MDNN: A Multimodal Deep Neural Network for Predicting Drug-Drug Interaction Events

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Introduction and Contribution

Drug-Drug Interactions (DDI) often occur in cases of simultaneous administration of multiple drugs, which may result in adverse drug reactions that cause injuries and huge medical costs. The correct use of multiple drugs can minimize the medical risks while maximizing the synergy benefits of drugs.

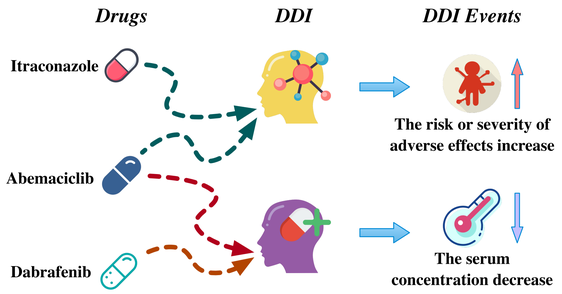


Figure 1: An example of DDI events. When drug *Abemaciclib* and drug *Dabrafenib* interaction together, an DDI event will be occurred and cause the decrease of body's serum concentration. However, it will raise the risk or severity of adverse effects when mixing drug *Abemaciclib* and drug *Itraconazole*.

Key Contribution:

- A new multimodal deep neural network with a two-pathway framework including the drug knowledge graph pathway and the heterogeneous feature pathway.
- MDNN learns the representations from multimodal data and mines the inter-modality similarities from multiple sources.
- MDNN exploits the topological structure information and semantic relations with drug knowledge graph.
- We conduct extensive experiments on a real-world dataset to demonstrate the effectiveness of our model compared with classic and the state-of-the-art methods.

Problem Formulation

We formulate DDI events prediction as a multi-class classification problem.

DDI Matrix: $\mathcal{Y} \in (0, y_{ij})^{N_d \times N_d}$
where N_d denotes the number of drugs. y_{ij} means that the interaction event y_{ij} exists between d_i and d_j.

Drug Knowledge Graph (DKG): a special type of knowledge graph for named drug knowledge graph (DKG), denoted by $\mathcal{G} = (\mathcal{D}, \mathcal{R}, \mathcal{T})$:

$$\mathcal{G} = \{(d, r_{dt}, t) | d \in \mathcal{D}, r_{dt} \in \mathcal{R}, t \in \mathcal{T}, \mathcal{D} \cap \mathcal{T} = \varnothing\},$$

where $\mathcal{D}$ and $\mathcal{T}$ describe a subset of drug entities and tail entities respectively, and $\mathcal{R}$ denotes the set of relations.

Heterogeneous Feature (HF): It consist of the target feature, substructure feature and enzyme feature. It is expressed as follows:

$$\mathcal{X}_d = \{X_t, X_s, X_e\} \in \mathbb{R}^{N_d \times (N_t + N_s + N_e)}.$$

DDI Events Prediction: Given the DDI events matrix, DKG and HF, we aim to predict specific interaction events between drug d_i and drug d_j .Our goal is to learn a prediction function:

$$\hat{y}_{ij} = \Gamma(d_i, d_j | \Theta, \mathcal{Y}, \mathcal{G}, \mathcal{X}_d)$$

where Θ denotes the model parameters.

MDNN Framework

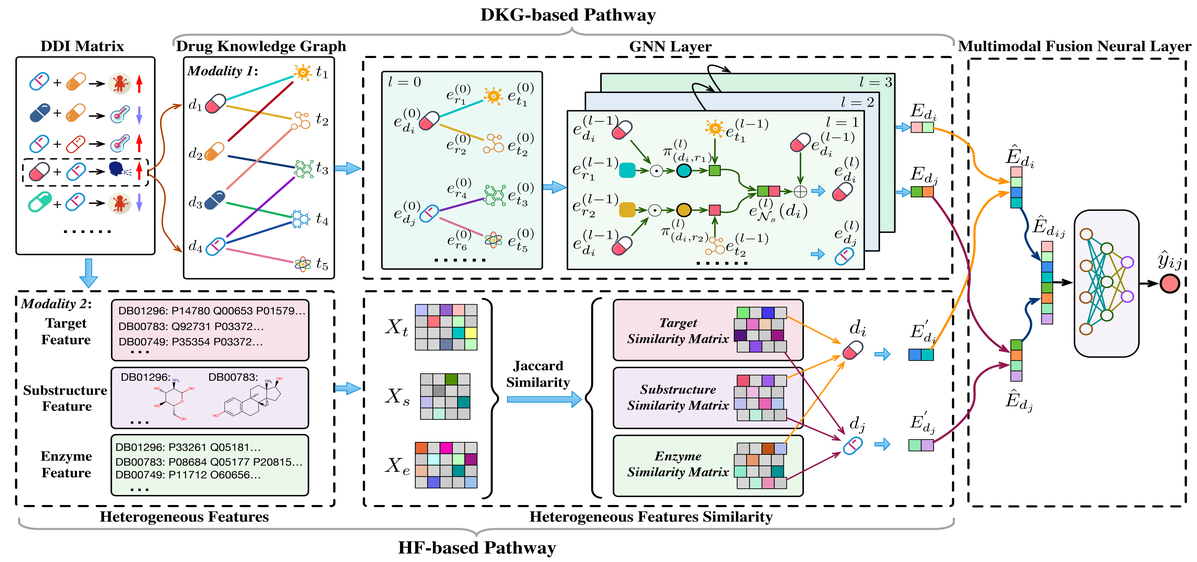


Figure 2: Illustration of the proposed MDNN, consisting of two core pathways: the DKG-based pathway and the HF-based pathway. (1) The DKG-based pathway utilizes the graph neural network to extract the topological structural information and semantic relations from the constructed drug knowledge graph (DKG). (2) The HF-based pathway mines the inter-modality similarities of each heterogeneous feature from multiple sources. (3) The multimodal fusion neural layer is applied to effectively assist the joint representation learning of both the structural information and attribute feature, which explore the cross-modality complementarity of the multimodal data.

Experiments & Results

Main Results:

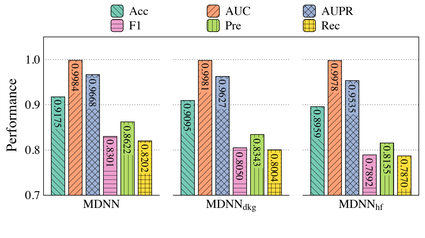
Methods	Acc	AUPR	AUC	F1	Pre	Rec
Logistic Regression	0.7920	0.8400	0.9960	0.5948	0.7437	0.5236
K-Nearest Neighbour	0.7214	0.7716	0.9813	0.4831	0.7174	0.4081
Random Forest	0.7775	0.8349	0.9956	0.5936	0.7893	0.5161
Deep Neural Network	0.8797	0.9134	0.9963	0.7223	0.8047	0.7027
DeepDDI [Ryu *et al.*, 2018]	0.8371	0.8899	0.9961	0.6848	0.7275	0.6611
DDIMDL [Deng *et al.*, 2020]	0.8852	0.9208	0.9976	0.7585	0.8471	0.7182
MDNN	**0.9175**	**0.9668**	**0.9984**	**0.8301**	**0.8622**	**0.8202**

Multi-task Analysis:

Task	Methods	Acc	AUPR	F1	Rec
Task A	DNN	0.6239	0.6361	0.2997	0.2840
	DeepDDI	0.5774	0.5594	0.3416	0.3890
	DDIMDL	0.6415	0.6558	0.4460	0.4319
	MDNN	**0.6495**	**0.6661**	**0.4471**	**0.4611**
Task B	DNN	0.4087	0.3776	0.1152	0.1093
	DeepDDI	0.3602	0.2781	0.1373	0.1450
	DDIMDL	0.4075	0.3635	0.1590	0.1452
	MDNN	**0.4575**	**0.4215**	**0.1697**	**0.1709**

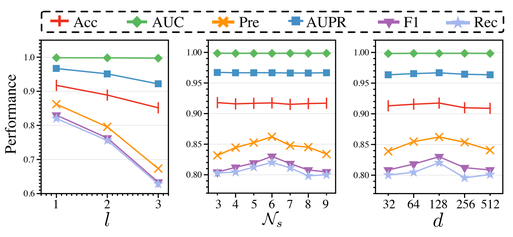
For task A, prediction models are constructed on the DDI between training drugs, and then make predictions for DDI events between training drugs and test drugs.For task B, making predictions between test drugs.

Abalation Study:



MDNNdkg is the model variant that only using DKG-based pathway to predict DDI events. MDNNhf is only using HF-based pathway to make DDI events prediction.

Parameter Sensitivity Analysis:



There are three essential parameters, which are the size of neighborhood sample Ns , the number of GNN layers l and the dimension of embedding d in DKG-based pathway.