ENHANCING DRUG-DRUG INTERACTION PREDICTION WITH CONTEXT-AWARE ARCHITECTURE

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ABSTRACT

In the field of disease treatment, the simultaneous use of multiple medications can lead to unforeseen adverse reactions, compromising patient safety and therapeutic efficacy. Consequently, predicting drug-drug interactions (DDIs) has emerged as a pivotal research focus on improving disease treatment. While recent advancements have been made in deep learning models for predicting drug pair relations, the nuanced consideration of individual or cellular conditions as influential contextual factors in DDIs is notably lacking. In this study, leveraging existing models, we introduce a methodology to predict DDIs through a context-aware architecture. The evident performance improvement compared to established methodologies underscores the crucial role of the context-aware mechanism in addressing context-conditional DDIs. Furthermore, we perform a systematic ablation analysis to assess the impact of model elements. Simultaneously, we also investigate the potential of incorporating pre-trained molecular representation learning models in this domain.

1 INTRODUCTION

In the treatment of various diseases, patients often require the simultaneous use of multiple medications. However, this polypharmacy scenario may give rise to drug-drug interactions (DDIs), leading to unexpected adverse drug events (ADEs) (Vo et al., 2022). The existence of DDI remains a significant challenge as it poses a potential threat to patient safety and treatment efficacy. With the continuous development of artificial intelligence technology, an increasing amount of research is focusing on DDI prediction (Rozemberczki et al., 2022) to improve disease treatment.

Nevertheless, adverse reactions and side effects between drugs often exhibit individual or even cell-specific characteristics. The same pair of drugs may result in different drug interactions in distinct individuals or cellular environments (contexts). Therefore, considering the context-dependent prediction of DDI within a specific context is essential to advance the process of personalized medicine.

Deep learning-based approaches commonly consider a pair of drugs as input (Rozemberczki et al., 2021). Recent attempts have aimed to highlight the context-dependent nature of DDI prediction by incorporating context information. However, these methods usually simplify the process by merely concatenating descriptors of drugs and context, without engaging in deep representation learning of context-aware DDI information (Preuer et al., 2018). In Figure 1, we classify and visualize these DDI prediction frameworks as 'w/o context' and 'w/ context (concatenate)' for distinguishing.

In this work, to improve context-conditional DDI prediction, we incorporate a bi-directional context-aware attention mechanism to discern dependencies between drug pair and context representations. Our model exhibits a significant performance improvement when compared with established methodologies. The ablation study results indicate the significance of acquiring context-aware representations, highlighting the efficacy of a context-aware architecture in enhancing DDI tasks.

2 METHODOLOGY

We utilize a pair of molecular graphs along with contextual information as inputs to our model. The drug encoder is constructed using graph isomorphism networks (GINs), drawing inspiration from the 2D graph molecular encoder that used in Liu et al. (2021). Contextual information is encoded using a

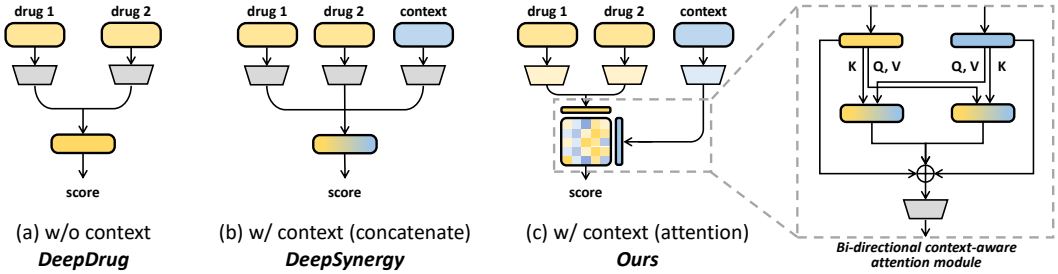

Figure 1: DDI Prediction Frameworks. (a) w/o context: models excluding contextual information (e.g. DeepDrug (Yin et al., 2020)). (b) w/ context (concatenate): models incorporating drug and context descriptors concatenation for prediction (e.g. DeepSynergy (Preuer et al., 2018)). (c) w/ context (attention): based on the prior works, we independently encode drugs and context, employing a bi-directional context-aware attention module to enhance DDI prediction.

multi-layer perceptron (MLP). To capture intricate dependencies between drug pairs and contextual factors, we integrate a bi-directional context-aware attention module. This module comprises two distinct components that capture attention respectively from drug pairs to context (drug2context) and from context to drug pairs (context2drug). The resulting attentions are subsequently concatenated with the representations of drugs and context for DDI prediction, enhancing the model's ability to perceive the connections between a pair of drugs with the context for further prediction.

3 Results

We benchmarked our model against the top-performing models outlined by Rozemberczki et al. (2022). Comprehensive information regarding the four benchmark DDI databases used and detailed experimental settings can be found in Appendix A.1, A.2. From the main results presented in Table 1, our model exhibits a notable performance improvement when compared to DeepDrug and DeepSynergy. This improvement indicates the efficacy of the integrated drug and context modules, along with the attention mechanism, in revealing context-conditional DDI. To understand the specific contributions of each module, we conducted ablation studies (Appendix A.3) and the results underscore the critical role of the context-aware mechanism in enhancing task performance.

Table 1: Performance comparison with DeepDrug (Yin et al., 2020) and DeepSynergy (Preuer et al., 2018). The experiments were iterated 10 times per database with random seeds, performance is reported as mean (standard deviations). The complete results could be found in Appendix A.6

database	DrugComb			DrugCombDB			TwoSides		
metrics	AUROC	AUPRC	F1	AUROC	AUPRC	F1	AUROC	AUPRC	F1
DeepDrug	0.643 (0.001)	0.703 (0.002)	0.724 (0.001)	0.740 (0.001)	0.573 (0.001)	0.435 (0.010)	0.923 (0.004)	0.904 (0.002)	0.857 (0.002)
DeepSynergy	0.702 (0.003)	0.758 (0.003)	**0.725 (0.002)**	0.763 (0.005)	0.598 (0.008)	0.488 (0.012)	0.940 (0.001)	0.919 (0.001)	0.887 (0.001)
Ours	**0.717 (0.002)**	**0.776 (0.002)**	0.716 (0.015)	**0.830 (0.001)**	**0.698 (0.001)**	**0.601 (0.015)**	**0.942 (0.002)**	**0.921 (0.003)**	**0.891 (0.003)**

Futhermore, we explored the feasibility of transferring molecular representations from pre-trained model to further enhance DDI prediction (Appendix A.4). The outcomes reveal that incorporating refined molecular representations indeed contributes to the accurate identification of DDIs, providing valuable insights into the potential for leveraging pre-trained models in this domain.

4 Conclusion and Future Work

To improve context-conditional DDI prediction, we employ distinct encoders to independently learn representations of drugs and contexts. We incorporate a bi-directional context-aware attention mechanism to discern dependencies between drug pairs and contexts. Our findings underscore the significance of learning context information for accurate predictions, highlighting the efficacy of a context-aware architecture in enhancing DDI tasks. Substituting the drug encoder with pre-trained 2D graph molecular encoder that captures 3D information further enhances performance, indicating the importance of acquiring meaningful drug representations in the relational learning of drug pairs.

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URM STATEMENT

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REFERENCES

Xiaomin Fang, Lihang Liu, Jieqiong Lei, Donglong He, Shanzhuo Zhang, Jingbo Zhou, Fan Wang, Hua Wu, and Haifeng Wang. Geometry-enhanced molecular representation learning for property prediction. *Nature Machine Intelligence*, 4(2):127–134, 2022.

Hui Liu, Wenhao Zhang, Bo Zou, Jinxian Wang, Yuanyuan Deng, and Lei Deng. Drugcombdb: a comprehensive database of drug combinations toward the discovery of combinatorial therapy. *Nucleic acids research*, 48(D1):D871–D881, 2020.

Shengchao Liu, Hanchen Wang, Weiyang Liu, Joan Lasenby, Hongyu Guo, and Jian Tang. Pre-training molecular graph representation with 3d geometry. In *International Conference on Learning Representations*, 2021.

Kristina Preuer, Richard PI Lewis, Sepp Hochreiter, Andreas Bender, Krishna C Bulusu, and Günter Klambauer. Deepsynergy: predicting anti-cancer drug synergy with deep learning. *Bioinformatics*, 34(9):1538–1546, 2018.

Benedek Rozemberczki, Stephen Bonner, Andriy Nikolov, Michael Ughetto, Sebastian Nilsson, and Eliseo Papa. A unified view of relational deep learning for drug pair scoring. *arXiv preprint arXiv:2111.02916*, 2021.

Benedek Rozemberczki, Charles Tapley Hoyt, Anna Gogleva, Piotr Grabowski, Klas Karis, Andrej Lamov, Andriy Nikolov, Sebastian Nilsson, Michael Ughetto, Yu Wang, et al. Chemicalx: A deep learning library for drug pair scoring. In *Proceedings of the 28th ACM SIGKDD Conference on Knowledge Discovery and Data Mining*, pp. 3819–3828, 2022.

Jae Yong Ryu, Hyun Uk Kim, and Sang Yup Lee. Deep learning improves prediction of drug–drug and drug–food interactions. *Proceedings of the national academy of sciences*, 115(18):E4304–E4311, 2018.

Nicholas P Tatonetti, Patrick P Ye, Roxana Daneshjou, and Russ B Altman. Data-driven prediction of drug effects and interactions. *Science translational medicine*, 4(125):125ra31–125ra31, 2012.

Thanh Hoa Vo, Ngan Thi Kim Nguyen, Quang Hien Kha, and Nguyen Quoc Khanh Le. On the road to explainable ai in drug-drug interactions prediction: A systematic review. *Computational and Structural Biotechnology Journal*, 20:2112–2123, 2022.

Qijin Yin, Xusheng Cao, Rui Fan, Qiao Liu, Rui Jiang, and Wanwen Zeng. Deepdrug: A general graph-based deep learning framework for drug-drug interactions and drug-target interactions prediction. *bioRxiv*, pp. 2020–11, 2020.

Shuyu Zheng, Jehad Aldahdooh, Tolou Shadbahr, Yinyin Wang, Dalal Aldahdooh, Jie Bao, Wenyu Wang, and Jing Tang. Drugcomb update: a more comprehensive drug sensitivity data repository and analysis portal. *Nucleic acids research*, 49(W1):W174–W184, 2021.

Gengmo Zhou, Zhifeng Gao, Qiankun Ding, Hang Zheng, Hongteng Xu, Zhewei Wei, Linfeng Zhang, and Guolin Ke. Uni-mol: A universal 3d molecular representation learning framework. In *The Eleventh International Conference on Learning Representations*, 2022.

Jinhua Zhu, Yingce Xia, Lijun Wu, Shufang Xie, Tao Qin, Wengang Zhou, Houqiang Li, and Tie-Yan Liu. Unified 2d and 3d pre-training of molecular representations. In *Proceedings of the 28th ACM SIGKDD Conference on Knowledge Discovery and Data Mining*, pp. 2626–2636, 2022.

A Appendix

A.1 Databases

In this work, we predict whether a pair of drugs will interact in a specific context of interest. In **DrugComb** and **DrugCombDB**, context refers to a specific cell line, predicting whether two drugs exhibit synergy in that particular cell line. In **DrugBankDDI**, context denotes specific reaction types (e.g., DDI_1 absorption decrease, DDI_9 serum concentration decrease), predicting if co-administration of two drugs leads to a particular reaction. In **TwoSides**, context represents specific adverse drug events (e.g., difficulty breathing, hypertension), predicting if a combination of two drugs leads to a specific adverse event.

DrugComb A database derived from real drug combination experiments, containing results from screening studies of drug combinations in various cancer cell lines. It encompasses 659,333 labels for the synergy between 4,146 drugs across 288 cancer cell lines (Rozemberczki et al., 2022; Zheng et al., 2021).

DrugCombDB A database curated from HTS assays, literature, FDA Orange Book and external databases. DrugCombDB includes 191,391 drug combinations, covering 2,956 unique drugs and 112 human cell lines (Rozemberczki et al., 2022; Liu et al., 2020).

TwoSides A database of polypharmacy side effects for pairs of drugs, containing 249,791 significant associations and 10 adverse events, with equal number of negative samples that generated without collisions of triples with positive labels (Rozemberczki et al., 2022; Tatonetti et al., 2012).

DrugBankDDI DrugBank gold standard DDI dataset that contains 86 DDI types, covering 192,284 DDIs contributed by 191,878 drug pairs, with equal number of negative samples that generated without collisions of triples with positive labels (Rozemberczki et al., 2022; Ryu et al., 2018).

A.2 Experimental Settings

For DrugComb, TwoSides and DrugBankDDI, we obtained the reported performances directly from (Rozemberczki et al., 2022). In the case of DrugCombDB, to ensure a fair comparison, we conducted all experiments on a NVIDIA GeForce RTX 3090. Each experiment was repeated 10 times with distinct random seeds, ensuring consistent separation of train (80%), validation (10%), and test (10%) sets and model parameter initialization. Under each setting, our model was trained for 80 epochs with a batch size of 512, learning rate of 1×10^{-5}, and a dropout rate of 0.2.

A.3 Ablation Study

To delineate the specific contributions of each module, we conducted ablation studies to quantitatively analyze the significance of individual components in the task. The results are summarized in Table 2. Notably, in the absence of context information, the model exhibits the poorest performance. Concatenating context representations learned from the MLP module enhances model performance, with additional improvement observed when employing the attention mechanism. Furthermore, different attention mechanisms contribute to varying degrees in enhancing model performance. Intriguingly, the Drug2Context attention outperforms Context2Drug, possibly due to the drug graph containing more enriched information compared to the context. This finding suggests a potential avenue for future research to acquire a more enriched representation of context.

Table 2: Ablation Study Results on DrugCombDB database. **Context**: Indicates whether context encoding was applied. **DDI Module**: Refers to the method used for combining drug and context representations. **Type**: Specifies the type of attention mechanism employed for prediction.

Context	DDI Module	Type	AUROC	AUPRC	F1
w/o	-	-	0.758 (0.001)	0.604 (0.004)	0.492 (0.008)
w/	Concatenate	-	0.786 (0.001)	0.607 (0.003)	0.583 (0.007)
	Attention	Drug2Context	0.823 (0.002)	0.689 (0.003)	0.593 (0.016)
		Context2Drug	0.819 (0.001)	0.681 (0.001)	0.571 (0.014)
		Bi-directional	**0.830 (0.001)**	**0.698 (0.001)**	**0.601 (0.015)**

A.4 Transfer Learning

Molecular representation learning (MRL) has garnered significant research attention in recent years, with numerous studies focusing on employing advanced methodologies to enhance molecular representation spaces through large-scale learning on diverse molecule datasets. These pre-trained models have demonstrated efficiency when transferred to downstream tasks such as molecular property prediction and drug-target interaction (Zhou et al., 2022; Zhu et al., 2022; Fang et al., 2022).

Motivated by these studies, we propose the idea of substituting our molecular module with a pre-trained 2D graph representation learning model whose encoder is enhanced by richer and more discriminate 3D geometry, to explore the impact of a refined molecular representation on DDI prediction performance. We selected the pre-trained 2D molecular encoder of GraphMVP (Liu et al., 2021) and conducted experiments, with results summarized in Table 3.

The results reveal that the pre-trained molecular encoding module significantly enhances the performance of context-conditional DDI prediction. Notably, the performance improvement is pronounced when employing a bi-directional context-aware attention mechanism instead of simply concatenating molecular representations with context representations. From the results, leveraging the advancements in context-conditional DDI prediction through pre-trained MRL models, future research could focus on refining and expanding enriched representations with increased contextual relevance.

Table 3: Transferring learning results on DrugCombDB database. **Pre-trained Molecular Module**: indicates the use of pre-trained molecular module. **DDI Module**: attention = bi-directional attention.

Pre-trained Molecular Module	DDI Module	AUROC	AUPRC	F1
w/o	concatenate	0.786 (0.001)	0.607 (0.003)	0.583 (0.007)
	attention	0.830 (0.001)	0.698 (0.001)	0.601 (0.015)
w/	concatenate	0.844 (0.001)	0.719 (0.001)	0.606 (0.007)
	attention	**0.929 (0.005)**	**0.868 (0.008)**	**0.768 (0.010)**

A.5 Training Process

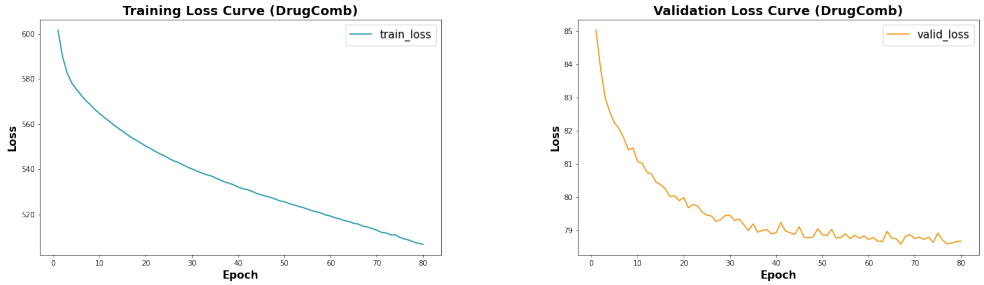
The model was trained with 80 epochs on each database, during which the validation loss consistently decreased along with the training loss (Figrue 2).

A.6 Extended Experimental Results

In addition to the main results in Table 1, we also compared our model with several other baselines following the experiment details in Appendix A.2. The comprehensive performance is in Table 4.

A.7 Reproducibility

To ensure reproducibility of our results, we have included our code base in the supplementary material including instructions for installing the Conda virtual environment, data preprocessing scripts, and training scripts. Additionally, our code is available on GitHub to facilitate reproducibility: https://github.com/solanoon/CabidaDDI



(a) Training Loss (b) Validation Loss

Figure 2: Training and validation loss curve.

Table 4: Performance comparison with baseline models. Experiments are repeated 10 times on each dataset with random seeds, and the reported performance refers to mean (standard deviations).

(a) Performance on DrugComb database

metrics	AUROC	AUPRC	F1
DeepDrug	0.643 (0.001)	0.703 (0.002)	0.724 (0.001)
GCN-BMP	0.594 (0.001)	0.662 (0.002)	0.707 (0.002)
MatchMaker	0.662 (0.002)	0.725 (0.001)	0.712 (0.002)
DeepSynergy	0.702 (0.003)	0.758 (0.003)	**0.725 (0.002)**
Ours	**0.717 (0.002)**	**0.776 (0.002)**	0.716 (0.015)

(b) Performance on TwoSides database

metrics	AUROC	AUPRC	F1
DeepDrug	0.923 (0.004)	0.904 (0.002)	0.857 (0.002)
GCN-BMP	0.709 (0.003)	0.694 (0.002)	0.592 (0.003)
MatchMaker	0.912 (0.002)	0.892 (0.001)	0.849 (0.001)
DeepSynergy	0.940 (0.001)	0.919 (0.001)	0.887 (0.001)
Ours	**0.942 (0.002)**	**0.921 (0.003)**	**0.891 (0.003)**

(c) Performance on DrugBankDDI database

metrics	AUROC	AUPRC	F1
DeepDrug	0.861 (0.003)	0.827 (0.003)	0.805 (0.002)
GCN-BMP	0.669 (0.001)	0.645 (0.002)	0.621 (0.001)
MatchMaker	0.987 (0.001)	0.981 (0.001)	0.959 (0.001)
DeepSynergy	0.992 (0.001)	0.987 (0.001)	0.968 (0.001)
Ours	**0.992 (0.000)**	**0.988 (0.000)**	**0.969 (0.001)**