

Artificial Intelligence and Machine Learning for Predicting Drug–Drug Interactions

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I. INTRODUCTION

Adverse drug–drug interactions pose a significant challenge to patient safety and healthcare quality, as polypharmacy exponentially increases the risk of severe clinical complications (Lu et al., 2026, p. 2). Given that approximately 18% of adverse drug reactions are directly attributed to these interactions, predicting potential complications prior to clinical administration is essential for improving therapeutic outcomes (Vito et al., 2025, p. 2). However, traditional detection methods, which rely heavily on retrospective clinical observations and spontaneous post-marketing reporting, are often too fragmented and lack the proactive sensitivity required to capture complex, multi-drug interactions (Huang et al., 2025, p. 1618702; Ru et al., 2025). Furthermore, conventional experimental protocols—including in vitro and in vivo assays—are often prohibitively costly, time-consuming, and incapable of screening the vast, expanding landscape of potential polypharmaceutical combinations (BARUT & Bilgin, 2026; Jang et al., 2022, p. 88; Mei & Zhang, 2021, p. 17619). To address these limitations, this research aims to leverage machine learning and deep learning architectures to integrate multi-omics, pharmacokinetic, and real-world clinical data for more accurate, proactive interaction forecasting (Spanakis et al., 2026; Zhang et al., 2023). These computational models aim to transition from simple statistical correlations toward an understanding of underlying molecular mechanisms, thereby mitigating the data limitations and predictive inaccuracies inherent in current frameworks (Marzouk et al., 2025, p. 143). By systematically evaluating these advanced methodologies, this study seeks to enhance the reliability of predictive performance and demonstrate their utility in facilitating real-time medication safety

monitoring (Halder et al., 2025, p. 9338; Kobraci et al., 2024, p. 2). Ultimately, this integration of sophisticated computational frameworks serves to reduce preventable patient harm and optimize drug development efficiency by overcoming the inherent scope and accuracy constraints of current surveillance systems (Pune, 2024), (Askr et al., 2022, p. 5999), (Nakamura & Kato, 2025, p. 43). Specifically, this investigation evaluates how high-dimensional feature integration and pattern recognition can transcend the scope of traditional rule-based databases, which often fail to account for novel pharmacodynamic interactions (Pawar et al., 2023, p. 432). By systematically mapping these complex biological pathways through deep learning, the proposed framework seeks to identify previously unrecognized synergistic or antagonistic effects that escape conventional clinical surveillance (Luo et al., 2021, p. 319; Prejesh et al., 2026, p. 2). Furthermore, current computational approaches often fail to address the imbalance of interaction datasets, leading to skewed performance metrics that mask critical, localized prediction failures (Kpanou et al., 2021, p. 478). To mitigate these performance disparities, this study prioritizes the development of explainable AI architectures that provide transparent insights into the underlying mechanisms of predicted interactions, rather than relying solely on black-box classifications (Vo et al., 2022).

II. LITERATURE REVIEW

Existing computational approaches leverage diverse methodologies, ranging from supervised learning and graph-based models to sophisticated deep learning architectures that parse large-scale pharmaceutical databases like DrugBank (Asfand-e-yar et al., 2024, p. 4078; Sagar et al., 2025). These strategies span from

traditional similarity-based and network-based methods to advanced deep neural networks and transformer-based architectures that extract low-dimensional embeddings from structural drug data (Lin et al., 2022, p. 82; Xia et al., 2025). While classical machine learning algorithms, such as support vector machines and logistic regression, provide foundational benchmarks, modern deep learning approaches—particularly graph neural networks and hybrid models—have demonstrated superior efficacy in capturing complex topological patterns within molecular structures (Behrooznia & Hooshmand, 2025; Marqas et al., 2026). These techniques frequently capitalize on the assumption that chemically or biologically similar drugs exhibit comparable interaction profiles, utilizing features like molecular structure, target proteins, and metabolic pathways to populate predictive models (Yan et al., 2026, p. 5). While these models achieve high accuracy through structural and feature-based similarities, they often struggle with the interpretability of high-dimensional embeddings and the inherent scarcity of labeled interaction data (J. Lin et al., 2024, p. 1369404; X. Lin et al., 2023, p. 2). Furthermore, reliance on molecular substructures can obscure critical functional distinctions between compounds, necessitating the integration of multimodal data to overcome the accuracy limitations inherent in single-source models (Jing et al., 2024, p. 40). Despite the proficiency of current deep learning architectures, such as the attention-based models or those integrating recurrent and mixture density networks, a primary challenge remains the persistent class imbalance and the limited generalization capabilities toward newly approved drugs lacking extensive historical interaction documentation (Gheorghita et al., 2025). Moreover, current research often neglects the cross-modality complementarity between drug targets and metabolic enzymes, failing to fully exploit the underlying biological mechanisms that govern these pharmacological events (Lyu et al., 2021, p. 3536). Additionally, significant methodological gaps persist regarding the integration of unannotated DDI data, as many current frameworks struggle to generalize beyond known interaction clusters (Yang et al., 2022, p. 8693). Furthermore, the lack of standardized benchmarks and rigorous validation protocols across disparate datasets hampers the direct comparability of model performance, obscuring the clinical

applicability of findings (Al-Rabeah & Lakizadeh, 2022, p. 15590; Guo et al., 2025).

III. METHODOLOGY

The methodology utilizes structured pharmaceutical datasets, such as DrugBank, to curate comprehensive interaction profiles, representing drugs through multimodal vectors that encompass SMILES-encoded chemical structures, target proteins, and metabolic pathway information (Huang et al., 2022, p. 562; Ma & Lei, 2023, p. 2). These representations are augmented by converting chemical substructures into high-dimensional binary feature vectors, where individual dimensions denote the presence or absence of specific molecular components. Beyond these structural fingerprints, biological properties—including gene ontology terms, drug-target interactions, and enzyme expression profiles—are integrated to construct dense, multimodal feature matrices (Yang et al., 2023, p. 111). To address high dimensionality and potential noise within these integrated features, autoencoder-based architectures are employed for dimensionality reduction, effectively condensing multifaceted data into representative latent vectors (Hao et al., 2022, p. 69). Following feature extraction, these latent vectors are utilized as input for supervised predictors, such as Deep Neural Networks or Convolutional Neural Networks, which are trained to classify drug pairs as interacting or non-interacting based on aggregated chemical and biological similarities (Feng et al., 2020, p. 420; Lee et al., 2019, p. 417; Pan et al., 2024, p. 1354541). To optimize these representations, preprocessing pipelines utilize the Jaccard coefficient to construct similarity networks, while algorithms such as random walk with restart and Word2vec are applied to derive robust, structural feature embeddings (Yan et al., 2021, p. 794207; Zhang et al., 2017, p. 20). Following this, the model training process adopts a binary classification framework where concatenated drug-pair vectors are passed through multi-layer perceptrons to identify the presence or absence of an interaction (Li et al., 2025, p. 275). To ensure order-invariance and improve model generalization, each drug pair is presented in both possible permutations, effectively doubling the training data and mitigating sparsity issues inherent in pharmacological datasets (Kobraei et al., 2024, p. 6). To evaluate predictive performance, the dataset is

partitioned using stratified cross-validation, ensuring that the distribution of positive and negative interactions remains consistent across training and test subsets (Kpanou et al., 2024, p. 53; Rohani & Eslahchi, 2019, p. 13654). To address inherent class imbalances within these datasets, undersampling techniques are frequently applied to majority classes alongside ensemble methods or class weight adjustments to ensure the robust classification of rare, high-severity interaction pairs (Pham et al., 2024, p. 57). Furthermore, the training architecture incorporates 5-fold cross-validation, typically allocating 80% of data for training, 10% for validation, and 10% for testing to prevent overfitting (Masumshah et al., 2021, p. 388). Beyond standard metrics such as accuracy and F1-score, models are validated using area under the receiver operating characteristic curve and precision-recall curves to account for the skewed distribution of known interaction labels (He et al., 2024, p. 578; Yu et al., 2022, p. 1). Finally, the selection of negative samples is critical for model robustness; techniques such as constructing drug-disease-gene networks help prioritize pairs with lower interaction probabilities, ensuring a more rigorous assessment of the classifier's ability to discriminate between genuine pharmacological events and non-interactions (Zheng et al., 2018, p. 519). Given the limitations of simple accuracy in highly imbalanced pharmacological data, researchers increasingly rely on metrics like the Area Under the Precision-Recall Curve to provide a more representative measure of model utility (Çelebi et al., 2019, p. 733; Kastrin et al., 2018, p. 9). In addition to standard holdout evaluation, retrospective analysis serves as a more rigorous validation scheme that accounts for temporal biases and the real-world discovery trajectory of pharmacological interactions (Shtar et al., 2019, p. 9). To mitigate potential bias during validation, sophisticated protocols often utilize drug-level holdout strategies, where all interactions associated with a specific subset of drugs are sequestered in the test set to ensure the model generalizes effectively to unseen chemical entities (Jin et al., 2017, p. 5). To minimize variance in these performance assessments, researchers often perform multiple independent runs of cross-validation, averaging the final results to provide a more stable estimate of predictive accuracy (Zheng et al., 2019, p. 670). Moreover, given that many models demonstrate suboptimal performance

when trained on limited positive samples, a threshold—typically set at fifty documented interaction instances—is often established to ensure the statistical reliability of the predictive outputs (Liu et al., 2017, p. 52). Regularization techniques, such as L2-penalty integration, are concurrently implemented during the optimization phase to counteract model complexity and prevent overfitting across these training iterations (Luo et al., 2014, p. 2). Moreover, addressing cold-start scenarios—where interactions for novel drugs with no prior documented associations must be predicted—is essential for ensuring that models remain robust when evaluated against unseen pharmacological entities (Shi et al., 2019, p. 33; Zhang et al., 2015, p. 12343). This rigorous approach to model development often employs K-fold cross-validation schemes, where a portion of drugs is entirely sequestered from the training phase to simulate real-world clinical application for new therapeutic agents (Yu et al., 2018, p. 18). To ensure the reliability of these evaluations, nested cross-validation is frequently employed to facilitate hyperparameter tuning while simultaneously generating unbiased performance estimates on held-out test sets (Ohnuki et al., 2024, p. 109). Furthermore, grid search strategies are frequently utilized in conjunction with these validation loops to optimize architectural hyperparameters—such as learning rates and layer depths—thereby maximizing the sensitivity of the models to nuanced pharmacological patterns (Wang et al., 2021, p. 6). Furthermore, advanced validation schemas like CV1 and CV2 are implemented to specifically assess model generalizability toward new chemical entities, distinguishing between the prediction of interactions involving novel drugs versus those between two unseen compounds (Shi et al., 2018, p. 415). Rigorous model development requires maintaining a strictly independent test set that remains unseen during hyperparameter tuning to avoid optimistic bias (Mullowney et al., 2023, p. 901; Pant et al., 2024, p. 2691). Accordingly, utilizing cross-study evaluations or leave-drug-combinations-out validation schemes can further mitigate the risk of overestimating generalizability by ensuring that models are tested against data distributions not encountered during the training phase (Baptista et al., 2023, p. 14). These methodological safeguards are imperative, as models failing to account for such data leakage often yield

artificially inflated performance metrics that obscure their true translational potential (Pahikkala et al., 2014, p. 332; Thafar et al., 2019, p. 795). Beyond rigorous splitting strategies, the integration of early stopping mechanisms and comprehensive hyperparameter tuning remains vital to suppress overfitting, especially when training complex deep learning architectures on sparse pharmacological datasets (Partin et al., 2023, p. 1086111). To ensure unbiased performance estimates, some protocols utilize rigorous nested cross-validation, where an inner loop is dedicated to hyperparameter optimization while the outer loop assesses the model's predictive accuracy on completely independent data (Sturm et al., 2020, p. 29).

IV. RESULTS

Empirical evaluations reveal that deep learning architectures, such as DeepDDS and graph-based neural networks, achieve high predictive performance, with many models reporting AUC and AUPR scores exceeding 0.85 across diverse benchmarks like the AstraZeneca and Merck datasets (Besharatifard & Vafaei, 2024, p. 26). Comparative benchmarks indicate that while linear regression approaches frequently struggle with complex, non-linear drug interactions, achieving PR-AUC values as low as 0.15 in drug-level holdout scenarios, deep learning models maintain superior discriminative capacity (Wang et al., 2025, p. 3488). Moreover, ensemble methods frequently surpass individual model performance by aggregating diverse predictive features, thereby demonstrating heightened robustness when evaluated against drug pairs that lack overlapping target properties (Menden et al., 2019, p. 2681). Notably, models incorporating drug-target networks and transcriptomic profiles exhibit enhanced generalizability, though they remain challenged by the limited size of current high-throughput screening datasets and the difficulty of distinguishing between *in vitro* synergy and clinical toxicity (Adam et al., 2020, p. 25; Boniolo et al., 2021, p. 997). Comparative analyses underscore that while models relying on monolithic data representations often show performance degradation in leave-drug-out tasks, those integrating multi-source features—such as chemical structures combined with gene expression profiles—demonstrate significantly higher reliability

(Abbasi & Rousu, 2024, p. 10; El-Hafeez et al., 2024, p. 2442). For instance, models such as CASynergy have demonstrated superior predictive stability by achieving the highest AUC and AUPR metrics on large-scale datasets, effectively balancing precision and recall through the integration of molecular graph structures. Similarly, comparative assessments of architectural frameworks like SYNDEEP reveal that sophisticated deep learning models can outperform traditional methods—including Support Vector Machines and K-Nearest Neighbors—by achieving marked improvements in accuracy and F-score metrics across diverse feature sets (Torkamannia et al., 2023, p. 6185). Quantitative comparisons across models like MultiSyn, PRODeepSyn, and XGBoost further highlight that while traditional algorithms can achieve competitive accuracy—often reaching approximately 0.85—they frequently face limitations in precision and Kappa scores, suggesting difficulty in reliably identifying synergistic interactions within highly heterogeneous, sparse datasets (Monem et al., 2023, p. 22472).

V. DISCUSSION

The findings underscore a shift from monolithic data reliance toward integrative frameworks that leverage heterogeneous datasets to better capture the complex, multi-scale dynamics of pharmacologic interactions (Liu et al., 2024, p. 1677). By incorporating graph-based architectures and attention mechanisms, current models are increasingly capable of identifying higher-order biological priors that remain inaccessible to traditional, feature-flat methodologies (Mozaffarilegha & Gharaghani, 2025, p. 1614759). This progress directly addresses the mechanism-of-action knowledge gap by tracing synergy through target-protein inhibition profiles, which facilitates a more nuanced understanding of drug-cell interactions. Accurate prediction of these interactions holds profound clinical implications, as it enables the prospective identification of adverse drug-drug pairs and the optimization of polypharmacy regimens to maximize therapeutic efficacy while minimizing systemic toxicity. However, the clinical translation of these computational tools faces substantial implementation hurdles, particularly regarding the high cost and logistical complexity of acquiring multi-omics data in resource-constrained medical

environments (Çelebi et al., 2019, p. 8953). Furthermore, the inherent lack of model interpretability poses a significant barrier to adoption, as clinicians require transparent rationales to validate AI-driven suggestions before integrating them into high-stakes bedside decision-making (Srithanyarat et al., 2024, p. 21). To mitigate these technical and socio-technical challenges, future iterations must prioritize the development of explainable artificial intelligence frameworks that provide mechanistic insights into predicted synergies, thereby fostering trust within the clinical community (Zhao et al., 2024, p. 2). Moreover, addressing the current concentration of models within oncology research is critical to expanding the utility of these computational approaches to other essential therapeutic domains, such as infectious or pediatric diseases (Ji et al., 2019, p. 610).

VI. CONCLUSION

AI-based interaction prediction contributes a paradigm shift in medication safety by offering automated, real-time decision support that transcends the limitations of traditional clinical tools (Al-Ashwal et al., 2023, p. 145). By integrating diverse datasets—including patient-specific genomics and real-world health records—these systems provide personalized insights that significantly reduce adverse events in complex polypharmacy regimens (Dara et al., 2024, p. 188; Marzouk et al., 2025, p. 157). To fully realize this potential, future efforts must prioritize the creation of robust feedback loops that allow real-world outcomes to continuously refine model accuracy while ensuring seamless integration into clinical workflows via user-friendly decision support interfaces (SONAJI et al., 2024, p. 303). Furthermore, rigorous prospective validation across broader clinical cohorts and diverse therapeutic modules is essential to mitigate data selection biases and establish the causal mechanisms necessary for reliable deployment (Cheng et al., 2019, p. 1204; Dong et al., 2024, p. 1401556). Establishing cross-institutional data sharing standards will be equally vital to facilitate the integration of multi-omics and longitudinal health information, ultimately enabling more comprehensive and actionable drug safety assessments (Carini & Seyhan, 2024, p. 437). Finally, the adoption of standardized regulatory frameworks, such as the EU AI Act and FDA SaMD guidelines, is critical to ensuring the ethical,

transparent, and responsible clinical implementation of these predictive technologies (Lu et al., 2026, p. 56).

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