

Predicting Drug-Drug Interactions Using Knowledge Graphs

Lizzy Farrugia¹, Lilian M. Azzopardi², Jeremy Debattista¹, and Charlie Abela¹

¹ Department of Artificial Intelligence, Faculty of ICT, University of Malta
lizzy.farrugia@um.edu.mt, jerdebattista@gmail.com,
charlie.abela@um.edu.mt

² Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta
lilian.azzopardi@um.edu.mt

Abstract. In the last decades, people have been consuming and combining more drugs than before, increasing the number of Drug-Drug Interactions (DDIs). To predict unknown DDIs, recently, studies started incorporating Knowledge Graphs (KGs) since they are able to capture the relationships among entities providing better drug representations than using a single drug property. In this paper, we propose the medicX end-to-end framework that integrates several drug features from public drug repositories into a KG and embeds the nodes in the graph using various translation, factorisation and Neural Network (NN) based KG Embedding (KGE) methods. Ultimately, we use a Machine Learning (ML) algorithm that predicts unknown DDIs. Among the different translation and factorisation-based KGE models, we found that the best performing combination was the ComplEx embedding method with a Long Short-Term Memory (LSTM) network, which obtained an F_1 -score of 95.19% on a dataset based on the DDIs found in DrugBank version 5.1.8. This score is 5.61% better than the state-of-the-art model DeepDDI [1]. Additionally, we also developed a graph auto-encoder model that uses a Graph Neural Network (GNN), which achieved an F_1 -score of 91.94%. Consequently, GNNs have demonstrated a stronger ability to mine the underlying semantics of the KG than the ComplEx model, and thus using higher dimension embeddings within the GNN can lead to state-of-the-art performance.

1 Introduction

Drug-Drug Interactions (DDIs) occur when two or more medications are co-administered simultaneously and cause an Adverse Drug Reaction (ADR). An estimated 44% of men and 57% of women older than 65 in the US take five or more medications, which is bound to worsen, given the population's rapid ageing and the trend of increasing medication use [2]. Moreover, the risk of an ADR increases by 7 to 10% with each medication [3].

Currently, drug developers rely on clinical trials to detect unknown DDIs, whilst pharmacists and doctors depend on a textbook, such as the British National Formulary (BNF), when they are unsure of a known DDI. Amran et al.

[4] reported that less than 50% of ADRs are usually detected during these trials since these are very labour-intensive, time-consuming, and expensive, whilst the remaining ADRs are first-hand experienced by patients during the post-marketing surveillance, known as Pharmacovigilance (PV). Therefore, a framework that can predict potential DDIs, and serve as a reference point to known and potentially dangerous DDIs is essential for healthcare professionals to prescribe safe medications to patients, to provide better and safer healthcare [5].

Many researchers have focused on applying different Machine Learning (ML) algorithms to predict unknown DDIs, including the state-of-the-art model DeepDDI [1]. However, this approach presents a limitation since drugs within their deep network are represented using a single drug property, which is not always available, and thus, their model cannot predict potential DDIs for such instances. Furthermore, one property may not always be enough to represent a drug. These drawbacks motivated other researchers, such as Celebi et al. [6], to create better drug representations by building a Knowledge Graph (KG) encompassing different drug relationships with other critical drug-related concepts, such as diseases, targets, and genes. KGs bring the ability to represent entities and relations with high reliability, explainability, and reusability. These relations are then embedded into a single feature using Knowledge Graph Embedding (KGE) methods. Various graph learning methods exist, including Graph Neural Networks (GNNs) [7], a relatively new research area in Artificial Intelligence (AI), which has not been extensively applied in the DDI domain.

1.1 Aim & Objectives

In this study, our aim is to build the medicX framework that accurately predicts potential DDIs by leveraging KG and ML techniques. To address this aim, we set two objectives.

- Objective 1 (O1): Generate a KG relating various drug-related concepts such as drugs, diseases, side effects, and DDIs [6, 8]. This first entails the acquisition of different drug-related data from repositories such as DrugBank [9] and SIDER [10], since these are highly reputed sources, and secondly, the integration and alignment of this data into a more comprehensive KG. Although there are already other available biomedical KGs, such as Bio2RDF [11], the data has not been updated since 2014. To evaluate this objective, we define a set of Competency Questions (CQs), a common technique for ontology assessments [11].
- Objective 2 (O2): To predict new DDIs, we need to investigate, train and fine-tune various KGE approaches using the KG mentioned in Objective O1 to obtain high-quality drug feature vectors. Among these KGE approaches, we will compare TransE, ComplEx and GNNs. In addition, an investigation will follow to produce an accurate ML algorithm that relies on the obtained embeddings to differentiate between an interacting and a non-interacting drug pair. Finally, similar to other studies [6, 8], we plan to train and evaluate the DDI predictor based on the positive DDIs found in the DrugBank version 5.1.8 dataset.

The rest of the paper is structured as follows: In Section 2, we present research related to KGs and unknown DDI prediction, and in Sections 3 and 4, we present the implementation details and evaluation methodology adopted to evaluate the solutions related to the objectives mentioned above, and finally, in Section 5, we provide some concluding remarks.

2 Related Work

In this section, we present research that adopted KGs to achieve their goals and different techniques that other works have implemented to predict DDIs.

2.1 Biomedical Knowledge Graphs

With the ever-growing number of biomedical databases and the increasing popularity of semantic web technologies, there is a pressing need to develop systems that can integrate this data and offer an endpoint for users to query.

Himmelstein et al. [12] developed Hetionet, a KG developed for Project Rephetio to systematically identify why drugs work and predict new therapies for drugs. Furthermore, the Drug Repurposing Knowledge Graph [13] is a KG that builds upon Hetionet by integrating several additional data resources and was initially developed as part of a project for drug repurposing to target suitable treatments for COVID-19. Both graphs comprise thousands of individual interconnections among various biomedical concepts, such as diseases, side effects, and Anatomical Therapeutic Chemical (ATC) Classification codes, extracted from several repositories, including DrugBank and SIDER. Similarly, Zheng et al. [14] developed PharmKG, a multi-relational attributed biomedical KG, which contains thousands of gene, compound, and disease nodes connected by a set of semantic relationships derived from the abstracts of biomedical literature. Moreover, Abdelaziz et al. [15] proposed Tiresias, a similarity-based system that encodes and stores a KG in Resource Description Framework (RDF) format, then inputted into Apache Spark for similarity calculation and model building for DDI prediction.

Bio2RDF [11] is a biological database that applies semantic web technologies to publicly available databases to provide interlinked life science data related to entities such as drugs, proteins, pathways and diseases. Their method first entailed designing the ontology and converting public biomedical datasets to RDF format documents. This process is known as *rdifizing* and was achieved using Jakarta Server Pages (JSP), a technology that can create dynamically generated web pages based on HTML and XML. Virtuoso Open Source, a semantic web software, was then used to merge, query, and visualise the data. Although the Bio2RDF KG stopped being maintained in 2014, *bio2rdf-scripts*, written in PHP, are available for each dataset. The scripts convert the raw data from the data sources to N-quad documents and have been adopted by several researchers [6, 16].

2.2 Predicting Unknown Drug-Drug Interactions

Traditionally, the discovery of DDIs relies on *in vitro* and *in vivo* experiments and focuses on small sets of specific drug pairs in a laboratory setting. However, with the emergence of available biomedical data and since laboratory screenings of DDIs are very challenging and expensive, there is growing interest in studying and predicting drug interactions using computational methods.

At present, DDI prediction methods are mainly divided into similarity and graph-based approaches. In similarity-based prediction, the underlying assumption is that if *Drug A* and *Drug B* interact to produce a specific biological effect, then drugs similar to *Drug A* (or *Drug B*) are likely to interact with *Drug B* (or *Drug A*) to produce the same effect [17].

Several studies [17, 18] use similarity measures, which are functions that take as input a particular drug property of *Drug A* and *Drug B*, and calculate the similarity between them. The most popular drug similarity measure is the Tanimoto Coefficient (TC) [19]. The TC calculates the similarity between the molecular fingerprints of the drug pair. If the resultant TC is 0 that means that the molecular structure of the drug pair is *maximally dissimilar* to one another, whilst if the TC is 1, then the drug pair is *maximally similar*. However, creating a model that solely relies on the TC does not yield high results [17].

In addition to the TC similarity measure, other researchers [1, 18] incorporated other similarity measures or ML approaches. For example, Ryu et al. [1] created a state-of-the-art framework called DeepDDI that can predict DDIs and drug-food interactions. Besides the TC similarity measure to calculate the similarity profile of drugs based on their SMILES notation, they also employed a Principal Component Analysis (PCA) and a deep feed-forward NN to reduce the feature space and predict the type of unknown drug-drug and drug-food interactions.

A drawback of relying on a few features is that they may not always be available and can be challenging and costly to obtain. A popular approach adopted by multiple studies [1, 17] is to remove those biological entities without features via pre-processing. However, this usually results in a small-scale pruned dataset and thus is not pragmatic and useful in reality. Furthermore, Vilar et al. [17] observed that relying on a handful number of features may not be precise enough to represent or characterise DDIs, and may fail to help build a robust and accurate DDI model.

For these reasons, recent studies [8, 15] focus has turned towards representing drug knowledge by leveraging a KG and then applying KGE models to derive drug features by mapping nodes to a d -dimensional embedding space so that similar nodes in the graph are embedded close to each other. These models are typically categorised into translation, factorisation and NN-based models.

Translation-based models, such as TransE [20] and TransR [21], assume that after applying a relational translation when we add the embedding of the head to the embedding of the relation, the result should be the embedding of the tail entity. On the other hand, factorisation-based models, such as RESCAL [22], DistMult [23] and ComplEx [24], capture nodes and relations as multidimen-

sional tensors, which are then factorised into low-dimensional vectors. GNNs [7] are an active, new field of research that use deep learning methods to perform inference on data described by graphs. GNNs can be regarded as an embedding methodology that distils high-dimensional information about each node’s neighbourhood into a dense vector embedding.

Abdelaziz et al. [15] compared different features, including word and graph embedding-based features, which were calibrated and fed into a Logistic Regression (LR) algorithm to predict potential DDIs. They concluded that HoIE [25], a factorisation-based KGE method, produced the most powerful feature.

Furthermore, Celebi et al. [6] and Karim et al. [8] evaluated different translation and factorisation-based KGEs. From their experiments, Celebi et al. [6] concluded that RDF2Vec [26] performed the best, whilst Karim et al. [8] concluded that translation-based models have low expressive power since they do not capture semantic information, unlike the ComplEx [24] KGE model, which obtained the best results in their evaluation. Moreover, Celebi et al. [6] demonstrated that Random Forests (RFs) outperformed LR and Naive Bayes (NB) classifiers. Karim et al. [8] confirmed Celebi et al.’s [6] remarks but concluded that a more complex ML algorithm, such as their Convolutional-LSTM model, can obtain better results, achieving an F_1 -score improvement of 7% over the RF classifier.

Recently, there has been an increasing interest in applying GNNs for DDI prediction [7, 27]. Ji et al. [28] demonstrated that such models have the generality to consider the type of entity and relation, path information and underlying structure information and thus can resolve the limitations of translation and factorisation-based models in representing all the features of a KG.

For example, Feng et al. [27] developed Deep Predictor for DDIs (DPDDI), which incorporates a Graph Convolutional Network (GCN) model that learns low-dimensional feature representations of drugs by capturing the topological relationship of drugs in a DDI network. A predictor then concatenates the latent feature vectors of any two drugs and trains a 5-layer Deep Neural Network (DNN) to predict potential DDIs.

Zitnik et al. [7] presented Decagon, a graph auto-encoder approach to predict polypharmacy side effects. In their methodology, the authors collected protein-protein, drug-protein and drug-drug interaction and side effect data. Each DDI is labelled by a different edge type, which signifies the kind of side effect, and hence, formulated the problem of predicting polypharmacy side effects as solving a multi-relational link prediction task. They then developed a multi-layer Relational-GCN (R-GCN), an extension of GCNs that can differentiate between different types of relations in a KG to produce higher quality embeddings. The R-GCN module acts as an encoder and operates on the graph to produce embeddings for the nodes. A decoder in the form of a tensor factorisation model then predicts a candidate edge, which is ultimately followed by a sigmoid function to compute the probability that a given edge is one of the given side effects.

3 The medicX Approach

In the previous section, we discussed research related to our objectives. In this section, we discuss the implementation of the two main components of our system, developed using the Python language.

3.1 Building the Knowledge Graph

We decided to create a KG using a multi-step approach that integrates drug data from different bioinformatics sources to create a more comprehensive KG than the existing ones that can ultimately infer new knowledge and generate high-quality drug features.

Similar to Celebi et al. [6] and Karim et al. [8], we converted data from DrugBank [9], KEGG [29], PharmGKB [30] and SIDER [10] datasets to RDF, providing a more fluid and effective model for integrating and querying the data using the bio2rdf-scripts. The advantage of using this approach instead of using the actual Bio2RDF KG or any existing KG is that this method helped us create a KG that contains the most recent and up-to-date data.

Initially, we investigated the overlap among different reliable DDI repositories, including DrugBank, KEGG, Drugs.com, Liverpool Covid-19 Interactions, TWOSIDES [31] and PharmGKB, and observed that the overlap is minimal, highlighting the importance of merging DDIs from multiple sources [32]. Therefore, we decided to employ several data mining tools, such as asynchronous requests, BeautifulSoup [33] and Selenium to scrape DDIs from these portals. As various drug databases represent drugs using identifiers specific to them, we mapped the drugs across different repositories using numerous techniques to create a holistic list of unique DDIs. As a result, we managed to accumulate 2,477,864 unique DDIs.

Indications, also known as associated conditions, and ATC codes are frequently used as features to represent the drugs in similarity-based approaches [18]. For this reason, we scraped associated conditions from the DrugBank portal, as these are not available in their XML dataset, and downloaded the ATC Classification System [34] ontology, available from BioPortal.

We then designed our ontology, which we refer to as the medicX ontology, to encompass the extracted associated conditions and the DDIs, using the Web Ontology Language (OWL) and RDF Schema (RDFS) ontology schemas through the RDFLib [35] library. Finally, to enable interoperability in our KG, we aligned the medicX ontology with the Bio2RDF and ATC Classification System ontologies by determining correspondences among semantically related entities, using relations such as *owl:equivalentClass*, *owl:sameAs* and *rdfs:subClassOf*. Then, we created a rdflizer that converts the mined associated conditions and DDIs to RDF notation.

After performing the steps mentioned above, we imported the resulting processed RDF documents into a triple store. In our study, we opted to use Ontotext’s GraphDB³, which can smoothly integrate heterogeneous data from multi-

³ <https://graphdb.ontotext.com/>

ple sources and store hundreds of billions of facts about any conceivable concept, unlike other research work that used alternative graph databases such as the Blazegraph⁴ Database, used by Karim et al. [8], and Virtuoso Open Source⁵, which hosts the Bio2RDF KG.

3.2 Predicting Unknown Drug-Drug Interactions

In order to be able to predict DDIs, once the data is in the form of a KG, we first convert the drug entities into semantically meaningful fixed-length vector representations using KGE models and then feed these embeddings into a ML classifier that can distinguish between interacting and non-interacting drug pairs. In this research, we explore and compare different translation, factorisation, and NN-based KGE algorithms to discover which model is the most suitable to address the DDI link prediction problem.

Translation and Factorisation-based Approach Recent research has released open-source libraries to facilitate the adaptation of these KGE models in various applications. For example, Celebi et al. [6] used the OpenKE library [36] to train the TransE and TransD models, whilst Karim et al. [8] used the Pytorch BigGraph library [37] amongst other libraries. Moreover, in 2020, Amazon launched DGL-KE [38], a high-performance, easy-to-use, and scalable toolkit to generate some of the most popular KGEs from large graphs. This library builds upon Deep Graph Learning (DGL) [39], an open-source library to implement GNNs, and allows one to train a KGE model with a simple input argument in the command line script. In addition, DGL-KE contains various optimisations that accelerate KGE training on KGs. We used the DGL-KE library to train and compare the TransE, TransR, RESCAL, DistMult and ComplEx KGE models.

Given the dense representations created by one of the translation or factorisation based KGE methods, we concatenated the embedding vectors of each drug in the pair and then fed them into a ML model. We used concatenation as a feature aggregation operator since the concatenate operator performs better than other operators, such as inner product and summation [16, 27].

We adopted three different supervised ML algorithms with varying levels of complexities; RF, Multi-Layer Perceptron (MLP) and LSTM. The RF and MLP are available from scikit-learn [40], whilst we built the LSTM model using Keras [41].

The parameters used for building our RF classifier were inspired by Celebi et al. [6]. The number of estimators is 200, and the maximum depth of the tree is 8. On the other hand, we train the MLP classifiers using a single layer of 100 neurons for a maximum of 100 epochs using the Adam [42] version of stochastic gradient descent optimiser with a learning rate of 0.001. Finally, we used Rectified Linear Unit (ReLU) as the activation function widely adopted in deep learning research.

⁴ <https://blazegraph.com/>

⁵ <https://virtuoso.openlinksw.com/>

Our LSTM network contains two hidden layers of LSTM, one with 100 neurons and another with 64 neurons. The output of each LSTM layer is then passed to the dropout layer to regularise learning to avoid overfitting. The final output layer has one neuron for forecasting whether an interaction exists. Every LSTM layer expects a three-dimensional input, $s \times f \times t$, where s is the sample size, t is the time-step, and f is the feature size. In our case, s is the number of interacting and non-interacting drug pairs, t is one since we are only using one feature, which is the KGE at one point in time, and f is the length of our concatenated feature vector of *Drug A* and *Drug B*. The efficient Adam optimiser [42] is also applied with the binary cross-entropy loss function, and the model is trained for 100 epochs.

Graph Neural Network-based Approach Additionally, we also implement a graph auto-encoder, illustrated in Figure 1, using PyTorch [43] and DGL [39], based on the approach presented by Schlichtkrull et al. [7].

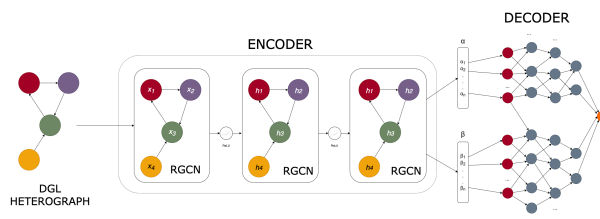


Fig. 1. Graph Auto-Encoder Architecture

The encoder takes the positive training relations graph and additional node feature vectors to the first R-GCN layer. Then, in each layer, the R-GCN propagates the latent node feature information across the edges of the graph while considering the relation type of the edge. A single layer of this model is defined as;

$$h_i^{(k+1)} = \phi\left(\sum_r \sum_{j \in N_r^i} c_r^{ij} W_r^{(k)} h_j^{(k)} + c_r^i h_i^{(k)}\right) \quad (1)$$

where $h_i^{(k)}$ is the hidden state of node v_i in the k^{th} layer of the NN, r is the relation type and matrix W_r^k is a relation-type weight matrix. ϕ denotes the activation function, which transforms the representations to be used in the layer of the neural model, c_r^{ij} and c_r^i are normalisation constants and N_r^i denotes the set of neighbours of node v_i under relation r .

We stack a number of R-GCN layers using the *HeteroGraphConv* module in DGL. The resulting representation of the first R-GCN layer is accumulated and passed through the ReLU activation function to produce the hidden state of each node, which is then used as input to the second R-GCN layer.

On the other hand, the decoder aggregates our drug pairs’ entity representations, generated by the R-GCN, into a single vector and computes a probability for every potential edge in the graph that has a destination and source node of type drug, using a simple NN.

In each iteration, we trained the encoder and decoder concurrently, and then given a set of drug pairs and the ground-truth interaction values in the training dataset, we applied the binary cross-entropy as the loss function to assign higher probabilities to observed edges than to random non-edges. Finally, to optimise all trainable parameters in the model, we used the Adam [42] algorithm with a learning rate of 0.01. Gandhi et al. [44] noted that for training tasks to achieve reasonable accuracy in GNNs, several 100s or even 1000s of epochs are needed. For this reason, we set the minimum number of epochs to 500.

4 Evaluation

This section presents the evaluation methodology we adopted to evaluate the solutions to the objectives outlined in Section 1.1.

To benchmark the performance of our classifier, we adopt a combination of the evaluation metrics used by Ryu et al. [1], Celebi et al. [6] and Karim et al. [8]. These metrics include accuracy, precision, recall, F_1 measure, Area Under the Receiver Operating Characteristic (AUC), Area Under the Precision-Recall Curve (AUPR) and Matthias Correlation Coefficient (MCC).

Like several other studies [6, 8], we decided to evaluate our models on the known DDIs in the DrugBank version 5.1.8 dataset.

We used 70% of the positive DDIs, in the DrugBank dataset, for the training, 30% for evaluating the models, and 10% from the training set was randomly used for the validation. Since, in reality, we do not know all the DDIs, some of the unknown DDIs may indeed be positive. However, regarding all unknown interactions as the negative set, on the other hand, produces a data balance issue, affecting performance metrics such as AUPR and F_1 -score [6]. Therefore, similar to Celebi et al. [6], we randomly sampled an equivalent number of negative samples from the unknown drug pairs as positive samples for each set.

4.1 Knowledge Graph

We built a KG comprising 18,322,022 nodes and 180,800,521 triples. Figure 2 depicts part of the KG that shows some of the nodes connected to the *haloperidol* and *risperidone*, two anti-psychotic medications, drug nodes. We note that the drugs interact since they are linked to a common DDI node. In addition, we observed that both drugs interact with *insulin glargine*, a drug used to manage type I and type II diabetes, and have two common associated conditions; schizophrenia and psychosis.

Whilst we were analysing the relevancy of the KG in the real world, we compiled a list of CQs, listed in Table 1, which we also used for evaluation purposes. After building the KG, we wrote the questions as SPARQL queries, similar to

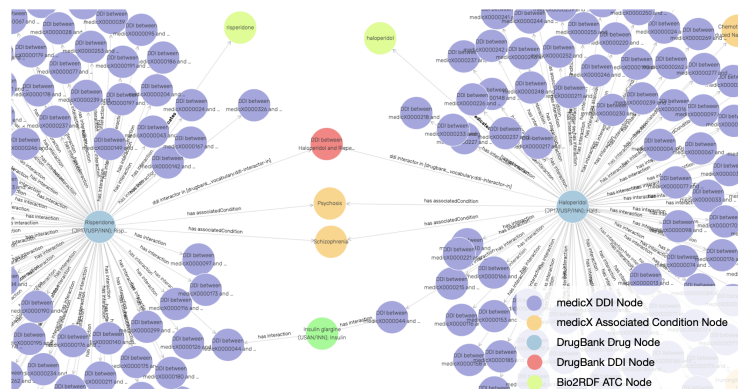


Fig. 2. *haloperidol* and *risperidone* Sub-graph

Belleau et al. [11], and executed them in GraphDB using the GraphDB Workbench. In addition to what we noticed earlier in Figure 2, we discovered that our KG contains 11,107 and 7,402 DDIs for *haloperidol* and *risperidone*, respectively. Also, we uncovered that *Baricitinib*, *Bamlanivimab*, *Moderna COVID-19 Vaccine*, *Pfizer-BioNTech Covid-19 Vaccine* and *Remdesivir* are all used to either treat or prevent Covid-19. Moreover, the SPARQL endpoint listed 155 adverse reactions for *haloperidol*. These range from mild reactions such as increased sweating and nausea to serious ones, including Parkinsonian Disorders and sudden death. When we executed the final query, we observed that 36 drugs in our KG are anti-psychotics, which included *haloperidol* and *risperidone*.

Table 1. Competency Questions

CQ1 Do <i>haloperidol</i> and <i>risperidone</i> interact with one another?
CQ2 Which drugs interact with <i>haloperidol</i> and <i>risperidone</i> ?
CQ3 Which drugs can be administered to treat Covid-19?
CQ4 What are side effects of <i>haloperidol</i> ?
CQ5 Which drugs are antipsychotics?

As a result, these answers depict the similarities between *haloperidol* and *risperidone*, and how these may lead to a greater additive or synergistic effect (a DDI). These insights show the usefulness of KGs as they can help us better understand the dynamics between entities, such as drugs in this case, and why they may cause DDIs when consumed together. Moreover, with the power of SPARQL together with the flexibility of RDF, we managed to integrate previously disjoint systems. For example, using SPARQL we can navigate from a DrugBank node to several ADRs within the SIDER dataset, which shows how KGs can provide a unified view of varied unconnected data sources. Furthermore, we observed that by having the essential relationships between concepts built into our ontology, ontology languages, such as OWL and RDFS, enable automated reasoning about

data using a built-in reasoner in the graph database, improving reusability and interoperability within a KG.

4.2 Predicting Unknown Drug-Drug Interactions

Among the different translation and factorisation-based KGE models, we noted that the TransE and TransR models overall obtained the worst performance, whilst DistMult and ComplEx obtained the best performance. This observation follows since TransE cannot model complex and diverse relations, such as symmetric, transitive, one-to-many, many-to-one, and many-to-many relations in KGs, and TransR does not consider the diversity of node types. Similar to Karim et al. [8], we noted that more complex models, such as the LSTM classifier, outperformed the RF and MLP classifiers, in the best case resulting in an F_1 -score of 89.63%, whilst the RF performed the worst, with the lowest F_1 -score of 72.23%.

In addition, throughout our research, we observed that embedding quality increases with higher dimensionality, and as a result, we set the embedding size to 900. Moreover, we investigated the influence of the number of negatives per positive training sample, known as negative sampling. We decreased the negative sample size from 256 to 20, as Karim et al. [8] concluded that this value obtained their best result and found that a larger sample size performs better in our case. Ultimately, we generated a ComplEx-LSTM model that obtained an F_1 -score of 95.19%.

We built several graph auto-encoders with varying numbers of R-GCN layers in the encoder and hidden layers in the decoder. We observed that building a slightly more complex architecture improves the performance of graph auto-encoders. For example, by stacking three R-GCN layers in the encoder, and creating a DNN with three hidden layers, instead of one in both components, the F_1 -score increased by 17.5%. Moreover, by increasing the input and output embedding and the hidden layer size in the R-GCN layer the model’s performance improved by almost 2%.

Several researchers, such as Wang et al. [45], noted that instead of using randomly distributed initial node features, such as the distribution proposed by Xavier et al. [46], one should use trained embeddings as input to the first GNN layer. Therefore, we used the ComplEx KGE model in DGL-KE to create embeddings of size 50 and used these features as initial node features for the first R-GCN layer. This optimisation further improved the F_1 score by at least 3.18%, which confers that initial node features also impact the quality of the embeddings that the R-GCN model produces. The resulting graph auto-encoder achieved an F_1 -score of 91.94%.

Compared to the ComplEx KGE model, R-GCNs are memory intensive since they require memory to store input data, weight parameters, and activations as input propagates through the network [47]. Additionally, they are computationally more expensive since they introduce numerous parameters to the convolutions taking place. Hence due to memory restrictions, we kept the embedding size of the nodes relatively small compared to the embeddings produced by the

ComplEx KGE model. Although the ComplEx-LSTM model achieved an F_1 -score that is 3.25% better than the graph auto-encoder, we conclude that using a feature learning and extraction model such as R-GCN can generate better embeddings compared to translation and factorisation-based models, especially when using larger embeddings. This achievement is because of the GCNs ability to consider all types of relations among the entity links, path, and substructure information, using the incorporated CNNs.

4.3 Performance Comparison

We replicated and compared our ComplEx-LSTM and GNN-based models with four other research works [1, 6, 8, 17] mentioned in Section 2.2. Table 3 illustrates the respective results. We observed that our two-stage approach (ComplEx-LSTM) and graph auto-encoder achieved better results than all the other methods.

Our results showed that although Vilar et al.’s method does not obtain competitive results due to its naive approach, representing drugs using their respective SMILES notation is a good way, as can be seen from the results achieved by the DeepDDI model. Nonetheless, as we previously mentioned, the SMILES notation is not always available. Thus, such models cannot discover potential DDIs concerning drugs without a SMILES notation or a SMILES that a library, such as RDKit⁶, cannot decode.

Furthermore, we observed a significant difference between the approach by Celebi et al. [6] and our ComplEx-LSTM model, which most likely occurred because the authors used the RDF2Vec model and an RF. On the other hand, although Karim et al. [8] also used the ComplEx KGE model and a DNN as a predictor, our model achieved an increase of 12.04%. This distinction is because they used an embedding size of 300; they omitted DDIs while training the embedding model and because of their Convolutional-LSTM model.

Table 2. Comparison with other models

	Precision	Recall	F_1 -score	AUC	AUPR	MCC	Accuracy
Vilar et al. [17]	0.5138	0.5138	0.5132	0.5192	0.5156	0.0276	0.5138
Ryu et al. [1]	0.8958	0.8958	0.8958	0.9623	0.9621	0.7916	0.8958
Celebi et al. [6]	0.7887	0.782	0.7807	0.8627	0.8481	0.5707	0.7820
Karim et al. [8]	0.8374	0.8321	0.8315	0.9178	0.9138	0.6695	0.8321
Our ComplEx + LSTM	0.9519	0.9519	0.9519	0.9897	0.9901	0.9038	0.9519
Our Graph auto-encoder	0.9195	0.9194	0.9194	0.9789	0.9794	0.8389	0.9194

We also evaluated our DDI prediction models for cold start drugs, with no known DDI information in the training set to determine whether our models are adequate for drug discovery applications, as was performed by Celebi et al. [6].

⁶ <https://github.com/rdkit/rdkit>

Table 3. Comparison with other models

	Precision	Recall	F_1 -score	AUC	AUPR	MCC	Accuracy
Vilar et al. (2012)	0.5138	0.5138	0.5132	0.5192	0.5156	0.0276	0.5138
Ryu et al. (2018)	0.8958	0.8958	0.8958	0.9623	0.9621	0.7916	0.8958
Celebi et al. (2018)	0.7887	0.782	0.7807	0.8627	0.8481	0.5707	0.7820
Karim et al. (2019)	0.8374	0.8321	0.8315	0.9178	0.9138	0.6695	0.8321
Our ComplEx + LSTM	0.9519	0.9519	0.9519	0.9897	0.9901	0.9038	0.9519
Our Graph auto-encoder	0.9195	0.9194	0.9194	0.9789	0.9794	0.8389	0.9194

Our ComplEx-LSTM model obtains a recall of 89.29% and a precision of 54.59% for interacting drug pairs when only one drug in the drug pair is a new drug. On the other hand, when both drugs are cold start drugs, our model obtained a precision of 50.52% and a recall of 95.09%. We noted that the false-negative rate is low (high recall), and this is beneficial in most medical practices since such a model can help professionals determine potentially dangerous DDIs. Although the precision scores seem to be low, we consider the results to be realistic in predicting the interactions for drugs with insufficient interaction information. Hence, we can presume that our model can be helpful in drug discovery applications.

Lastly, by altering the LSTM to handle more than two class labels and using the trained ComplEx embeddings that obtained the best results in our binary classification, we implemented a multi-classifier that, besides distinguishing between positive and negative DDIs, can classify a positive DDI as one out of 86 positive DDI data types mentioned in the DeepDDI dataset. In Table 4, we compare our results with those reported by Ryu et al. [1] and Celebi et al. [6] in their paper. As a result, we observed that, apart from a slight improvement and faster training, our model, unlike DeepDDI, can predict DDIs of drugs that do not have the SMILES feature.

Table 4. Multi-class Classifiers comparison

	Precision	Recall	F_1 -score	MCC	Accuracy
Ryu et al. [1]	0.9	0.85	0.86	-	0.92
Celebi et al. [6]	0.82	0.87	0.85	-	0.84
ComplEx - LSTM	0.9086	0.8441	0.8649	0.9367	0.9549

5 Conclusion

We managed to address both objectives we laid out in Section 1.1. We built a KG that can easily be queried to extract knowledge regarding drugs, DDIs, side effects and indications and showed that apart from acting as a data structure, KGs can be used by factorisation-based KGE models and GNNs to generate

high-quality feature representations that can be used by ML algorithms or deeper networks for DDI prediction.

Throughout our evaluation, we learned that KGs can capture relationships between drugs and graph databases are able to discern valuable insights on why drugs might interact with one another based on links to common nodes such as side effects and indications. Furthermore, KGE models provide better drug representation than traditional feature extraction and selection methods, to predict potential DDIs, as they do not rely on a limited number of drug properties.

There is still work that can be done to improve the performance and efficiency of our system. We plan to enrich the KG with other structured and unstructured data from other medical sources, including PubMed, which is a search engine that provides accessibility to biomedical literature. Moreover, we want to consult professionals in the biomedical area to find out what other drug information is helpful to include in our KG. For the second objective, we would like to extend our graph auto-encoder to predict multiple DDI types by replacing the interaction relations with the interaction types and defining a decoder that can predict among them [7]. Finally, we noted that the negative set in our evaluation consists of drug pairs, for which evidence regarding their interaction has not been found yet, and may still interact with one another. Therefore, we may have discrepancies within our dataset and cannot correctly identify true negative and false positive drug pairs [48]. Hence, we want to train our models using a dataset containing only true negatives in their negative set to create a more precise and reliable DDI predictor.

Bibliography

- [1] 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.
- [2] Kathleen Woodruff. Preventing polypharmacy in older adults. *American Nurse Today*, 5(10):1–8, 2010.
- [3] J Garber and S Brownlee. Medication overload: America’s other drug problem. *Brookline: The Lown Institute*, 2019.
- [4] Md Shah Amran. Adverse drug reactions and pharmacovigilance. In *New Insights into the Future of Pharmacoepidemiology and Drug Safety*. IntechOpen, 2021.
- [5] Lizzy Farrugia and Charlie Abela. Mining drug-drug interactions for health-care professionals. In *Proceedings of the 3rd International Conference on Applications of Intelligent Systems*, pages 1–6, 2020.
- [6] Remzi Celebi, Erkan Yasar, Huseyin Uyar, Ozgur Gumus, Oguz Dikenelli, and Michel Dumontier. Evaluation of knowledge graph embedding approaches for drug-drug interaction prediction using linked open data. 2018.
- [7] Marinka Zitnik, Monica Agrawal, and Jure Leskovec. Modeling polypharmacy side effects with graph convolutional networks. *Bioinformatics*, 34(13):i457–i466, 2018.
- [8] Md. Rezaul Karim, Michael Cochez, Joao Bosco Jares, Mamtaz Uddin, Oya Beyan, and Stefan Decker. Drug-drug interaction prediction based on knowledge graph embeddings and convolutional-lstm network. In *Proceedings of the 10th ACM International Conference on Bioinformatics, Computational Biology and Health Informatics*, pages 113–123, 2019.
- [9] David S Wishart, Craig Knox, An Chi Guo, Dean Cheng, Savita Shrivastava, Dan Tzur, Bijaya Gautam, and Murtaza Hassanali. Drugbank: a knowledgebase for drugs, drug actions and drug targets. *Nucleic acids research*, 36(suppl_1):D901–D906, 2007.
- [10] Michael Kuhn, Ivica Letunic, Lars Juhl Jensen, and Peer Bork. The sider database of drugs and side effects. *Nucleic acids research*, 44(D1):D1075–D1079, 2015.
- [11] François Belleau, Marc-Alexandre Nolin, Nicole Tourigny, Philippe Rigault, and Jean Morissette. Bio2rdf: towards a mashup to build bioinformatics knowledge systems. *Journal of biomedical informatics*, 41(5):706–716, 2008.
- [12] Daniel Scott Himmelstein, Antoine Lizee, Christine Hessler, Leo Brueggeman, Sabrina L Chen, Dexter Hadley, Ari Green, Pouya Khankhanian, and Sergio E Baranzini. Systematic integration of biomedical knowledge prioritizes drugs for repurposing. *Elife*, 6:e26726, 2017.
- [13] Vassilis N. Ioannidis, Xiang Song, Saurav Manchanda, Mufei Li, Xiaoqin Pan, Da Zheng, Xia Ning, Xiangxiang Zeng, and George Karypis. Drkg - drug repurposing knowledge graph for covid-19. <https://github.com/gnn4dr/DRKG/>, 2020.

- [14] Shuangjia Zheng, Jiahua Rao, Ying Song, Jixian Zhang, Xianglu Xiao, Evandro Fei Fang, Yuedong Yang, and Zhangming Niu. Pharmkg: a dedicated knowledge graph benchmark for biomedical data mining. *Briefings in bioinformatics*, 22(4):bbaa344, 2021.
- [15] Ibrahim Abdelaziz, Achille Fokoue, Oktie Hassanzadeh, Ping Zhang, and Mohammad Sadoghi. Large-scale structural and textual similarity-based mining of knowledge graph to predict drug–drug interactions. *Journal of Web Semantics*, 44:104–117, 2017.
- [16] Xuan Lin, Zhe Quan, Zhi-Jie Wang, Tengfei Ma, and Xiangxiang Zeng. Kgnn: Knowledge graph neural network for drug–drug interaction prediction. In *IJCAI*, 2020.
- [17] Santiago Vilar, Rave Harpaz, Eugenio Uriarte, Lourdes Santana, Raul Rabadan, and Carol Friedman. Drug–drug interaction through molecular structure similarity analysis. *Journal of the American Medical Informatics Association*, 19(6):1066–1074, 2012.
- [18] Assaf Gottlieb, Gideon Y Stein, Yoram Oron, Eytan Ruppim, and Roded Sharan. Indi: a computational framework for inferring drug interactions and their associated recommendations. *Molecular systems biology*, 8(1): 592, 2012.
- [19] T.T. Tanimoto. *An Elementary Mathematical Theory of Classification and Prediction*. International Business Machines Corporation, 1958.
- [20] Antoine Bordes, Nicolas Usunier, Alberto Garcia-Duran, Jason Weston, and Oksana Yakhnenko. Translating embeddings for modeling multi-relational data. *Advances in neural information processing systems*, 26, 2013.
- [21] Yankai Lin, Zhiyuan Liu, Maosong Sun, Yang Liu, and Xuan Zhu. Learning entity and relation embeddings for knowledge graph completion. In *Twenty-ninth AAAI conference on artificial intelligence*, 2015.
- [22] Maximilian Nickel, Volker Tresp, and Hans-Peter Kriegel. A three-way model for collective learning on multi-relational data. In *Icml*, 2011.
- [23] Bishan Yang, Wen-tau Yih, Xiaodong He, Jianfeng Gao, and Li Deng. Embedding entities and relations for learning and inference in knowledge bases. *arXiv preprint arXiv:1412.6575*, 2014.
- [24] Théo Trouillon, Johannes Welbl, Sebastian Riedel, Éric Gaussier, and Guillaume Bouchard. Complex embeddings for simple link prediction. In *International Conference on Machine Learning*, pages 2071–2080. PMLR, 2016.
- [25] Maximilian Nickel, Lorenzo Rosasco, and Tomaso Poggio. Holographic embeddings of knowledge graphs. In *Proceedings of the AAAI Conference on Artificial Intelligence*, volume 30, 2016.
- [26] Petar Ristoski and Heiko Paulheim. Rdf2vec: Rdf graph embeddings for data mining. In *International Semantic Web Conference*, pages 498–514. Springer, 2016.
- [27] Yue-Hua Feng, Shao-Wu Zhang, and Jian-Yu Shi. Dpddi: a deep predictor for drug–drug interactions. *BMC bioinformatics*, 21(1):1–15, 2020.
- [28] Shaoxiong Ji, Shirui Pan, Erik Cambria, Pekka Marttinen, and S Yu Philip. A survey on knowledge graphs: Representation, acquisition, and applications. *IEEE Transactions on Neural Networks and Learning Systems*, 2021.

- [29] Minoru Kanehisa and Susumu Goto. Kegg: kyoto encyclopedia of genes and genomes. *Nucleic acids research*, 28(1):27–30, 2000.
- [30] Michelle Whirl-Carrillo, Ellen M McDonagh, JM Hebert, Li Gong, K Sangkuhl, CF Thorn, Russ B Altman, and Teri E Klein. Pharmacogenomics knowledge for personalized medicine. *Clinical Pharmacology & Therapeutics*, 92(4):414–417, 2012.
- [31] Nicholas P Tatonetti, P Ye Patrick, Roxana Daneshjou, and Russ B Altman. Data-driven prediction of drug effects and interactions. *Science translational medicine*, 4(125):125ra31–125ra31, 2012.
- [32] Serkan Ayvaz, John Horn, Oktie Hassanzadeh, Qian Zhu, Johann Stan, Nicholas P Tatonetti, Santiago Vilar, Mathias Brochhausen, Matthias Samwald, Majid Rastegar-Mojarad, et al. Toward a complete dataset of drug–drug interaction information from publicly available sources. *Journal of biomedical informatics*, 55:206–217, 2015.
- [33] Leonard Richardson. Beautiful soup documentation. *April*, 2007.
- [34] Armin Skrbo, Begler Begović, and Selma Skrbo. Classification of drugs using the atc system (anatomic, therapeutic, chemical classification) and the latest changes. *Medicinski arhiv*, 58(1 Suppl 2):138–141, 2004.
- [35] D Krech. Rdfib: A python library for working with rdf. *Online <https://github.com/RDFLib/rdfib>*, 2006.
- [36] Xu Han, Shulin Cao, Lv Xin, Yankai Lin, Zhiyuan Liu, Maosong Sun, and Juanzi Li. Openke: An open toolkit for knowledge embedding. In *Proceedings of EMNLP*, 2018.
- [37] Adam Lerer, Ledell Wu, Jiajun Shen, Timothee Lacroix, Luca Wehrstedt, Abhijit Bose, and Alex Peysakhovich. PyTorch-BigGraph: A Large-scale Graph Embedding System. In *Proceedings of the 2nd SysML Conference*, Palo Alto, CA, USA, 2019.
- [38] Da Zheng, Xiang Song, Chao Ma, Zeyuan Tan, Zihao Ye, Jin Dong, Hao Xiong, Zheng Zhang, and George Karypis. Dgl-ke: Training knowledge graph embeddings at scale. In *Proceedings of the 43rd International ACM SIGIR Conference on Research and Development in Information Retrieval*, pages 739–748, 2020.
- [39] Minjie Wang, Da Zheng, Zihao Ye, Quan Gan, Mufei Li, Xiang Song, Jinjing Zhou, Chao Ma, Lingfan Yu, Yu Gai, Tianjun Xiao, Tong He, George Karypis, Jinyang Li, and Zheng Zhang. Deep graph library: A graph-centric, highly-performant package for graph neural networks. *arXiv preprint arXiv:1909.01315*, 2019.
- [40] F. Pedregosa, G. Varoquaux, A. Gramfort, V. Michel, B. Thirion, O. Grisel, M. Blondel, P. Prettenhofer, R. Weiss, V. Dubourg, J. Vanderplas, A. Passos, D. Cournapeau, M. Brucher, M. Perrot, and E. Duchesnay. Scikit-learn: Machine learning in Python. *Journal of Machine Learning Research*, 12: 2825–2830, 2011.
- [41] François Chollet et al. Keras. <https://keras.io>, 2015.
- [42] Diederik P Kingma and Jimmy Ba. Adam: A method for stochastic optimization. *arXiv preprint arXiv:1412.6980*, 2014.

- [43] Adam Paszke, Sam Gross, Francisco Massa, Adam Lerer, James Bradbury, Gregory Chanan, Trevor Killeen, Zeming Lin, Natalia Gimelshein, Luca Antiga, Alban Desmaison, Andreas Kopf, Edward Yang, Zachary DeVito, Martin Raison, Alykhan Tejani, Sasank Chilamkurthy, Benoit Steiner, Lu Fang, Junjie Bai, and Soumith Chintala. Pytorch: An imperative style, high-performance deep learning library. In H. Wallach, H. Larochelle, A. Beygelzimer, F. d'Alché-Buc, E. Fox, and R. Garnett, editors, *Advances in Neural Information Processing Systems 32*, pages 8024–8035. Curran Associates, Inc., 2019.
- [44] Swapnil Gandhi and Anand Padmanabha Iyer. P3: Distributed deep graph learning at scale. In *15th {USENIX} Symposium on Operating Systems Design and Implementation ({OSDI} 21)*, pages 551–568, 2021.
- [45] Meihong Wang, Linling Qiu, and Xiaoli Wang. A survey on knowledge graph embeddings for link prediction. *Symmetry*, 13(3):485, 2021.
- [46] Xavier Glorot and Yoshua Bengio. Understanding the difficulty of training deep feedforward neural networks. In *Proceedings of the thirteenth international conference on artificial intelligence and statistics*, pages 249–256. JMLR Workshop and Conference Proceedings, 2010.
- [47] Ao Zhou, Jianlei Yang, Yeqi Gao, Tong Qiao, Yingjie Qi, Xiaoyi Wang, Yunli Chen, Pengcheng Dai, Weisheng Zhao, and Chunming Hu. Optimizing memory efficiency of graph neural networks on edge computing platforms. *arXiv preprint arXiv:2104.03058*, 2021.
- [48] Narjes Rohani and Changiz Eslahchi. Drug-drug interaction predicting by neural network using integrated similarity. *Scientific reports*, 9(1):1–11, 2019.