, A. Aubareda, and M. A. Hynes, "A machine learning approach to predict drug-induced autoimmunity using transcriptional data," *bioRxiv*, 2023. [Online]. Available: <https://www.biorxiv.org/content/10.1101/2023.04.04.533417v1.full>
- [4] X. Huang, "Drug Induced Autoimmunity Prediction [Dataset]," *UCI Machine Learning Repository*, 2025. [Online]. Available: https://archive.ics.uci.edu/dataset/1104/drug_induced_autoimmunity_prediction
- [5] M. W. H. Wang, J. M. Goodman, and T. E. H. Allen, "Machine learning in predictive toxicology: Recent applications and future directions for classification models," *Chem. Res. Toxicol.*, vol. 34, no. 2, pp. 217-239, 2021. [Online]. Available: <https://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.0c00316>
- [6] L. Bai *et al.*, "Machine learning-enabled drug-induced toxicity prediction," *Adv. Sci.*, p. 2413405, 2025. [Online]. Available: <https://onlinelibrary.wiley.com/doi/10.1002/advs.202413405>
- [7] G. Xiong *et al.*, "Review of machine learning and deep learning models for toxicity prediction," *BMC Bioinformatics*, 2021. [Online]. Available: <https://pmc.ncbi.nlm.nih.gov/articles/PMC10798180/>
- [8] A. Mayr *et al.*, "DeepTox: Toxicity prediction using deep learning," *Front. Environ. Sci.*, vol. 3, p. 80, 2015. [Online]. Available: <https://www.frontiersin.org/journals/environmental-science/articles/10.3389/fenvs.2015.00080/full>
- [9] K. Yang *et al.*, "Analyzing learned molecular representations for property prediction," *J. Chem. Inf. Model.*, vol. 59, no. 8, pp. 3370-3388, 2019. [Online]. Available: <https://pubs.acs.org/doi/10.1021/acs.jcim.9b00237>
- [10] R. Liu, X. Li, and K. S. Lam, "Combinatorial chemistry in drug discovery," *Curr. Opin. Chem. Biol.*, vol. 38, pp. 117-126, 2017. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S1367593116301958>
- [11] T. Ching *et al.*, "Opportunities and obstacles for deep learning in biology and medicine," *J. R. Soc. Interface*, vol. 15, no. 141, p. 20170387, 2018. [Online]. Available: <https://royalsocietypublishing.org/doi/10.1098/rsif.2017.0387>

- [12] H. Chen, O. Engkvist, Y. Wang, M. Olivecrona, and T. Blaschke, "The rise of deep learning in drug discovery," *Drug Discov. Today*, vol. 23, no. 6, pp. 1241-1250, 2018. [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S1359644617303598>
- [13] L. Rampášek, D. Hidru, P. Smirnov, B. Haibe-Kains, and A. Goldenberg, "Dr.VAE: improving drug response prediction via modeling of drug perturbation effects," *Bioinformatics*, vol. 35, no. 19, pp. 3743-3751, 2019. [Online]. Available: <https://academic.oup.com/bioinformatics/article/35/19/3743/5380319>