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# Enhancing drug-drug interaction event prediction from knowledge graphs by multimodal deep neural networks

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**Abstract:** This study tackles the challenging issue of predicting drug-drug interactions (DDI) in pharmacology. Despite advancements in deep learning for DDI prediction, many techniques fail to fully leverage multimodal data correlations, limiting accuracy. To address this, we propose the knowledge graphs by multimodal deep neural network (KGMDNN) framework, enhancing DDI prediction by integrating features from drug knowledge graphs (DKG) and heterogeneous features (HF). KGMDNN uses a dual-path structure to obtain multimodal drug representations, effectively capturing drug relationships and connections within DKG to improve prediction accuracy. Our method excels in learning joint representations of structural information and multimodal data, as demonstrated through numerous real-world dataset experiments. Additionally, testing various drug knowledge graphs confirmed the model's robustness. KGMDNN outperforms both classic and state-of-the-art models in prediction metrics and interpretability.

**Keywords:** DDI event prediction; drug-drug interaction; graph neural network; GNN; knowledge graph; heterogeneous information; multi-modal data.

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## 1 Introduction

Given the rapid increase in the variety of drugs and the common practice of using multiple drugs together, the importance of drug safety is becoming increasingly

prominent (Giacomini et al., 2007; Zhang et al., 2020). For example, the interaction of drug *Itraconazole* and *Abemaciclib* causes greater risk, while the combined use of Amlodipine and Dabrafenib may lead to a decrease in serum concentration. These drug-drug interactions (DDIs) can not only harm patients and increase medical costs (Vilar et al., 2014, 2018), but also reduce medical risks and optimise treatment effects through the correct combination of drugs (Moridi et al., 2019). Therefore, accurately predicting DDI events in clinical settings is crucial. DDI prediction can reduce drug development costs, and can optimise the process of drug design (Chu et al., 2019; Liang et al., 2019). It can also decrease the potential risk to patients in drug administration by helping clinicians to make more impactful decisions and establish suitable therapy programs (Yang et al., 2021b).

In recent years, the prediction of drug-drug interaction (DDI) events has experienced significant advancements, particularly with the incorporation of deep learning models. These models have diversified the scope of DDI prediction, employing techniques such as graph neural networks (GNNs) to analyse chemical structural similarities (Huang et al., 2020), multi-task learning for differentiating types of DDI (Jin et al., 2017; Zitnik et al., 2018; Ryu et al., 2018), semi-supervised learning to harness both labelled and unlabelled drug data (Chu et al., 2019), and knowledge graph summarisation to anticipate pharmacological impacts of multi-typed DDIs (Yu et al., 2021). In order to predict DDI tasks, some efforts have been made, for example the similarity features is noticeable to obtain drug features, with using multiple data sources (Ma et al., 2018; Zhang et al., 2015; Deng et al., 2020). However, despite these innovative approaches, a critical gap remains in many current methodologies. Often, they fail to adequately address the importance of correlations between DDI events and multimodal data. Moreover, the need to consider the complementarity of cross-modality data for more accurate predictions has been somewhat overlooked.

In addition to these deep learning strategies, knowledge graphs (Sun et al., 2021) have increasingly become vital in the realm of DDI prediction (Karim et al., 2019). Their ability to integrate various data sources effectively has made them a prominent tool in the field. The popularity of knowledge graphs extends beyond just DDI prediction; they have been successfully implemented in various AI applications, including link prediction (Chen et al., 2021), recommendation (Zhou et al., 2020), healthcare misinformation (Cui et al., 2020), and bioinformatics (Lin et al., 2020). This broad applicability has stimulated the publication of numerous biomedical knowledge bases in the format of knowledge graphs, making them an indispensable resource in modern pharmacology and healthcare informatics. This evolving landscape of DDI prediction, marked by the integration of deep learning models and the strategic use of knowledge graphs, sets the stage for more robust and accurate methods in understanding and predicting drug interactions.

In response to these issues, we propose a new framework named knowledge graphs by multimodal deep neural network (KGMDNN), aimed at enhancing the predictive capability for DDI events. KGMDNN adopts a dual-path framework that combines a path based on drug knowledge graphs (DKG) and another based on heterogeneous features (HFs) to obtain multimodal drug representations. The DKG built from DrugBank can reveal the intrinsic relationships between drugs and related entities to improve predictive performance and provide explanations. This can be an effective tool for predicting DDI events, as it allows for the identification of potential interactions between drugs based on their relationships with other entities in the graph. Additionally,

KGMDNN learns drug representations through GNN layers and uses multimodal fusion neural layers and attention mechanisms to predict DDI events, effectively improving prediction accuracy and interpretability. Specifically, this paper's key contributions are outlined as follows:

- We propose a novel multimodal framework, KGMDNN, characterised by its innovative dual-path framework. This framework is comprised of two distinct paths: a path based on the DKG-based path, and a path based on HF-based path. KGMDNN leverages this dual structure to predict DDI events, capitalising on the associations between these events and the multimodal representations of drugs.
- The KGMDNN framework has the following two salient advantages:
  a KGMDNN is adept at learning representations from multimodal data, enabling the discovery of similarities across various modalities from multiple sources. This feature ensures a comprehensive and in-depth understanding of drug characteristics and their interactions.
  b Both topological structural and semantic information are aggregated by leveraging the constructed DKG. This approach results in a more nuanced and accurate representation of drug interactions, enhancing the prediction capability of the mode.
- The paper showcases extensive experimental validation on a relevant dataset, illustrating that the KGMDNN model surpasses both classic and state-of-the-art methods in predicting DDI events. These experiments underscore the model's efficacy and potential for real-world application, highlighting its superiority in the field of DDI prediction.

## 2 Materials and methodology

### *2.1 Related work*

#### *2.1.1 DDI prediction*

The prediction of DDIs has become increasingly vital in clinical and pharmaceutical settings, prompting extensive research to enhance DDI prediction methodologies (Luo et al., 2021; Nader et al., 2021). One key approach involves integrating multiple drug features, especially within the framework of DKGs. This method focuses on utilising a diverse array of drug characteristics and properties to predict DDIs. For instance, certain studies incorporate multiple sources of data and make predictions about DDI using the combined similarity (Callegari et al., 2021; Wu et al., 2020b). Other studies propose computational methods for predicting potential DDIs based on the assumption that drugs have a tendency to interact with other drugs that share similar characteristics. Vilar et al. (2012) proposed a novel method for identifying DDIs by analysing similarities in molecular structures, demonstrating the potential of similarity-based approaches in DDI prediction. Li et al. (2015) extended this concept by introducing a systems pharmacology framework that integrates various aspects such as molecular chemical space and biological network connectivity. Further, Zhang et al. (2015) presented a

comprehensive framework that not only incorporates drug feature similarities but also assigns appropriate weights to these features, enhancing the prediction accuracy. By considering multiple features of drugs, it is possible to capture the complexity of DDI more accurately and improve the prediction of DDI events.

Another significant avenue in DDI prediction involves the application of deep learning techniques. These methods predominantly use neural networks to learn drug representations from integrated features, thereby improving prediction accuracy. A notable instance is the DeepDDI (Ryu et al., 2018) framework, which employs molecular structures of drugs to predict types of DDIs. Kastrin et al. (2018) explored the potential of DDI prediction using a link prediction methodology, a novel approach in this domain. A multitask dyadic prediction model (Jin et al., 2017) is developed, which is a significant contribution to the field, offering a more nuanced approach to DDI prediction. Additionally, the MLRDA framework (Chu et al., 2019), a multitask semi-supervised learning model, leverages information from unlabelled drug data, showcasing the effectiveness of using diverse data sources in DDI prediction.

Despite these advancements, a notable gap in current methodologies is the limited consideration of the cross-modality complementarity of different drug features. Most existing methods focus on single aspects of drug features or apply uniform deep learning models without fully exploiting the interplay between different drug characteristics. This gap highlights the need for a more integrated and holistic approach in DDI prediction.

### *2.1.2 Methods based on GNNs*

The application of GNNs (Wu et al., 2020a; Zhang and Xu, 2021) has been increasingly prominent in various domains, including DDI prediction. GNNs are particularly adept at handling graph-structured data (Ma et al., 2019; Fu et al., 2021) and have shown effectiveness in diverse tasks such as social networks (Yang et al., 2021a; Huang et al., 2021; Ji et al., 2021), text classification (Liu et al., 2016, 2017), recommendation (Wang et al., 2020; He et al., 2020), etc. Their ability to learn relational information by aggregating features from adjacent nodes or edges makes them well-suited for complex relational tasks.

Motivated by the effective performance of GNNs in various tasks (Jia et al., 2020; Song et al., 2020), in DDI prediction, GNNs have been utilised to enhance prediction performance. Decagon (Zitnik et al., 2018), for instance, employed relational GNNs to delineate the potential adverse reactions of drug pairs. Ma et al. (2018) introduced a semi-supervised graph autoencoder for multi-view graph auto-encoders, showcasing the potential of GNNs in capturing intricate drug interactions. Asada et al. (2018) adopted a neural approach using convolutional graph networks to extract DDIs from textual data, while Yue et al. (2020) focused on integrating graph embeddings in DDI prediction. These models, by encoding both graph structure and node features, offer an advantage over traditional methods that typically integrate multiple, but isolated, data sources.

A significant challenge in current models is their limited attention to multiple related correlations within knowledge graphs (Deng et al., 2020). In biomedical fields, knowledge graphs (Hogan et al., 2021; Wang and Chen, 2020) provide structured information about relationships and semantic associations between entities (Nicholson and Greene, 2020), which are essential for integrating structural information into the latent vector representation of drugs. Celebi et al. (2019) utilised knowledge graph embedding techniques for DDI prediction. KG-DDI (Karim et al., 2019) developed a

deep-learning approach based on multiple data sources, including knowledge graphs. KGNN (Lin et al., 2020) presented a practical framework for capturing drugs and their potential neighbourhoods, and SumGNN (Yu et al., 2021) employed local subgraph modules for predicting multi-type DDIs.

Despite these advancements, there remains a need for a greater focus on the consistency and complementarity of multimodal drug data. The proposed model in this research addresses this gap by employing a specially designed GNN. This model is engineered to capture both topological information and semantic relationships within the graph structure, while also exploring the cross-modal complementarity of drug data. This approach distinguishes itself from current methodologies and seeks to enhance the precision of DDI prediction by considering This approach distinguishes itself from current methodologies and seeks to enhance the precision of DDI prediction by taking into account the complex interplay of multimodal drug data. Such an approach is anticipated to provide a more nuanced comprehension of DDIs, ultimately enhancing the efficacy of prediction models in clinical and pharmaceutical applications.

### 2.2 Problem formulation

Our research concentrates on predicting DDI events. We will firstly introduce some fundamental definitions in this section.

- *DDI matrix:* The concept of DDI event prediction is intricately linked with the DDI matrix, which serves as a fundamental representation of interactions between various drugs. The matrix is denoted as $\mathcal{Y} \in (0, y_{ij})^{Z_d \times Z_d}$, where $Z_d$ represents the total count of drugs in the matrix. Each element $y_{ij}$ within the matrix is a label indicating the type of interaction between the drugs $a_i$ and $a_j$. The set of interaction types is denoted as $\mathcal{L} = y_1, y_2, ..., y_{Z_l}$, where $Z_l$ is the number of types of interaction events. A value of $y_{ij} = 0$ implies no interaction between the drugs $a_i$ and $a_j$. Conversely, a non-zero $y_{ij} \in \mathcal{L}$ signifies a specific type of interaction between them.
- *DKG:* The DKG is a pivotal component in the prediction of DDI events, providing a structured framework to understand drug interactions. The DKG is represented as $\mathcal{G} = (\mathcal{D}, \mathcal{R}, \mathcal{T})$, encapsulating the relationships and properties of drugs and their related entities. $\mathcal{D}$ and $\mathcal{T}$ are sets of drug entities and tail entities, respectively, where tail entities refer to drug-related nodes like targets. $\mathcal{R}$ denotes the set of relations between drug entities and tail entities. The DKG is defined as follows:

$$\mathcal{G} = (d, r_{dt}, t) | d \in \mathcal{D}, r_{dt} \in \mathcal{R}, t \in \mathcal{T}, \mathcal{D} \cap \mathcal{T} = \varnothing \tag{1}$$

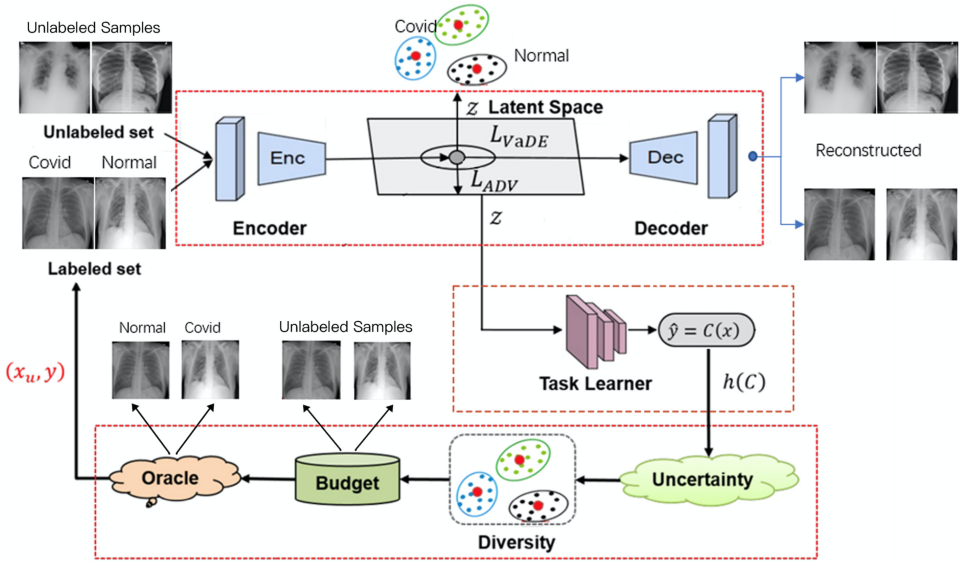
- *HF:* Consist of target features, substructure features, enzyme features, and molecular features. They are denoted by

$$\mathcal{X}_d = \{X_t, X_s, X_e, X_m\} \in \mathbb{R}^{Z_d \times (Z_t + Z_s + Z_e + Z_m)}, \tag{2}$$

where $X_t \in \mathbb{R}^{Z_d \times Z_t}$, $X_s \in \mathbb{R}^{Z_d \times Z_s}$, $X_e \in \mathbb{R}^{Z_d \times Z_e}$, and $X_m \in \mathbb{R}^{Z_d \times Z_m}$ represent the matrix of the target,the substructure, the enzyme, and the molecular feature. $Z_t$, $Z_s$, $Z_e$, and $Z_m$ denotes the number of target features, substructure features, enzyme features, and molecular features.

- *DDI event prediction:* The goal of the paper is to predict the likelihood $\hat{y}_{ij}$ of interaction events. From the previous we obtained the DDI matrix $\mathcal{Y}$, DKG $\mathcal{G}$ and HF $\mathcal{X}_d$, now we defines the prediction method as: $\hat{y}_{ij} = \Gamma(a_i, a_j|\Theta, \mathcal{Y}, \mathcal{G}, \mathcal{X}_d)$, where $\Theta$ is the learned parameters during the training phase to optimise the prediction function.

**Figure 1** The figure shows the two-core pathways of KGMDNN: 1 – by utilising GNN, the knowledge graph-based pathway can extract both topological structure information and semantic relationships; 2 – the HF-based pathway identifies inter-modality similarities across multiple sources by mining each HF; 3 – the multimodal fusion neural layer measures the cross-modal complementarity of the multimodal data, allowing for effective joint representation learning by combining structural information and attribute features (see online version for colours)




## 2.3 *Proposed method*

- *HF-based pathway:* Conversely, the HF-based pathway focuses on the calculation of drug similarity for DDI events using a range of HFs. These features include targets, substructures, enzymes, molecular features, and more, which are represented as binary vectors. The similarity between drugs is measured using the Jaccard similarity index. To address the issue of feature sparsity, the model employs principal component analysis (PCA) to compress these features, resulting in various similarity matrices for each feature type.
- *Integration and fusion:* The final and most critical step in the KGMDNN framework is the integration of these two pathways. This is achieved through a multimodal fusion neural layer, which seamlessly combines the structural information derived from the DKG-based pathway with the HFs processed in the HF-based pathway. This layer is key to exploring the cross-modal complementarity of the data, allowing for a more nuanced and comprehensive understanding of drug interactions.

- *Conclusions:* In summary, KGMDNN represents a sophisticated and innovative approach to DDI prediction. By leveraging the dual-pathway framework, the model not only utilises the structural and semantic information but also incorporates heterogeneous drug features. This comprehensive approach is expected to significantly improve the accuracy of DDI predictions, paving the way for more reliable and effective applications in clinical and pharmaceutical settings.
- *Overview:* KGMDNN is a multimodal deep neural network designed specifically for predicting DDIs. As shown in Figure 1, the core of this framework is its dual-pathway structure, includes DKG-based and HF-based. A GNN is employed in DKG-based pathway to examine and extract key topological structure details and semantic connections between drugs from DKG. The HF-based pathway focuses on deriving predictive information from various drug features, aiming to significantly improve the model's overall learning performance. The dual-pathway structure of KGMDNN aims to thoroughly capture the complex structural and semantic information inherent in drug interactions and utilise heterogeneous drug features to refine the accuracy and reliability of DDI predictions. A pivotal aspect of KGMDNN is its multimodal fusion neural layer. This layer is crucial in integrating the structural information obtained from the DKG-based pathway with the HFs derived from the HF-based pathway and exploring the cross-modal complementarity of the data, thereby ensuring a holistic and comprehensive analysis for predicting DDIs.

### *2.3.1 The DKG-based pathway*

The DKG-based pathway is adept at capturing the intricate relationships and properties within the DKG, using GNN to interpret and process this data effectively. This is achieved using a DKG, which is constructed by aggregating entities related to each drug from comprehensive sources like DrugBank. The entities include various drug-related aspects such as targets, transporters, and more, forming triples that represent the drugs, their functions, and related entities. This rich semantic framework provides a deep understanding of the drugs' roles and interactions.

The framework designed for predicting DDIs incorporates two pivotal components: DKG and GNN layers, each playing a crucial role in the prediction process.

- *DKG:* To construct the DKG, relevant entities such as targets and transporters are meticulously collected from DrugBank for each drug. These entities provide insights into the general functions of the drugs, thereby enriching the framework with valuable semantic information. In the DKG, information is structured in triples – each consisting of a drug, its general function, and a the Uniprot ID, for example, drug *DB05812* has a triple in the DKG representation <*DB05812*, *toxic substance binding*, *P02768*>, allowing for the capture of both the topological and semantic relationships present in the graph.
- *The GNN layer:* The second component, the GNN layer, is integral in learning from the structure of the DKG. After the DKG's construction, the focus shifts to understanding the topological structure and semantic information of the targeting relationships. For this, the GNN is an ideal choice due to its nonlinear modeling and automatic learning capabilities, adept at feature mining and learning node

representations within the DKG. Through iterative updates, the GNN layer refines the embedding representation of each drug node. This is achieved by leveraging attribute transfer from adjacent nodes and the semantic information of edges within the DKG. The objective here is to effectively capture both the drug's topological structure and its semantic relations within the graph. The matrix of the DKG $\mathcal{G}$ is initialised as:

$$E_{\mathcal{G}} = \left[ \underbrace{e_{d_1}^{(0)}, ..., e_{Z_d}^{(0)}}_{drug\ embedding}, \underbrace{e_{r_1}^{(0)}, ..., e_{Z_r}^{(0)}}_{relation\ embedding}, \underbrace{e_{t_1}^{(0)}, ..., e_{Z_k}^{(0)}}_{tail\ embedding} \right], \tag{3}$$

where $Z_d$, $Z_r$ and $Z_k$ denote the count of drugs, relations and tail entities. To initialise the three embeddings, we use $e_d^{(0)} \in \mathbb{R}^d$, $e_r^{(0)} \in \mathbb{R}^d$ and $e_t^{(0)} \in \mathbb{R}^d$, where $d$ represents the dimension.

By stacking additional GNN layers, We can explore the topological structure information, gathering information from the higher-hop neighbours. To balance efficiency and maintain a same computation pattern for each batch, we opt to uniformly sample a fixed-size set $\mathcal{N}_s(a_i)$ instead.

We sample a fixed size set of $\mathcal{N}s(a_i)$ of drug $a_i$ and calculate the semantic feature score between drug $a_i$ and tail entity $t_n$ with relation $rin$ as follows:

$$\pi_{(a_i,r_{in})}^{(l)} = sum[(e_{a_i}^{(l-1)} \odot e_{r_{in}}^{(l-1)})W_1^{(p)} + b_1^{(p)}] \tag{4}$$

where $e_{r_{in}}^{(l-1)}$ is the representation of the relationship between the drug $a_i$ and the tail entity $t_n$. The representation $e_{a_i}^{(l-1)}$ of drug $a_i$ is derived after the prior message passing step, which considers the messages received from its ($l$-1) hop neighbours. We then times their Hadamard product to a trainable weight matrix $W_1^{(p)}$ and adds a bias vector $b_1^{(p)}$, where $p$ is the count of fully connected layers. We subsequently define the $l^{th}$ layer neighbourhood representation of drug $a_i$ as follows:

$$e_{\mathcal{N}_s(a_i)}^{(l)} = \sum_{t_n \in \mathcal{N}_s(a_i)} \pi_{(a_i,r_{in})}^{(l)} e_{t_n}^{(l-1)} \tag{5}$$

At last, we obtain a vector from the two embedding using the function:

$$E_{a_i} = e_{a_i}^{(l)} = \sigma((e_{a_i}^{(l-1)} \oplus e_{\mathcal{N}_s(a_i)}^{(l)})W_2 + b_2), \tag{6}$$

where $W_2^{(p)}$ is weight matrix and $b_2^{(p)}$ is bias. $\sigma$ represents activation function. The operator $\oplus$ denotes concatenation. Finally, the representation of each drug $a_i$ is obtained after $L$ GNN layers. Overall, the embedding propagation layer allows the model to incorporate the structural information by propagating the representations of drugs and their neighbours.

### 2.3.2 The HF-based pathway

The primary objective of the HF-based pathway is to assess the similarity between drugs, providing insights into potential DDIs. Drugs are represented as binary feature vectors in this pathway. Each vector element signifies the presence or absence of specific drug descriptors. The pathway employs the Jaccard similarity measure to determine the pairwise similarities between drugs. And the Jaccard similarity for drugs $a_i$ and $a_j$ is given by:

$$J(a_i, a_j) = \frac{|a_i \cap a_j|}{|a_i \cup a_j|} = \frac{|a_i \cap a_j|}{|a_i| + |a_j| - |a_i \cap a_j|} \tag{7}$$

This measure quantifies the degree of similarity between two drugs based on their feature sets, aiding in the prediction process and construct various similarity matrices: $E^t \in \mathbb{R}^{Z_d \times Z_d}$ for target similarity matrix, $E^s \in \mathbb{R}^{Z_d \times Z_d}$ for the substructure similarity matrix, $E^e \in \mathbb{R}^{Z_d \times Z_d}$ for the enzyme similarity matrix, and $E^m \in \mathbb{R}^{Z_d \times Z_d}$ for the molecular feature similarity matrix. Principal component analysis (PCA) is used to compress these features, aiming to reduce sparsity in the data. The compression leads to reduced-dimension matrices for each feature type, represented by $k_1$, $k_2$, $k_3$, $k_4$ from $E^t \in \mathbb{R}^{Z_d \times k_1}$, $E^s \in \mathbb{R}^{Z_d \times k_2}$, $E^e \in \mathbb{R}^{Z_d \times k_3}$, $E^m \in \mathbb{R}^{Z_d \times k_4}$, enhancing computational efficiency and manageability. We can further obtain the embedding of drug $a_i$ as $E^t_{a_i} \in E^t$, $E^s_{a_i} \in E^s$, $E^e_{a_i} \in E^e$, and $E^m_{a_i} \in E^m$. Similarly, the embedding of drug $a_j$ can be obtained as $E^t_{a_j} \in E^t$, $E^s_{a_j} \in E^s$, $E^e_{a_j} \in E^e$, and $E^m_{a_j} \in E^m$.

**Algorithm 1** KGMDNN algorithm

**Input:** DDI matrix $\mathcal{Y}$; drug knowledge graph $\mathcal{G}$; heterogeneous features $\mathcal{X}_d$; hyper-parameter: $l$, $\mathcal{N}_s$, $d$, $k$.
**Output:** $\Gamma(a_i, a_j|\Theta, \mathcal{Y}, \mathcal{G}, \mathcal{X}_d)$

Initialisation $\mathcal{G}$
**while** KGMDNN not converge **do**
  **for** $(a_i, a_j)$ in $\mathcal{Y}$ **do**
    // DKG-based pathway
    $\mathcal{N}_0 \leftarrow e, \forall e \in \mathcal{D} \cup \mathcal{T}$
    $\{\mathcal{N}_l\}_{l=1}^{L} \leftarrow$ neighbourhood sampling (entity $e$)
    $e^{(0)} \leftarrow e, \forall e \in \mathcal{N}_0$
    **for** $l = 1, ..., L$ **do**
      **for** $e \in \mathcal{N}_l$ **do**
        $e^{(l)}_{\mathcal{N}_l} \leftarrow \sum_{t_n \in \mathcal{N}_l(e)} \pi^{(l)}_{(e,r_{in})} e^{(l-1)}_{t_n}$
        $e^{(l)} \leftarrow e^{(l-1)} \oplus e^{(l)}_{\mathcal{N}_l}$
      **end for**
    **end for**
    $E_{a_i} \leftarrow e^{(l)}_{a_i}$, $E_{a_j} \leftarrow e^{(l)}_{a_j}$
    // HF-based pathway
    **for** $X \in \mathcal{X}_d$ **do**
      $e^x \leftarrow$ Jaccard similarity $(X)$
    **end for**
    $\alpha_x \leftarrow$ Calculate weight score (entity $e^x$)
    $E^{'}_{a_i} \leftarrow \alpha E_{a_i} \oplus \alpha_t e^t_{a_i} \oplus \alpha_s e^s_{a_i} \oplus \alpha_e e^e_{a_i} \oplus \alpha_m e^m_{a_i}$
    $E^{'}_{a_j} \leftarrow \alpha E_{a_j} \oplus \alpha_t e^t_{a_j} \oplus \alpha_s e^s_{a_j} \oplus \alpha_e e^e_{a_j} \oplus \alpha_m e^m_{a_j}$
    $\hat{E}_{d_{ij}} \leftarrow E^{'}_{a_i} \oplus E^{'}_{a_j}$

23: Calculate $\hat{y}_{ij} = f(\hat{E}_{d_{ij}})$
24: Update parameters $\Theta$
25: **end for**
26: **end while**
27: **return** $\Gamma$

### *2.3.3 Multimodal neural fusion layer*

We use a multimodal neural fusion layer to leverage the infromation from two previous pathways. To start with, we introduce an attention mechanism that calculates attention coefficients for the embedding representation of each drug mode. This ensures maximum contribution of different mode embedding representations towards predicting DDI events. For each embedding of different features, we calculate the attention coefficient. The formula is:

$$\alpha_t = sum[E^t_{a_i} W + b]. \tag{8}$$

After obtaining the attention coefficient, we can concatenate each representation vector of different features as the final embedding of $a_i$, which is formulated as

$$E^{'}_{a_i} = \alpha E_{a_i} \oplus \alpha_t E^t_{a_i} \oplus \alpha_s E^s_{a_i} \oplus \alpha_e E^e_{a_i} \oplus \alpha_m E^m_{a_i}. \tag{9}$$

The embedding $E^{'}_{a_i}$ of drug $a_i$ includes both the HF information as well as the semantic and structural information of its relation.

After obtaining $E^{'}_{a_i}$ for $a_i$, we can also abtain the embedding $E^{'}_{a_j}$ of drug $a_j$ using the same method and link them to be thefinal multimodal embedding $\hat{E}_{d_{ij}}$ of drug $a_i$ and drug $a_j$:

$$\hat{E}_{d_{ij}} = E^{'}_{a_i} \oplus E^{'}_{a_j}. \tag{10}$$

Then, we use the multimodal fusion embedding $\hat{E}_{d_{ij}}$ for prediction:

$$\hat{y}_{ij} = \rho(\hat{E}_{d_{ij}} W^{(q)}_3 + b^{(q)}_3), \tag{11}$$

The trainable weight matrix $W^{(q)}_3$, bias vector $b^{(q)}_3$, and number of fully connected layers $q$ are used in conjunction with the activation function softmax, denoted by $\rho$, to generate the final predicted score $\hat{y}_{ij}$ using the softmax function. To optimise model convergence and prevent overfitting, we employ batch normalisation and dropout layers, respectively. We apply L2 regularisation to avoid overfitting. Furthermore, The cross-entropy loss function is utilised. Algorithm 1 outlines the entire training process.

## 3 Results

Our experiment consists ablation study (Subsection 3.3.1), parameter sensitivity analysis (Subsection 3.3.2), robustness verification (Subsection 3.4) and multi-task analysis (Subsection 3.5).

### 3.1 Experimental setup

#### 3.1.1 Dataset

We experiment on DDI matrix, DKG, and HFs. We describe their properties below and in Table 1:

- *DDI matrix:* This dataset was sourced from DDIMDL[1] and includes a comprehensive list of 572 drugs involved in 65 different types of interaction events. It encompasses 37,264 drug pairs in all.
- *DKG:* The DKG is constructed using data from DrugBank[2] (version 5.1.7). It comprises 572 drugs, 1,614 entities, 76,871 triplets, and 157 different drugs-tail relations.
- *HFs:* Obtained from DDIMDL (Deng et al., 2020), this dataset includes 1,162 target features, 583 substructure features, 202 enzyme features, and a selection of molecular features. Molecular features are Molecular ACCess System (MACCS) keys. Molecular Design Limited Information Systems developed the MACCS keys with 166 public keys, each corresponding to a specific molecular characteristic. In this paper, we select 13 MACCS keys and seven other molecular features (Baranwal et al., 2020).

#### 3.1.2 Baselines

The baselines we used for comparisons in our study are as follows:

- *MDNN:* MDNN (Lyu et al., 2021) is a multimodal deep neural network specifically designed for DDI event prediction.
- *DDIMDL:* DDIMDL (Deng et al., 2020) is a joint deep neural network framework for learning representations of drug-drug pairs.
- *KGNN:* KGNN (Lin et al., 2020) is a GNN model that focuses on aggregating local neighbourhoods with external knowledge graphs.
- *DeepDDI:* DeepDDI (Ryu et al., 2018) is a deep learning-based approach, employing PCA for dimensionality reduction.
- *Other traditional methods:* We also consider various conventional methods, including logistic regression, random forest, and others.

### 3.2 Evaluation metrics

In this predicting DDIs tasks, accuracy (Acc), F1-score (F1), area under the ROC curve (AUC), precision (Pre), area under the precision-recall-curve (AUPR), and recall (Rec) were employed to evaluate the performance of the models.

#### 3.2.1 Parameter and evaluation settings

The batch size was established as 1,024, with the number of iterations was 100. The Adam optimisation algorithm was chosen for its efficiency, with a learning rate of 0.001.

Parameters were optimised using a random search method at each iteration. We set the neighbourhood sampling $\mathcal{N}_s$ = 4, one GNN layer ($l$ = 1) was utilised, L2 regularisation weight was established at 1e-8. Other parameters are set as $p$ = 2, $q$ = 3, $d$ = 64, $k_1$ = 256, $k_2$ = 256, $k_3$ = 128, and $k_4$ = 128. To perform a comprehensive evaluation of the proposed method, we employ a five-fold cross-validation approach, in which all DDI pairs are divided at random into five groups, and we calculate the average of the results of the five iterations to be the final evaluation scores. To prevent overfitting, the training will stop automatically if there is no changes after ten epochs.

**Table 1** The overall information of dataset

| *Category* | *Name* | *Number* |
|---|---|---|
| DDI matrix | Drugs | 572 |
| | Events | 65 |
| | Drug-drug pairs | 37,264 |
| Drug knowledge graph | Triples | 76,871 |
| | Drugs | 572 |
| | Relations | 157 |
| | Tail nodes | 1042 |
| Heterogeneous features | Targets | 1,162 |
| | Substructures | 583 |
| | Enzymes | 202 |
| | Molecular features | 20 |

**Table 2** Performance of KGMDNN against comparative approaches

| *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 | 0.8371 | 0.8899 | 0.9961 | 0.6848 | 0.7275 | 0.6611 |
| KGNN | 0.8782 | 0.9357 | 0.9969 | 0.7443 | 0.7845 | 0.7284 |
| DDIMDL | 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 |
| *KGMDNN* | *0.9191* | *0.9706* | *0.9987* | *0.8422* | *0.8891* | *0.8246* |

### *3.3 Results and analysis*

The performance of the KGMDNN and the baseline models are detailed in Table 2. From the results, KGMDNN achieved the best performance. Our KGMDNN model significantly improved in all evaluation metrics compared to all the baselines. Specifically, the model we proposed demonstrates superior performance compared to DDIMDL across various metrics. Our proposed model achieves 3.39% increase in Acc, 5.52% in AUPR, 0.11% in AUC, 8.37% in F1, besides 4.2% in Pre, and a remarkable 10.64% increase in Rec. The obvious promotion on the DDIMDL model confirms

that it is not only the topological structural information but also semantic relation that produce accurate drug embeddings. Furthermore, the multimodal information fusion is also important. In addition, comparing with the baseline KGNN, our KGMDNN model still performs much better. Our model improves MDNN by 0.16% in Acc, 0.38% in AUPR, 0.03% in AUC, 1.21% in F1, 2.69% in Pre and 0.44% in Rec. This demonstrates the high effectiveness of KGMDNN.

**Figure 2** The performance of KGMDNN compared to $KGMDNN_{dkg}$ and $KGMDNN_{hf}$ (see online version for colours)

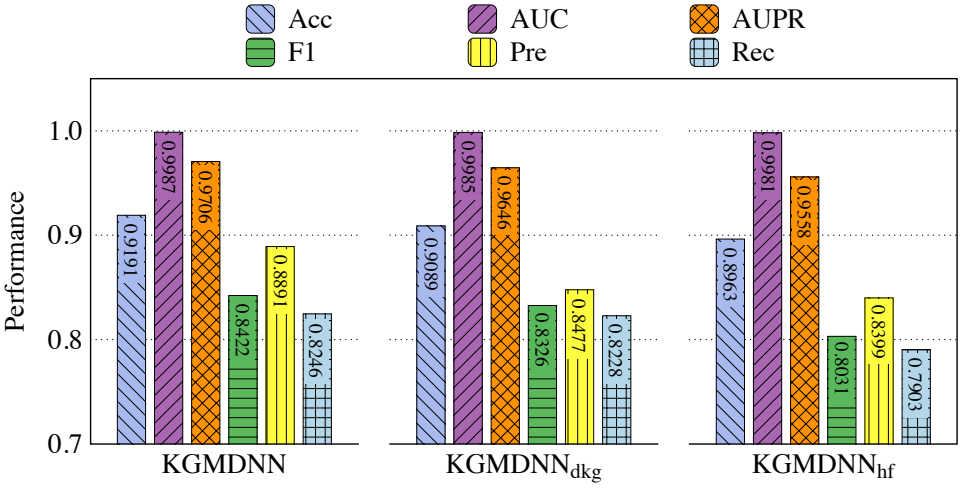
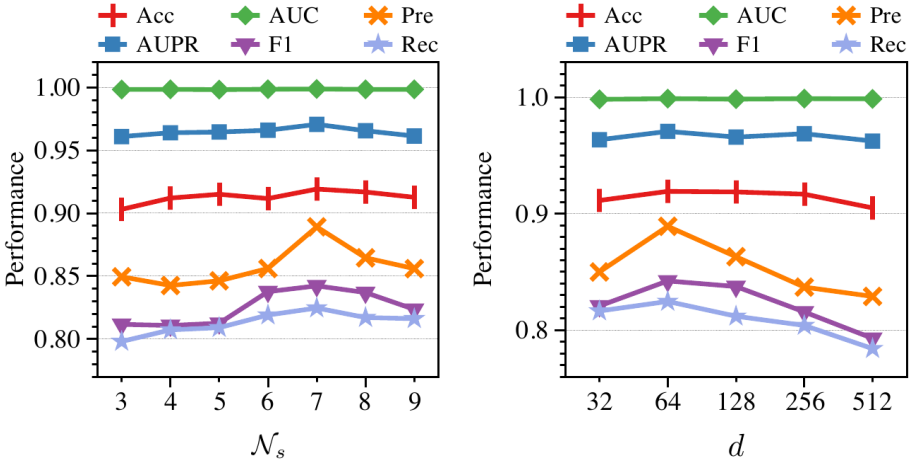



**Figure 3** Parameter sensitivity analysis on effect of neighbourhood sample $\mathcal{N}_s$ and initialisation dimension $d$ in DKG-based pathway in our proposed KGMDNN (see online version for colours)




These results underscore the effectiveness of KGMDNN, particularly its ability to exploit topological and semantic relationships in drug embeddings and the importance of fusing multimodal information. Our model's better performance is attributed to leverage

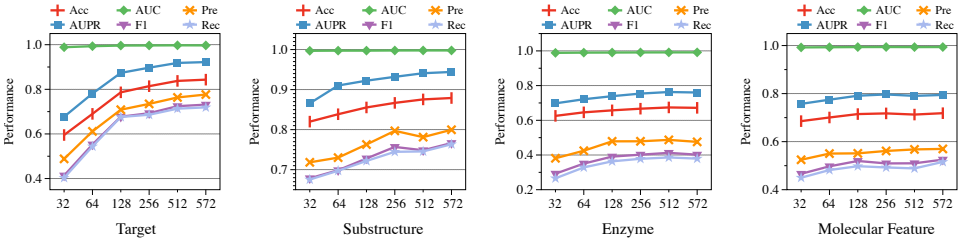
the topological embedding representation of drugs within the DKG, as well as its capability for cross-modal embedding representation of multimodal data. KGMDNN's beter preformance may be due to

a the use of GNN models in KGMDNN

b the utilisation of cross-modal complementary information of multimodal data in KGMDNN.

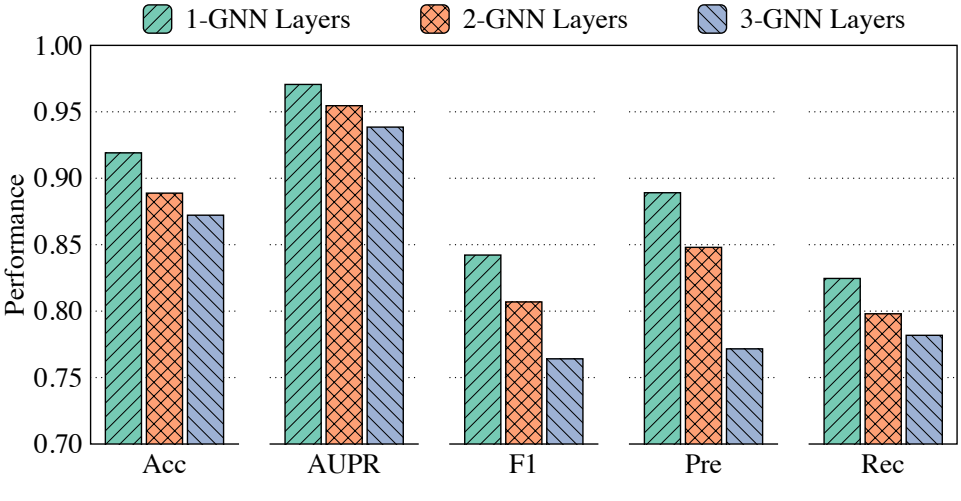
Overall, this is a promising achievement in the prediction of DDI events.

**Figure 4** Parameter sensitivity analysis on effect of each HF (see online version for colours)




Notes: We only use target features, substructure features, enzyme features and molecular features to explore the effect of different embedding dimensions respectively.

**Figure 5** Parameter sensitivity analysis of different number of GNN layers in the DKG-based pathway in our proposed KGMDNN (see online version for colours)




### *3.3.1 Ablation study*

The ablation study focused on evaluating the individual contributions of the KGD-based pathway ($KGMDNN_{dkg}$) and the HF-based pathway ($KGMDNN_{hf}$) in KGMDNN.

- $KGMDNN_{dkg}$: This variant focuses only on the topological structures and semantic relations from the DKG for learning drug-drug pair embeddings.
- $KGMDNN_{hf}$: This variant solely utilises cross-modality embeddings of drug-drug pairs using HFs such as target, substructure, and enzyme features.

We illustrate the experimental results in Figure 2 and make some discussions.

From Figure 2, we observe that KGMDNN outperforms its variants, which separately disregard different components of KGMDNN. Both $KGMDNN_{dkg}$ and $KGMDNN_{hf}$ demonstrated inferior performance compared to the full KGMDNN model, indicating the critical role of each component in the framework. The superior performance of the complete KGMDNN model over its variants highlights the importance of integrating multimodal features and inter-modality representation from multiple sources. The results validate that the combination of topological representation, semantic relationships, and HFs is crucial for enhancing DDI event prediction performance.

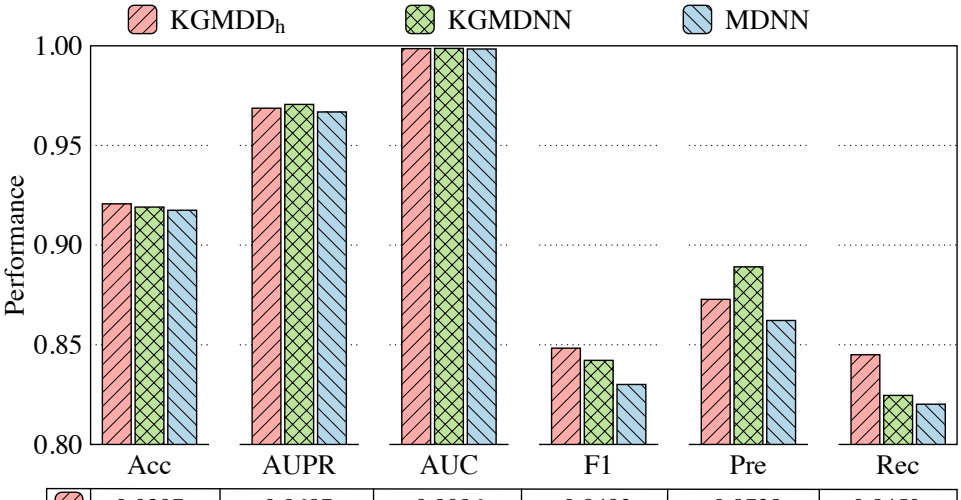
### 3.3.2 Parameter sensitivity analysis

The analysis covers several critical parameters: the number of GNN layers ($l$), the size of the neighbourhood sample ($\mathcal{N}_s$), and the dimension of the initialisation embedding ($d$) in the DKG-based pathway. The dimension of each HF embedding in the HF-based pathway while the other parameters are fixed. Figures 3 and 5 present the results in detail. In addition, we explore the effect of each HF when only using target feature, substructure feature and enzyme feature respectively. Figure 4 depicts the outcomes.

- *Effect of GNN layers:* The number of GNN layers was varied from 1 to 3, with the model exhibiting optimal performance at $l = 1$. From Figure 5, we notice a decline in performance was noted for higher values of $l$, possibly due to noise introduction.
- *Effect of neighbourhood size:* To examine the effect of the neighbourhood size, we investigate how the proposed framework works as the neighbourhood size varies while keeping other parameters fixed. The effect of varying neighbourhood size ($\mathcal{N}_s$) on the DKG-based pathway was examined.. As shown in Figure 3, The model performed best at $\mathcal{N}_s$ = 7. Smaller values of $\mathcal{N}_s$ might not capture sufficient structural information, whereas larger values could introduce noise.
- *Effect of initialisation dimension in DKG-based pathway:* Additionally, we check the effect of the embedding dimension $d$ in the DKG by varying it from 32 to 512. The predictive performance peaks when $d$ = 64, as shown in Figure 3. Intuitively, performance can be improved by an appropriated that effectively encodes substantial information on drugs and DKG entities. However, the model suffers from overfitting when d is too large.
- *Effect of each HF:* In this experiment, we analyse the impact of various heterogeneous drug features on the prediction of DDI events prediction. Our goal is to verify the effectiveness of each HF in different dimensions. In other words, we only consider different dimensions of one HF for this task. We first use target features, substructure features, enzyme features, and molecular features of the

drug to calculate the Jaccard similarity matrix respectively. Then we can obtain em- bedding representations of different dimensions after using PCA. In Figure 4, we change the value from 32 to 572 only using target features, substructure features, enzyme features, and molecular features, respectively in order to show the embedding dimension's effect. Intuitively, the larger the dimension of the embedded representation,the more effective information it contains, and the more improved predictive performance of the model. However, the model will be misled by noises when using target, substructure, enzyme, and molecular features simultaneously for DDI event prediction.

**Figure 6** Performance of $KGMDNN_h$ using another DKG extracted from the Hetionet (see online version for colours)




| | Acc | AUPR | AUC | F1 | Pre | Rec |
|---|---|---|---|---|---|---|
| KGMDDh | 0.9207 | 0.9687 | 0.9986 | 0.8483 | 0.8728 | 0.8450 |
| KGMDNN | 0.9191 | 0.9706 | 0.9987 | 0.8422 | 0.8891 | 0.8246 |
| MDNN | 0.9175 | 0.9668 | 0.9984 | 0.8301 | 0.8622 | 0.8202 |

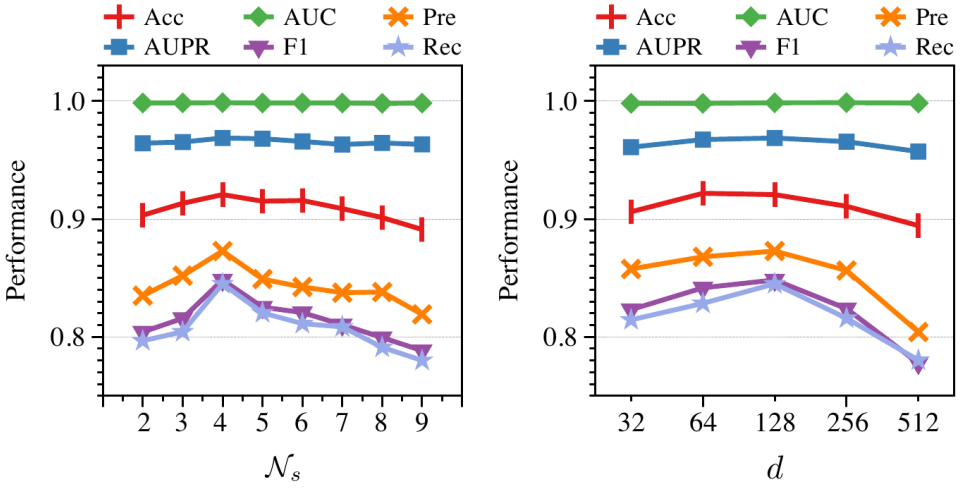
Notes: Compared with KGMDNN and MDNN, $KGMDNN_h$ also achieved better performance.

### *3.4 Robustness verification*

We utilise other DKG datasets to examine our model's performance. The robustness of KGMGNN is shown in Table 3. This DKG is extracted from Hetionet[3] (Himmelstein et al., 2017). Specifically, in the Hetnet, we first obtain the one-hop neighbour nodes of the drug in the DDI matrix and then obtain the neighbour nodes of all one-hop neighbours. Therefore, we can obtain a DKG.

$KGMDNN_h$ and KGMDNN mean that we use the DKG extracted from Hetionet and DrugBank in our model. For $KGMDNN_h$, since the DKG contains different information, we set different hyperparameters. We set the neighbourhood sampling $\mathcal{N}_s$ = 4, GNN layers $l$ = 1, L2 weight = 1e-8, $p$ = 2, $q$ = 3, dimension $d$ = 128, $k_1$ = 256, $k_2$ = 256, $k_3$ = 256 and $k_4$ = 128. It is worth mentioning that other hyper-parameter settings are the same as KGMDNN.

**Figure 7** Parameter sensitivity analysis of different number of neighbourhood $\mathcal{N}_s$ and the initialisation dimension $d$ in the DKG-based pathway in our $KGMDNN_h$ (see online version for colours)




As shown in Figure 6, the evaluation of various DKGs is calculated by using KGMGNN to obtain comprehensive performance outcomes. The results demonstrate that both KGMDNN$_h$ and KGMDNN show good performance on different DKGs. The KGMDNN$_h$ achieves the best Acc value (0.9207) using the DKG extracted from Hetionet, while the Acc value of KGMDNN and MDNN are 0.9191, 0.9175. Concurrently, the KGMGNN also obtains the highest AUPR value (0.9706), while the AUC value and Pre value are 0.9987 and 0.8891. Even if we use different DKGs in our framework, our model has very good performance, which fully reflects the robust- ness of our model. Even if we use different DKGs in our framework, our model has very good performance, which fully reflects the robustness of our model.

**Table 3** The overall information of DKG extracted from Hetionet

| *Category* | *Name* | *Number* |
|---|---|---|
| Drug knowledge graph | Triples | 162,860 |
| | Drugs | 572 |
| | Relations | 12 |
| | Entities | 19,258 |
| Entities | Compound | 1,237 |
| | Side effect | 5,042 |
| | Gene | 11,885 |
| | Disease | 117 |
| | Symptom | 403 |
| | Anatomy | 386 |
| | Pharmacologic class | 188 |

We adopt our method on different parameters for predicting the DDI events to explore further the effect of neighbourhood size and GNN layer using this DKG in our

proposed model. Figure 7 shows the results of the parameter sensitivity analysis on $KGMDNN_h$. The performance for the DDI event prediction achieves peak when $\mathcal{N}_s$ = 4. This indicates that the DKG benefits the performance, but the too large value of neighbourhood size may cause the noise to increase. The performance for the prediction of the DDI event achieves peak value when $d$ = 128, which indicates that too large initialisation dimension in the DKG-based pathway will be affected by the over-fitting.

**Table 4** Performance comparison of KGMDNN with other methods on two different tasks

| *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 |
| | $KGMDNN_h$ | 0.6627 | 0.6918 | 0.4331 | 0.4791 |
| | *KGMDNN* | *0.6667* | *0.7017* | *0.4502* | *0.4914* |
| 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 |
| | $KGMDNN_h$ | *0.4891* | 0.4415 | 0.1758 | 0.1777 |
| | *KGMDNN* | 0.4738 | *0.4453* | *0.1766* | *0.1881* |

### *3.5 Multi-task analysis*

In this subsection, we further analyse the effectiveness of KG- MDNN in other tasks. We averagely divided the drugs involved into five subsets for two separate tasks. We randomly selected four subsets to train. The remaining subset was used to evaulate our model performance. Task A involves building a prediction model for DDIs based on training drugs to forecast DDIs between training and testing drugs. This task is typically used to predict interactions between newly developed drugs and known pharmacological side effects. On the other hand, Task B involves constructing a prediction model for DDIs based on training drugs, subsequently the model to predict DDIs only between test drugs. This task is typically used to predict interactions between newly developed drugs. Based on the performance presented in Table 4, we infer that our framework exhibits superior results compared to alternative approaches in both tasks. It demonstrates that our designed framework effectively improves the accuracy of DDI event prediction, providing strong and reliable support for DDI event prediction research.

## 4 Discussion

The KGMDNN model, a novel approach introduced for predicting DDIs, is primarily characterised by its dual-pathway structure. This structure comprises a DKG-based pathway, utilising a GNN to extract rich structural and semantic information, and a HF-based pathway, which focuses on harnessing predictive information from

various drug-related modalities. The integration of these two pathways enables KGMDNN to effectively combine topological and semantic data from the DKG with the complementary information obtained from HFs. This comprehensive approach significantly enhances the model's capability of predicting DDIs.

In terms of performance, experimental results have demonstrated that KGMDNN outperforms both classical and contemporary state-of-the-art models in DDI event prediction. These results are promising, indicating the model's effectiveness and potential as a reliable tool in the pharmaceutical field.

Looking towards the future, efforts are underway to further enhance KGMDNN model performance on the accuracy, especially in handling larger drug databases. A key focus of these future developments is to leverage deep learning techniques effectively while mitigating the risk of overfitting. The current work has laid a robust and scalable foundation, which is essential for exploring these advanced applications.

A pertinent real-world application of the KGMDNN model is its potential use in predicting DDIs involving Paxlovid, a drug specifically developed for COVID-19 treatment. Paxlovid's composition, which includes ritonavir, a potent inhibitor of liver cytochrome P450 enzymes, necessitates a careful assessment of potential DDIs. The model's application is expected to be particularly beneficial in understanding the interactions of Paxlovid with various drugs, some of which may be contraindicated or have strong interactions, such as Simvastatin, Rivaroxaban, Nitrendipine, and Amlodipine.[4]

While KGMDNN has not been specifically trained on Paxlovid data due to the rapid development and urgency surrounding COVID-19 treatments, there are plans to compile a dataset and adapt the model for this new application. Once trained with the relevant data, KGMDNN is expected to demonstrate its capabilities in accurately predicting DDIs for Paxlovid, thus assisting healthcare professionals and patients in making more informed decisions.

In summary, the KGMDNN model represents a significant step forward in the field of DDI prediction. Its innovative approach and promising results underscore its potential for broader applications, including the pressing need to address DDIs in emerging treatments like Paxlovid. The model not only exemplifies advancement in predictive analytics but also emphasises the critical role of such tools in navigating the complexities of modern medical treatments.

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## Notes

1 https://github.com/YifanDengWHU/DDIMDL.

2 https://go.drugbank.com/.

3 https://het.io/.

4 Data originated from: https://www.drugs.com/drug-interactions/nirmatrelvir-ritonavir, paxlovid.html.