Interaction between pharmacological agents can trigger unexpected adverse events. Capturing richer and more comprehensive information about drug-drug interactions (DDI) is one of the key tasks in public health and drug development. Recently, several knowledge graph embedding approaches have received increasing attention in the DDI domain due to their capability of projecting drugs and interactions into a low-dimensional feature space for predicting links and classifying triplets. However, existing methods only apply a uniformly random mode to construct negative samples. As a consequence, these samples are often too simplistic to train an effective model. In this paper, we propose a new knowledge graph embedding framework by introducing adversarial autoencoders (AAE) based on Wasserstein distances and Gumbel-Softmax relaxation for drug-drug interactions tasks. In our framework, the autoencoder is employed to generate high-quality negative samples and the hidden vector of the autoencoder is regarded as a plausible drug candidate. Afterwards, the discriminator learns the embeddings of drugs and interactions based on both positive and negative triplets. Meanwhile, in order to solve vanishing gradient problems on the discrete representation—an inherent flaw in traditional generative models—we utilize the Gumbel-Softmax relaxation and the Wasserstein distance to train the embedding model steadily. We empirically evaluate our method on two tasks, link prediction and DDI classification. The experimental results show that our framework can attain significant improvements and noticeably outperform competitive baselines.

**Keywords** Drug-drug interaction · Knowledge graph embedding · Adversarial learning · Wasserstein distance

1 Introduction

For optimal therapeutic effect, it is often necessary to take advantage of drug combinations. However, the intended efficacy of a drug may be changed substantially when co-administered alongside another agent. Formally, drug-drug interactions (DDI) are pharmacological interactions between drug ingredients which can alter the function of drugs, cause adverse drug reactions (ADR) and even medical malpractice. While ideally we would like to discover all possible interactions between drugs during clinical trial, some unrecognized interactions may only be revealed after the
Figure 1: A simple instance of a DDI knowledge graph.
• To the best of our knowledge, we are the first to introduce adversarial autoencoders to knowledge graph representation learning. The latent vector of the autoencoder is capable of generating more reasonable negative samples and the discriminator utilizes these negative and positive triplets to train the KG embedding model.

• Different from traditional adversarial learning for KG embedding which requires intensive RL heuristics, we apply Gumbel-Softmax relaxation and Wasserstein distance to resolve the problem of vanishing gradients on discrete data and accelerate the convergence of the KG embedding model.

• We evaluate the performance of the proposed model on link prediction and triple classification tasks. The experimental results show that our model outperforms existing KG embedding models.

The remainder of this article is organized as follows. Section 2 introduces related work on knowledge graph embedding models and their applications in DDI. In Section 3 we illustrate the overall framework and training procedure of the proposed adversarial learning model in detail. Section 4 delineates benchmark datasets, parameter initialization settings and experimental details. Finally, concluding remarks are discussed in Section 5.

2 Related Work

In this section, we introduce current research on drug-drug interaction detection and prediction. Additionally, we give a brief overview of several prominent existing knowledge graph embedding methods.

2.1 Drug-drug interaction detection and prediction

DDI prediction is a key task in pharmacology. Traditional studies [13, 14, 15] depend on in vivo and in vitro experiments which do not scale well due to laboratory requirements. With the advancement of computing methods and resources, researchers moved their attention towards large-scale structured databases.

Several studies have proposed automatic DDI discovery schemes. For instance, [1] employed five machine learning approaches, including k-nearest neighbors, naive Bayes, logistic regression, decision trees and support vector machines, to predict the authenticity of DDIs. [16] proposed a random walk method to predict DDIs by integrating side effects. [17] introduced an ensemble learning framework for DDI prediction. [4] utilized deep neural networks to improve DDI prediction. Unsupervised methods [18, 19] were also applied for DDI prediction.

Recently, knowledge graph embedding has received more attention due to its strong capability of overcoming data incompleteness and sparsity problems. These KG embedding methods have been demonstrated to offer competitive performance in DDI prediction tasks. Among them, [20] used multi-view graph autoencoders to integrate multiple types of drug-related information, and added an attention mechanism to calculate the corresponding weights of each view for better interpretability. [3] developed a new graph convolutional neural network for graph embedding in which an end-to-end model was built for multi-relational link prediction on a multi-modal graph.

In the following, we will discuss a representative range of knowledge graph embedding techniques in greater detail.

2.2 Existing knowledge graph embedding approaches

There has been an increasing amount of literature on knowledge graph embedding to represent both entities and relations in a low-dimensional continuous feature space. We have broadly categorised these existing embedding methods into three categories: translation-based methods, tensor factorization-based methods and neural network-based methods.

2.2.1 Translation-based embedding methods

[21] proposed translation invariance in the word embedding algorithm word2vec that allows words with similar connotation to have similar representations. Following this principle, [6] proposed the TransE knowledge graph embedding model. TransE interprets relations as translation vectors between head and tail entities on the low-dimensional feature vector space, namely \( h + r \approx t \). A score function is defined to measure the plausibility of each triplet fact \((h, r, t)\). The score indicates the distance between \( h + r \) and \( t \), and the function is formulated as follows:

\[
    f_r(h, t) = \| h + r - t \|_{\ell_1/\ell_2}
\]

where \( \ell_1, \ell_2 \) are \( L_1 \)-norm and \( L_2 \)-norm respectively. It is worth to note that the embedding model yields a low score if a triplet \((h, r, t)\) is valid and a high score otherwise.

Although TransE delivers solid performance, it struggles to solve complex relations, such as \( 1 - N, N - 1 \), and \( N - N \). TransH [22] was proposed to overcome this drawback by introducing relation-specific hyperplanes. Specifically, it...
TransR [23] expanded relation-specific hyperplanes to relation-specific spaces. In TransR, entities are projected to an entity embedding space $\mathbb{R}^d$ and relations are projected to a relation embedding space $\mathbb{R}^k$, i.e., $h, t \in \mathbb{R}^d$ and $r \in \mathbb{R}^k$. Given a triplet $(h, r, t)$, TransR projects $h$ and $t$ into a space corresponding to relation $r$, i.e.,

$$h_\perp = M_r h, \quad t_\perp = M_r t$$

(4)

where $M_r \in \mathbb{R}^{k \times d}$ denotes a projection matrix to embed entity vectors into the relation-specific space. Moreover, the formulation of score functions is again defined as follows:

$$f_r(h, t) = \|h_\perp + r - t_\perp\|_{\ell_1/\ell_2}$$

(5)

Since then, a large number of embedding models investigated different ways to improve performance. For instance, TransA [24] abandoned traditional Euclidean distances and adopted adaptive Mahalanobis distance as a better metric on account of its flexibility and adaptability [25]. TransG [26] proposed to modify the model by introducing multidimensional Gaussian distributions to replace the original conclusive numerical space and constructed a probabilistic embedding model to represent entities and relations.

2.2.2 Tensor factorization-based embedding methods

Tensor factorization is another effective approach to knowledge graph embedding. RESCAL [27] is the representative approach in this direction. Under RESCAL, all triplet facts in the KG are projected into a 3D binary tensor $X$ to express the inherent structure. $X_{ijk} = 1$ indicates that the observed triplet ($i$-th entity, $k$-th relation, $j$-th entity) is available in the graph; otherwise, $X_{ijk} = 0$ refers to an unknown or non-existent triplet. Afterwards, the rank-$d$ factorization is applied to obtain latent semantics in the KG. The principle that this model follows is formulated as:

$$X_k \approx AR_k A^T, \text{ for } k = 1, 2, \cdots, m$$

(6)

where $A \in \mathbb{R}^{n \times d}$ is a matrix which has the capability of capturing the latent semantic representation of entities and $R_k \in \mathbb{R}^{d \times d}$ is a matrix that models the pairwise interactions in the $k$-th relation. According to this principle, the score function $f_r(h, t)$ is defined as:

$$f_r(h, t) = h^\top M_r t$$

(7)

Here, $h, t \in \mathbb{R}^d$ represent embedding vectors of entities like in the above models, the matrix $M_r \in \mathbb{R}^{d \times d}$ denotes the latent semantic meanings in relation $r$. To simplify the computational complexity of RESCAL, DistMult [28] restricted $M_r$ to diagonal matrices, i.e., $M_r = \text{diag}(r)$, $r \in \mathbb{R}^d$. The score function is transformed to:

$$f_r(h, t) = h^\top \text{diag}(r) t$$

(8)

The original DistMult model is symmetric in head and tail entities for every relation; Complex [29] leveraged complex-valued embeddings to extend DistMult to asymmetric relations. The embeddings of entities and relations exist in the complex space $\mathbb{C}^d$, instead of the real space $\mathbb{R}^d$ in which DistMult embedded. The score function is modified to:

$$f_r(h, t) = \text{Re}(h^\top \text{diag}(r) \bar{t})$$

(9)

where $\text{Re}(\cdot)$ denotes the real part of a complex value, and $\bar{t}$ represents the complex conjugate of $t$. By using this score function, triplets that have asymmetric relations can obtain different scores depending on the sequences of entities.

Simple [30] proposed the inverse embedding of relations and leveraged it to calculate the average Canonical Polyadic score of $(h, r, t)$ and $(t, r^{-1}, h)$. The score function is formulated as:

$$f_r(h, t) = \frac{1}{2} (h \circ rt + t \circ r^t)$$

(10)

where $r'$ denotes the embedding of inversion relation and $\circ$ indicates the element-wise Hadamard product. RotatE [31] proposed a rotational model in which each relation is regarded as a rotation from source entity to the target entity in complex space, as $t = h \circ r$,
2.2.3 Neural network-based embedding methods

Deep neural networks have become popular in a multitude of fields due to their strong generalization and representation abilities. They have been widely used for knowledge graph embedding.

Given an observed triplet fact \((h, r, t)\), NAM [32] first projects each entity and relation into an embedding space, then \(h\) and \(r\) are concatenated as input \(z^0 = [h; r]\) to feed into the upper \(L + 1\) layer, i.e.,

\[
z^\ell = \text{ReLU}(M^\ell z^{\ell-1} + b^\ell) \quad (\ell = 1, \cdots, L)
\]

where \(M^\ell\) and \(b^\ell\) are the weight matrix and bias in layer \(\ell\), respectively. After that, the output of the last hidden layer \(z^L\) is incorporated with the tail entity vector \(t\) to calculate the final result via a Sigmoid activation function \(\sigma(\cdot)\):

\[
f_r(h, t) = \sigma(z^L t)
\]

ConvKB [33] was proposed to capture semantic information contained in entities and relations by incorporating convolutional neural networks (CNN). For each triplet \((h, r, t)\), the embedding vectors \(h\), \(r\) and \(t\) are concatenated to a matrix \(A = [h; r; t]\) as an input layer, and after a convolution operation, the final output is obtained.

The above methods all obtain negative samples via random sampling. Inspired by generative adversarial networks (GAN), [9] and [10] applied GANs to sample plausible negative training examples for KG embedding via policy gradients. They employed the generator \(G(z; \theta)\) to construct negative triplets and utilized the discriminator \(D(x; \phi)\) as an embedding model to distinguish artificial from real triplets. The overall objective function can be phrased as a minimax game:

\[
\min_{\theta} \max_{\phi} (\log D(x; \phi) + \log(1 - D(G(z; \theta); \phi)))
\]

In summary, most previous methods used random sampling or generative adversarial networks to generate negative training triplets. While GANs improved model performance, they also drastically increased computational complexity and brought instability to the training process. In this paper, we describe a new framework based on adversarial autoencoders for improving the representation ability of models by generating high quality plausible negative samples to train the discriminator.

3 Method

Given a knowledge graph composed of a collection of triplet facts \(\Omega = \{<h, r, t>\}\), and a pre-defined embedding dimension \(d\), knowledge graph embedding aims to represent each entity \(h \in \mathbb{E}\) and relation \(r \in \mathbb{R}\) in a \(d\)-dimensional continuous vector space, where \(\mathbb{E}\) and \(\mathbb{R}\) are the sets of entities and relations, respectively. In other words, a KG is represented as a set of \(d\)-dimensional vectors, which can capture information of the graph, in order to simplify computations on the KG.

Figure 2 illustrates the proposed adversarial learning framework. At the beginning, a head or tail drug is discarded randomly from an authentic drug-drug interaction, and the resulting fragmentary triplet (Tramadol, increase neuroexcitatory activities, ?) is picked up as the input of the encoder. The encoder receives it and generates a one-hot vector which indicates another drug that has a similar effect or structure to Amitriptyline (such as Maprotiline which obtains the highest probability) from the collection of candidate drugs, this one-hot vector needs to be fed to both the decoder and the discriminator. For the decoder direction, the final outputs are two new vectors corresponding to the inputs of the encoder. The decoder restricts them to be as close to the inputs of the encoder as possible. As a consequence, we can not only guarantee that the model can generate different drugs, but also ensure that the generated drugs are proximal to the original ones in feature space. For the discriminator direction, the drug “Maprotiline” is selected to construct the final negative triplet (Tramadol, increase neuroexcitatory activities, Maprotiline). Finally, the negative and positive triplets are jointly fed into the knowledge graph embedding model for learning embedding vectors.

3.1 Autoencoder for sampling negative triplet facts

The goal of the autoencoder is to provide more plausible negative triplets for the discriminator than what can be obtained via traditional random negative sampling.

\(^1\)To simplify the problem, we transform entities and relations into uniformly sized embedding spaces, i.e. \(d = k\).
3.1.1 Shortcomings of traditional negative sampling

Since [6] proposed to obtain corrupted triplets via uniform negative sampling, many researchers have applied this strategy to sample negative triples in the training process. This sampling strategy randomly selects a candidate entity from the entity set $E$ to replace the head or tail entity from the original positive triplet. It is worth to note that all candidate entities in entity set $E$ share the same probability of being drawn. Obviously, this sampling method cannot contribute much to training an effective embedding model. As an example, given a valid triplet $(\text{Tramadol}, \text{increase neuroexcitatory activities}, \text{Amitriptyline})$, our goal is to replace the tail drug with another acceptable drug to reassociate a plausible triplet. Given the word “neuroexcitatory” in the relation and the drug type of “Amitriptyline”, it is intuitive to the domain expert that the tail drug should be a kind of pain reliever. If we choose the candidate drug in a random manner, many constructed negative triplets such as $(\text{Tramadol}, \text{increase neuroexcitatory activities}, \text{Esomeprazole})$ or $(\text{Tramadol}, \text{increase the neuroexcitatory activities}, \text{Minoxidil})$ can be trivially picked up as false by the discriminator, resulting in only infrequent parameter updates. By comparison, another generated triplet such as $(\text{Tramadol}, \text{increase neuroexcitatory activities}, \text{Acetaminophen})$ seems to be a more reasonable DDI, because “Acetaminophen” is more pharmacologically similar to “Tramadol” than “Minoxidil”.

As a consequence, we introduce an autoencoder to construct more plausible negative triplets instead of traditional uniform sampling. Here, the encoder aims to generate drugs as the generator in an adversarial learning framework, while the decoder restricts the manner and type of the generated drug, forcing it closer to the input drug and interaction. However, there is still a “non-differentiability” problem in discrete data generation.

3.1.2 Gumbel-Softmax relaxation with discrete data

In this section, we first illustrate why training adversarial learning models with discrete data is a vital issue. From a mathematical perspective, assuming the total number of drugs (entities) is $E$, the next generated one-hot index vector $y \in \mathbb{R}^E$ can be obtained by sampling:

$$y \sim \sigma (o)$$  \hspace{1cm} (14)

where $o \in \mathbb{R}^E$ denotes the output logits of the last layer in the generator, $\sigma(\cdot)$ indicates the Softmax function. The sampling operation in Equation (14) implies a step function that is not differentiable at the end of the generator output.
Because the differential coefficient of a step function is 0 almost everywhere, we have \( \frac{\partial y}{\partial \theta_G} = 0 \), a.e., where \( \theta_G \) are the parameters of the generator. According to the chain rule, the gradients of the generator loss \( l_G \) with respect to \( \theta_G \) are calculated as:

\[
\frac{\partial l_G}{\partial \theta_G} = \frac{\partial y}{\partial \theta_G} \frac{\partial l_G}{\partial y} = 0 \quad \text{a.e.} \tag{15}
\]

As a result, the gradients of the generator loss cannot be propagated back to the generator. This phenomenon is called the “vanishing gradient” or “non-differentiability” issue of adversarial learning models in discrete data domains.

From an instance point of view, even though a Softmax output vector of the generator \( \alpha = [0.25, 0.35, 0.25, 0.15] \) can improve the performance of the generator to optimize \( \alpha \) to \( \beta = [0.05, 0.70, 0.15, 0.10] \) allowing localizing a specific entity, the final sampling result has not changed, i.e., \( \text{Onehot}(\alpha) = \text{Onehot}(\beta) = [0, 1, 0, 0] \). The identical sampling one-hot vectors are repeatedly fed to the discriminator, so that the gradients obtained by the discriminator are inoperative, and the convergence direction of the generator is indistinct, no matter how powerful the discriminator may be.

In order to solve the “non-differentiability” issue, this paper leverages a Gumbel-Softmax relaxation technique which can approximate patterns sampled from a categorical distribution by defining a continuous distribution on the simplex. In the generator, each drug and interaction are initially transformed from a one-hot index vector to a specific embedding \( \text{vec}(\cdot) \) by using the projection matrix \( W \). After that, we reshape the tensor \( T \) into a single vector \( t \) allowing localizing a specific entity, \( \text{Onehot}(\beta) = \text{Onehot}(\beta) = [0, 1, 0, 0] \). The identical sampling one-hot vectors are repeatedly fed to the discriminator, so that the gradients obtained by the discriminator are inoperative, and the convergence direction of the generator is indistinct, no matter how powerful the discriminator may be.

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3.2 Knowledge graph embedding discriminator

The discriminator used in our framework is constructed following previous research. As described in Section[2] the individual models have different structures and score functions. The embeddings of drugs and interactions are obtained by minimizing the ranking loss associated with positive and negative triplets. Different from previous models in which negative samples are generated via random sampling from whole drug set, we apply an autoencoder to construct more plausible triplets to refine the performance of the model.

3.3 Training strategy

The training procedure is comprised of three main parts: i) the parameter update of the autoencoder in which \( G \) and \( A \) indicate the generator (the encoder) and the decoder, respectively; ii) the parameter update of the discriminator \( D; \) iii) the parameter update of the generator \( G. \)

The autoencoder is designed to learn an effective representation of data. In this paper, we employ the encoder network \( G(z; \theta) \) to generate high-quality negative drugs and apply the decoder network \( A(x; \eta) \) to restrict the sampling direction to obtain more plausible samples. To update parameters \( \theta \) and \( \eta, \) we train the autoencoder by minimizing the reconstruction error \( L_{G,A}: \)

\[
\min L_{G,A} = \min_{(\mu=\theta, \eta)} \| x - A(G(z; \theta)) \| ^2
\]  

(19)

The goal of the discriminator network \( D(x; \phi) \) is to distinguish a sample \( x \) as originating either from the real distribution \( p_r(x) \) or the generated distribution \( p_\theta(x) \). Given an original training sample \( (x, y), y \in \{1, -1\} \) signals whether it is a true sample from \( p_r(x) \) or a generated sample form \( p_\theta(x) \), the optimization objective of the discriminator \( L_D \) is to minimize cross-entropy:

\[
\min L_D = \min_{\phi} -(y \log p(y=1|x) + (1-y) \log p(y=0|x))
\]  

(20)

If the distribution \( p(x) \) is a mixture of distributions \( p_r(x) \) and \( p_\theta(x) \) in equal proportions, i.e., \( p(x) = \frac{1}{2}(p_r(x)+p_\theta(x)) \), then Equation (20) can be rewritten as:

\[
\min L_D = \min_{\phi} -\left( \log D(x; \phi) + \log(1 - D(G(z^{(i)}; \theta); \phi)) \right)
\]  

(21)

The goal of the generator is the opposite of the discriminator, the generator tries to construct negative samples which can fool the discriminator into confusing a negative sample for a real one. Its objective function \( L_G \) is formulated as:

\[
\min L_G = \min_{\theta} (\log(1 - D(G(z; \theta), \phi)))
\]  

(22)

Compared with a traditional single-objective optimization task, the optimization goals of these two networks in the adversarial game are extremely challenging. There are many potential issues in the traditional adversarial network training process such as training instability and difficulty, uninformative loss functions of generator and discriminator, and a lack of diversity in the generated samples.

These problems are caused by the attempt to minimize the Jensen–Shannon (JS) divergence between the real distribution \( p_r(x) \) and the generated distribution \( p_\theta(x) \). The JS divergence can only be computed when two distributions \( P, Q \) have overlapping parts. When these two distributions do not overlap or the overlapping parts are negligible in size, their JS divergence is identically equal to \( \log 2 \). That means that when the real distribution \( p_r(x) \) and the generated distribution \( p_\theta(x) \) have no overlap, the outputs of the discriminator are 0 for all generated data, i.e. \( D(G(z, \theta)) = 0, \forall z \). As a result, the gradients of the generator vanish.

Inspired by Wasserstein GANs \[34\] in which Wasserstein distance (also known as Earth-Mover distance) is introduced as a more robust metric to replace the JS divergence, we use this distance measure to improve the performance of our knowledge graph embedding framework in this article. Given a real distribution \( p_r(x) \) and a generated distribution \( p_\theta(x) \), the 1st-Wasserstein distance between them is formalized as:

\[
W(p_r, p_\theta) = \inf_{\gamma \sim \Pi(P_r, P_\theta)} \mathbb{E}_{(x,y) \sim \gamma} [\|x - y\|]
\]  

(23)

where \( \Pi(P_r, P_\theta) \) is the set of all possible joint distributions with marginal distribution \( \gamma(x, y) \). When there are no overlapping or slightly overlapping parts between two distributions, the JS divergence becomes constant. In contrast, the 1st-Wasserstein distance can measure distances between two non-overlapping distributions.
Equation (23) is difficult to calculate directly, and needs to be transformed into a solvable form via the Kantorovich-Rubinstein duality theorem. According to this theorem, the Wasserstein distance between two distributions can be converted into an upper bound on the expected difference between distributions $p_r$ and $p_0$ for a function that satisfies the K-Lipschitz continuum. We rewrite the 1st-Wasserstein distance:

$$W(p_r, p_0) = \frac{1}{K} \sup_{\|f\|_L \leq K} \left( \mathbb{E}_{x \sim p_r} [f(x)] - \mathbb{E}_{x \sim p_0} [f(x)] \right)$$  \hspace{1cm} (24)$$

where $f(\cdot)$ is the K-Lipschitz function, that satisfies:

$$\|f\|_L \triangleq \sup_{x \neq y} \frac{|f(x) - f(y)|}{|x - y|} \leq K$$  \hspace{1cm} (25)$$

If a function is differentiable and its derivatives are bounded, then this function is a Lipschitz continuous function. Because the discriminator neural network $D(x; \phi)$ satisfies the above conditions, it is also a Lipschitz continuous function, allowing us to approximate the upper bound in Equation (24) as:

$$\min_{\phi} - (\mathbb{E}_{x \sim p_r} [D(x; \phi)] - \mathbb{E}_{x \sim p_0} [D(x; \phi)])$$  \hspace{1cm} (26)$$

Different from standard discriminator networks in which the final layer is a sigmoid function over an output range of $[0, 1]$, at this point, we only need to find a network $D(x; \phi)$ that maximizes the difference in expectations between the two distributions $p_r$ and $p_0$. As a consequence, the final layer in our discriminator $D(x; \phi)$ is a linear layer, and its range is not limited. That means that, for real samples, the score of $D(x; \phi)$ should be high, and for samples generated by the model, low scores are expected.

Moreover, to make $D(x; \phi)$ satisfy the K-Lipschitz continuity condition, we can approximate it by limiting the range of the parameter $\phi$, such that $\phi \in [-c, c]$, $c$ is a relatively small positive number.

The goal of the generator is to minimize the Wasserstein distance, making the real distribution $p_r$ and the generated distribution $p_0$ coincide as much as possible, i.e.:

$$\min_{\theta} -\mathbb{E}_{z \sim p(z)} [D(G(z; \theta); \phi)]$$  \hspace{1cm} (27)$$

Because $D(x; \phi)$ is an unsaturated function, the gradients of the generator parameters $\theta$ will not disappear. This solves the problem of instability in original adversarial framework. In addition, by replacing the JS divergence by the Wasserstein distance, the objective function of the generator in this framework can alleviate the mode collapse problem to a certain extent and make the generated samples more diverse. The detailed procedure of this adversarial framework for knowledge graph embedding is described in Algorithm [1].

### 4 Experiments

In this section, we first describe the experimental datasets, then introduce important hyper-parameter settings and comparison methods for our experiment. Afterwards, link prediction and DDI classification experiments are constructed for comparing performance of the proposed methods with benchmark and the state-of-the-art models. Finally, we project the high-dimensional embedding feature space to two-dimensions for visual inspection of qualitative example outputs.

#### 4.1 Datasets

We conduct our link prediction and DDI classification experiments on two widely used public datasets: DeepDDI and Decagon. For both datasets, we follow common practice by randomly extracting 80% of triplets as training data, 10% as validation data and the remaining 10% as test data. Statistics of these two datasets are collected in Table [1].

DeepDDI [20] is composed of 1,710 drugs and 86 different interaction types from DrugBank [35] capturing 192,284 drug-drug pairs as samples. 99.87% of drug-drug pairs only have one type of DDI.

Decagon [3] is composed of 637 drugs and 200 different interaction types from the TWOSIDES dataset [36] capturing 1,121,808 drug-drug pairs as samples. We follow common practice by sampling 200 medium frequency DDI types ranging from Top-600 to Top-800, ensuring that every DDI type has at least 90 drug combinations. 73.27% of drug-drug pairs have more than one type of DDI.
**Algorithm 1:** Adversarial training of the autoencoder with Wasserstein distance for drug-drug interaction knowledge graph embeddings.

**Input:** The set of positive DDIs $T = \{(h, r, t)\}$, the number of training iterations $e$, the number of discriminator iterations per generator iteration $n_{dis}$, mini-batch size $m$, the learning rate of the generator $\alpha$, the learning rate of the discriminator $\beta$, the clipping parameter $c$.

**Output:** Drugs and interactions embeddings learned by $D$.

1. **Initialize** the generator $G$ with parameters $\theta_0$, the decoder $A$ with parameters $\eta_0$, the discriminator $D$ with parameters $\phi_0$;
2. for $k = 1, \cdots, e$ do
3.  for $i = 1, \cdots, m$ do
4.   $L_{G,A}^{(i)} = \|x^{(i)} - A(G(z^{(i)}; \theta); \eta)\|^2$; // Update the autoencoder by minimizing $L_{G,A}^{(i)}$
5.  end
6.  $g_\mu \leftarrow \nabla_\mu \frac{1}{m} \sum_{i=1}^{m} L_{G,A}^{(i)}$, ($\mu = \theta, \eta$);
7.  $\theta \leftarrow \theta - \alpha \cdot \text{Adagrad} (\theta, g_\theta)$;
8.  $\eta \leftarrow \eta - \alpha \cdot \text{Adagrad} (\eta, g_\eta)$;
9.  for $t = 1, \cdots, n_{dis}$ do
10.   for $i = 1, \cdots, m$ do
11.     $L_D^{(i)} = -[D(x^{(i)}; \phi) - D(G(z^{(i)}; \theta); \phi)]$; // Update the discriminator by minimizing $L_D^{(i)}$
12.   end
13.  $f_\phi \leftarrow \nabla_\phi \frac{1}{m} \sum_{i=1}^{m} L_D^{(i)}$;
14.  $\phi \leftarrow \phi - \beta \cdot \text{Adagrad} (\phi, f_\phi)$;
15.  $\phi \leftarrow \text{clip}(\phi, -c, c)$;
16. end
17. for $i = 1, \cdots, m$ do
18.   $L_G^{(i)} = -D(G(z^{(i)}; \theta); \phi)$; // Update the generator by minimizing $L_G^{(i)}$
19. end
20.  $h_\theta \leftarrow \nabla_\theta \frac{1}{m} \sum_{i=1}^{m} L_G^{(i)}$;
21.  $\theta \leftarrow \theta - \alpha \cdot \text{Adagrad} (\theta, h_\theta)$;
22. end
23. Return Drug and interaction embeddings.

### Table 1: Statistics of the data sources

| Datasets | #Drugs | #DDI Types | #Train | # Valid | #Test |
|----------|--------|------------|--------|--------|-------|
| DeepDDI  | 1,710  | 86         | 153,828| 19,228 | 19,228|
| Decagon  | 637    | 200        | 897,446| 112,181| 112,181|

#### 4.2 Comparison methods

To comprehensively evaluate the performance of our proposed model, we select several representative methods from the three categories of knowledge graph embedding as baselines to be compared with our approach. These baselines are described as follows:

- **TransE** [6] represents both entities and relations in a low-dimensional feature space, and interprets relations as translation operations to concatenate the entities.
- **DistMult** [28] proposes a multi-relational learning method in which the bilinear objective is effective at capturing relational semantics.
- **ComplEx** [29] describes a simple tensor factorization method using embedding vectors with complex values to handle symmetric and asymmetric relations.
- **KBGAN** [10] introduces an adversarial learning framework for knowledge graph embedding in which a generator is applied to sample negative triplets for refining the performance of the discriminator.
Table 2: Evaluation results on link prediction. The best two results are highlighted in red, blue and are formatted in boldface.

| Methods | DeepDDI | Decagon |
|---------|---------|---------|
|         | MK | MRR | HITS@1% | HITS@3% | HITS@10% | MK | MRR | HITS@1% | HITS@3% | HITS@10% |
| Train12 | 54.128 | 0.235 | 0.040 | 0.267 | 0.624 | 54.128 | 0.120 | 0.084 | 0.110 | 0.292 |
| DrugMan12 | 42.900 | 0.147 | 0.053 | 0.206 | 0.376 | 20.237 | 0.213 | 0.051 | 0.201 | 0.424 |
| ComplEx10 | 16.290 | 0.510 | 0.369 | 0.562 | 0.779 | 16.644 | 0.497 | 0.358 | 0.568 | 0.781 |
| KBGAN10 | 16.049 | 0.513 | 0.330 | 0.569 | 0.785 | 20.679 | 0.213 | 0.051 | 0.201 | 0.424 |
| RotatE31 | 15.809 | 0.476 | 0.304 | 0.536 | 0.760 | 43.081 | 0.170 | 0.082 | 0.168 | 0.320 |
| Our model (ComplEx) | 12.400 | 0.545 | 0.304 | 0.569 | 0.790 | 20.682 | 0.217 | 0.053 | 0.204 | 0.427 |
| Our model (SimplE) | 14.172 | 0.404 | 0.354 | 0.569 | 0.790 | 41.343 | 0.172 | 0.097 | 0.176 | 0.331 |

- **SimplE** develops an embedding method based on Canonical Polyadic decomposition that extends the model to learn the two embedding vectors of each entity independently.
- **RotatE** embeds entities as complex-value vectors and defines relations as rotations from the head entity to the tail in complex vector space. In addition, it utilizes a new self-adversarial negative sampling method to train the embedding model.

4.3 Link prediction

Link prediction is a characteristic task which aims to infer the missing drug when given an existing drug and interaction query. Concretely, the target of link prediction is to predict the missing drug $t$ if given $(h, r)$ or predict $h$ given $(r, t)$. Results are obtained via ranking by discriminator scores.

4.3.1 Metrics

For each drug-drug interaction $(h, r, t)$ in the test set, the real head drug (or tail drug) is circularly replaced by all drugs in the drug set $E$. Then, the scores corresponding to all triplets are computed, all scores are ranked in descending order. However, some reconstructed DDIs might coincidentally be authentic in the DDI knowledge graph. In this case, the reconstructed DDI which is a true fact might yield a high ranking, resulting in an inaccurate assessment. To avoid this situation, following [31], we employ the "**Filtered**" setting to eliminate all reconstructed DDIs which appear either in the training, validation, or test datasets. Finally, model performance is measured in terms of:

- **MR**: the average rank of the real entities.
- **MRR**: the average reciprocal rank of the real entities.
- **HITS@N%**: the proportion of real entities that ranked in the top $N$. Here, we specially choose $N = 1, 3, 10$ to validate the performance of compared models.

It should be noted that good performance is indicated by low MR and high MRR and HITS@N% scores.

4.3.2 Training protocol

We utilize the Adagrad self-adaptive optimizer for training, and perform parameter optimization via limited grid search: the learning rate of the generator $\alpha \in \{0.01, 0.005, 0.001\}$, the learning rate of the discriminator $\beta \in \{0.5, 0.1, 0.05, 0.01\}$, the size $d$ of drug and interaction embedding vectors $\{50, 100, 200\}$, the mini-batch size $m \in \{256, 512, 1024\}$, the number of discriminator training iterations per generator iteration $n_{\text{dis}} \in \{1, 2, 5\}$ and the number of overall training iterations $e \in \{300, 500, 700, 1000\}$. The final parameter settings are determined on the validation set.

On the DeepDDI dataset, the best configurations are $\{\alpha = 0.005, \beta = 0.1, d = 200, m = 512, n_{\text{dis}} = 1, e = 300\}$ for our model with ComplEx, $\{\alpha = 0.005, \beta = 0.05, d = 200, m = 512, n_{\text{dis}} = 2, e = 500\}$ for our model with SimplE and $\{\alpha = 0.005, \beta = 0.05, d = 200, m = 512, n_{\text{dis}} = 2, e = 500\}$ for our model with RotatE. On the Decagon dataset, the best configurations are $\{\alpha = 0.005, \beta = 0.5, d = 200, m = 1024, n_{\text{dis}} = 1, e = 1000\}$ for our model with ComplEx, $\{\alpha = 0.005, \beta = 0.5, d = 200, m = 512, n_{\text{dis}} = 2, e = 1000\}$ for our model with SimplE and $\{\alpha = 0.005, \beta = 0.5, d = 200, m = 512, n_{\text{dis}} = 5, e = 1000\}$ for our model with RotatE.

4.3.3 Result

Table 2 shows a detailed comparison of the proposed approach and state-of-the-art methods on the two standard benchmark datasets. We can observe that:
### 4.4 DDI classification

DDI classification is an important pharmacological task that aims to determine the authenticity of a DDI triplet. As some existing articles [4, 5, 37] investigate DDI prediction, we follow them in casting DDI classification as a multi-label interaction prediction problem.

Given a pair of drugs, we first construct DDI triplets by repeatedly adding each interaction in the interaction set $R$ into the pair of drugs, then estimate the confidence in every generated triplet. Those interactions corresponding to high-score triplets are the ones we want to obtain.

**4.4.1 Metrics**

- **ROC-AUC**: the area under the receiver operating characteristic curve.
- **PR-AUC**: the area under the precision-recall curve.
- **P@K**: the mean percentage of true predicted labels among TOP-K over all samples. In this paper, $K = 1, 3, 5$ are selected as evaluation indicators to estimate the performance of models.

**4.4.2 Training protocol**

In this task, we use the models trained for link prediction. Thus, all settings and hyper-parameter configurations are retained from above.

**4.4.3 Result**

The drug-drug interaction classification results are displayed in Table 3. Since TransE and DistMult are comparably primitive models, their performance is not expected to be convincing for this task and the corresponding models are not included in this experiment. As can be seen from the table below:

- Similar to the link prediction task, our proposed method achieves consistent improvements in this scenario. On both datasets, the proposed framework refines the performance of all baseline embedding models.
- Where the improved ComplEx method outperformed other models on link prediction, on the classification task, the improved RotatE method yields the best results. This indicates that the two tasks measure different performance aspects of a knowledge graph embedding model. The result stresses the flexible adaptability and extensibility of our framework to different tasks.
Table 4: Some instances of negative samples constructed by random and generator sampling from the DeepDDI dataset.

In this table, all drugs are shown in bold and all interactions are denoted by star (★). Besides that, there is a parenthesis below each drug, which contains the function or character of the drug. The triplets in the first column are positive, the underlined drug signifies that it would be replaced by other drugs in the next two columns. The replacement drugs sampled randomly are listed in the second column, and the third column displays the drugs generated by our method.

| Positive triplets | Random sampling | Generator sampling |
|-------------------|-----------------|--------------------|
| **Midazolam**     | Lumefantrine    | Methadyl acetate   |
| (hypnotic sedative) | (antimalarial)   | (narcotic analgesic) |
| ★ increases the risk of adverse effects | Diltiazem        | Levacetylmethadol   |
| **Dezocine**      | Pefloxacin      | Nalbuphine         |
| (partial opiate)   | (antihypertensive) | (narcotic)         |
| **Treprostinil**  | Carmustine      | Ridogrel           |
| (treatment of pulmonary hypertension) | (treatment of brain tumors) | (prevention of thrombo-embolism) |
| ★ increases the antiplatelet activities | Plicamycin       | Milrinone          |
| **Tirofiban**     | Pipazethate     | Trapidil           |
| (prevention of blood clotting) | (antiinflammatory) | (vasodilator and anti-platelet agent) |
| **Indapamide**    | Mefenamic acid  | Hydrochlorothiazide|
| (thiazide-like diuretic) | (anti-inflammatory) | (thiazide diuretic) |
| ★ decreases the metabolism | Rolapitant       | Chlorthalidone     |
| **Saquinavir**    | Kappadione      | Chlороthiazone     |
| (HIV protease inhibitor) | (Neurokinin-1 receptor antagonist) | (thiazide-like diuretic) |
|                   | (Vitamin K derivative) |                  |

- The performance of RotatE on the two datasets is highly variable. A likely explanation lies in RotatE’s fixed composition method [31], utilizing the element-wise Hadamard product ($r_1 \circ r_2$). For instance, given data on three persons $(a, b, c)$, where $b$ is the elder brother (marked as $r_1$) of $a$ and $c$ is the older sister (marked as $r_2$) of $b$, we can easily infer that $c$ is the older sister of $a$. The relation between $c$ and $a$ is $r_2$ rather than $r_1 \circ r_2$. Perhaps this composition method can infer available information when the available number of relations is small, but once the number of observed relations increases, this capability will no longer yield added value.

4.5 Visualization

To highlight the capabilities of our proposed framework in a qualitative manner we include two visualization experiments. Table 4 compares traditional random negative samples with generated ones. We can note that the generator is able to select more semantically relevant drugs as negative samples. For instance, given a real triplet (Midazolam, increases the risk of adverse effects, Dezocine), the generator adopts three tail drugs, i.e. Methadyl acetate, Levacetylmethadol and Nalbuphine. All three drugs, similar to Dezocine, have narcotic effects. Thus, the negative triplets constructed by these drugs are more plausible and potentially deceptive.

Given such high-quality negative triplets, we can train better knowledge graph embedding models which have strengthened representation and generalization ability. Figure 3 shows an illustration of KG embedding vectors after dimension reduction.

Embedding vectors are projected to two-dimensional space by applying UMAP dimension reduction [38] (Figure 3(a)). We select three regions of the embedding space and zoom in on them to observe if the drugs in those areas are related in indication or category. Figure 3(b) lists 10 drugs in the red circle with consistently anti-fungal effect. Similarly, the vast majority of drugs in the yellow region are corticosteroids, and the green region contains asthma medication.

5 Conclusions

The goal of this study is to find a new approach to negative sampling that improves the performance of drug-drug interaction knowledge graph embedding models. In this paper, we propose an adversarial learning framework based on Wasserstein distances for this task. We evaluate the proposed method on link prediction and DDI classification tasks. Our experiments on two standard collections confirm that the performance of all baseline models can be significantly improved using our adversarial learning framework.
The approach has several major advantages over existing knowledge graph embedding models. First, we introduce an adversarial autoencoder framework to represent drug-drug interaction knowledge graphs. The autoencoder is employed to generate more plausible drugs as negative samples, and these negative triplets are fed to the discriminator along with authentic positive ones for improving the performance of embedding models. Our approach also utilizes a Gumbel-Softmax relaxation and Wasserstein distance to handle vanishing gradient issues on discrete data. Compared with traditional policy gradients in reinforcement learning, the proposed method can complete optimization tasks more efficiently. Most notably, the work presented here can be applied to refine the performance of most existing models without the need for major modifications.

The method presented here is not limited to the DDI domain. Going beyond the application and scope of this immediate work, future work will include evaluating the benefits the model presented here holds for other graph embedding tasks such as recommendation, classification and retrieval settings on hierarchical data.

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