A Neuro-Symbolic System over Knowledge Graphs for Link Prediction

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Abstract. Neuro-Symbolic Artificial Intelligence (AI) focuses on integrating symbolic and sub-symbolic systems to enhance the performance and explainability of predictive models. Symbolic and sub-symbolic approaches differ fundamentally in how they represent data and make use of data features to reach conclusions. Neuro-symbolic systems have recently received significant attention in the scientific community. However, despite efforts in neural-symbolic integration, symbolic processing can still be better exploited, mainly when these hybrid approaches are defined on top of knowledge graphs. This work is built on the statement that knowledge graphs can naturally represent the convergence between data and their contextual meaning (i.e., knowledge). We propose a hybrid system that resorts to symbolic reasoning, expressed as a deductive database, to augment the contextual meaning of entities in a knowledge graph, thus, improving the performance of link prediction implemented using knowledge graph embedding (KGE) models. An entity context is defined as the ego network of the entity in a knowledge graph. Given a link prediction task, the proposed approach deduces new RDF triples in the ego networks of the entities that correspond to the heads and tails of the prediction task on the knowledge graph (KG). Since knowledge graphs may be incomplete and sparse, the facts deduced by the symbolic system not only reduce sparsity but also make explicit meaningful relations among the entities that compose an entity ego network. As a proof of concept, our approach is applied over a KG for lung cancer to predict treatment effectiveness. The empirical results put the deduction power of deductive databases into perspective. They indicate that making explicit deduced relationships in the ego networks empowers all the studied KGE models to generate more accurate links.

Keywords: Neuro-Symbolic Artificial Intelligence, Deductive Systems, Knowledge Graph Embeddings, Drug-Drug Interactions

1. Introduction

Neuro-Symbolic Artificial Intelligence is a research field that combines symbolic and sub-symbolic AI models [1–3]. The symbolic models refer to AI approaches based on handling explicit symbols to conduct reasoning and support explainability. On the other hand, AI sub-symbolic systems are based on statistical and probabilistic learning from data mining and neural network models. Symbolic and sub-symbolic systems differ in how they represent and manage data to perform reasoning and prediction. As a result, they aim at solving complementary tasks whose

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integration has the potential to empower prediction with reasoning supported by symbolic formal frameworks [1, 4]. Neuro-symbolic integration aims to bridge the gap between symbolic and sub-symbolic systems; it resorts to translation algorithms to align symbolic to sub-symbolic representations and improve performance [1, 2, 5]. However, integrating neuro-symbolic into real-world applications is a challenging task. Even in controlled environments, neuro-symbolic integration may not be completed performed [6]. For instance, Fernlund et al. [7] describe systems that use machine learning to learn relations from expert observations. While these systems are successful in learning, they lack the expressive power of symbolic systems. Another example of neuro-symbolic systems combining connectionist inductive learning and logic programming to solve the problems in the molecular biology and power plant fault diagnosis [8]. Furthermore, Karpathy et al. [9] combine convolutional neural networks with bidirectional recurrent neural networks over sentences to recognize and label image regions. Despite these advances in neuro-symbolic AI integration, symbolic processing is not fully exploited, in particular, if reasoning methods are implemented on top of knowledge graphs [5].

Problem Statement and Proposed Solution: We tackle the problem of link prediction over knowledge graphs and propose an approach able to combine symbolic reasoning and sub-symbolic prediction. Our approach integrates a domain-agnostic symbolic system with knowledge graph embedding models. It resorts to symbolic reasoning to deduce relationships between entities that compose the ego network of the entities in a knowledge graph. Thus, contextual knowledge, represented by ego networks, is enhanced, and the sparsity of knowledge graphs is reduced. Since the behavior of knowledge graph embedding models can be affected in sparse graphs [10], training these models with these enhanced ego networks increases the chances of predicting accurate links between entities associated with these networks. We apply our hybrid approach in the context of lung cancer. The symbolic system implements a deductive database to infer drug-drug interactions in lung cancer treatments. Complementary, the sub-symbolic system resorts to knowledge graph embedding models to predict the effectiveness of a lung cancer treatment. These models transform RDF triples representing treatments, their drugs, and interactions among these drugs, into a low-dimensional continuous vector space that preserves the knowledge graph structure. The integration of both systems enables the prediction of a treatment’s response, taking into account the potential effect that drug-drug interactions have in the effectiveness of the treatment.

Results: We assess the performance of the proposed neuro-symbolic system on a knowledge graph built from clinical records of lung cancer patients; it comprises treatments prescribed to these patients, the responses of these treatments, and the drugs that have been administrated. Additionally, this knowledge graph integrates information about the drug-drug interactions between the oncological and non-oncological drugs composing a lung cancer treatment. These drug-drug interactions have been extracted from DrugBank\(^1\) following the named entity recognition and linking techniques proposed by Sakor et al. [11]. The prediction task is defined in terms of predicting links between treatments (i.e., heads) and instances of a class that represents the different types of lung cancer responses (i.e., tails). The link prediction task is implemented using eleven state-of-the-art KGE models. The experiments are executed following different configurations and baselines, with the goal of assessing the accuracy of our proposed neuro-symbolic system. Results of a 5-fold cross-validation process demonstrate that our integrated system improves the prediction accuracy of studied state-of-the-art KGE models. Moreover, the outcomes of this experimental study put the power of deductive databases into perspective, showing how they can empower the accuracy of link prediction tasks. More importantly, these results provide evidence of the paramount role of deductive reasoning and knowledge graph embedding models in predicting treatment response.

Contributions: This paper resorts to our previous work [12], where we propose a deductive system over knowledge graphs to formalize the process of drug-drug interactions. Built on these results, we present a hybrid approach able to combine symbolic reasoning expressed by deductive systems with the sub-symbolic expressiveness of KGE models, to enhance prediction accuracy. In a nutshell, our novel contributions are:

1. A domain-agnostic approach able to empower the predictive performance of sub-symbolic systems with a deductive database system. The deductive system reduces data sparsity issues by inferring implicit relationships in a KG. Consequently, the sub-symbolic system, implemented by KGE models, better represents into a low-dimensional continuous vector space statements described in the KG.

\(^1\)https://go.drugbank.com
2. Preliminaries and Motivation

Knowledge Graphs (KGs) are data structures converging data and knowledge as factual statements of a graph data model [13, 14]. Formally, a knowledge graph is a 10-tuple $KG = (V, E, L, C, I, D, R, N, \alpha, \text{ego})$, where:

- $V$ is a set of nodes that correspond to concepts (e.g., classes and entities).
- $E \subseteq V \times L \times V$ is a set of edges representing relationships, i.e., triples $(s, p, o)$, between concepts.
- $L$ is a set of properties.
- $C$ is a set of classes $C \subseteq V$.
- $I : V \rightarrow C$ is a function that maps each entity in $V$ to a class $C$.
- $D : L \rightarrow C$ maps a property to the class that corresponds to the domain of the property.
- $R : L \rightarrow C$ maps each property to a class that corresponds to the range of the property.
- $N : V \rightarrow 2^V$, where $2^V$ represents the power set of nodes $V$. $N(v)$ defines the neighbors of the entity $v$, i.e., $N(v) = \{v_i | (v, r, v_i) \in E \lor (v, r, v) \in E\}$.
Figure 1a depicts a knowledge graph $KG$, where the set of classes are represented by $C = \{Drug, Treatment, Response\}$. The class for each entity is represented by the function $I(\cdot)$, e.g., the entity $T1$ belongs to the class $Treatment$ and $I(T1) = \{D1, D2, D3, D4, low\_effect\}$. Furthermore, the set of edges between pairs of entities in the set of neighbors of entity $T1$ is defined by $\alpha(N(T1)) = \{(D1, interacts\_with, D2), (D2, interacts\_with, D4), (D3, interacts\_with, D2)\}$, where we can observe the three triples in Figure 1a. Note that although $low\_effect$ is in the ego network of the entity $T1$, this entity is not related to any other entity in this ego network.

**An ideal knowledge graph.** An ideal knowledge graph is a knowledge graph $KG' = (V, E', L, C, I, D, R, N, ego, \alpha)$ that contains all the true existing relations between entities in $V$. The Closed World Assumption (CWA) is assumed on $KG'$, i.e., what is unknown to be true in $KG'$ it is false.

**An actual knowledge graph.** An actual knowledge graph $KG = (V, E, L, C, I, D, R, N, \alpha)$ is a knowledge graph that follows the assumption Open World Assumption (OWA), i.e., what is not known to be true is just unknown and may be true.

**A complete knowledge graph.** A complete knowledge graph $KG_{comp} = (V, E_{comp}, L, C, I, D, \alpha)$ is a knowledge graph, which includes a relation for each possible combination of entities in $V$. Note that not all relationships in $KG_{comp}$ are necessarily true. A knowledge graph $KG$ may only contain a portion of the edges represented in $KG'$, i.e., $E \subseteq E'$. $KG$ represents those relations that are known, but it is not necessarily complete. On the other hand, since $KG_{comp}$ is a complete knowledge graph, $E \subseteq E' \subseteq E_{comp}$. The set of missing edges in $KG$ is defined as $\Delta(E', E) = E' - E$, i.e., it is the set of relations existing in the ideal knowledge graph $KG'$ that are not represented in $KG$. Figure 2 illustrates three knowledge graphs. Figure 2a is an ideal knowledge graph that states that only three relationships are true. The actual knowledge graph, presented in Figure 2b, is incomplete and only includes two relationships; $(C, p2, B)$ is unknown and is not part of the current knowledge graph. Figure 2c illustrates a complete knowledge graph, with a relation for each combination of entities in $V$ and properties in $L$. All the possible relationships are included in this graph.

![Fig. 2. Example of actual, ideal, and complete knowledge graph.](image-url)
An abstract target prediction over a knowledge graph $K^G$ is defined in terms of a tuple $\tau = (K^G, r, \text{prediction}, DS, KGE)$:

- $K^G$ is a knowledge graph $K^G = (V, E, L, C, I, D, R, \text{ego}, N, \alpha)$.
- $r$ represents a prediction property, $r \in L$.
- prediction indicates the head or the tail of triples to predict. A tail prediction of triples $\langle h, r, t \rangle$ is the process of finding $t$ for the incomplete triple $\langle h, r, ? \rangle$.
- $DS$ is a deductive database system over $K^G$.
- $KGE$ is a knowledge graph embedding model over $K^G$.

The deductive system $DS$ derives new facts from inference rules and facts stored in a database [15]; it is expressed as a set of extensional and intensional rules in Datalog. A Datalog rule corresponds to a Horn clauses [16], $L_1, \ldots, L_n \Rightarrow L_0$, where each $L_i$ is a literal of the form $p_i(t_1, \ldots, t_k)$. $p_i$ is a predicate symbol and $t_j$ are terms. A term is either a constant or a variable. The right-hand side of a Datalog clause is the head, and the left-hand side is its body. Clauses with an empty body represent facts. A Datalog program $P$ must satisfy the following safety conditions; each fact of $P$ is ground, and each variable that occurs in the head of a rule of $P$ must also occur in the body of the same rule. A rule is safe if all its variables are limited, where any variable appearing as an argument in a body predicate is limited. Datalog considers two sets of clauses: a set of ground facts called the Extensional Database (EDB) and a Datalog program $P$ called the Intensional Database (IDB). The predicates in the EDB and IDB are divided into two disjoint sets, EDB predicates, which occur in the EDB, and the IDB predicates, which occur in IDB. The head predicate of each clause in $P$ is an IDB predicate, and the EDB predicate can occur in the body of the rule. If $C_1$ and $C_2$ are the domain and range of $r$ respectively, then EDB comprises ground facts of the form: $p(s, o)$ where the triple $(s, p, o) \in \text{ego}(v) \cup \alpha(N(v))$, and $\alpha(v) \in \{C_1, C_2\}$. The EDB in our DS contains ground facts from the ego networks and from their neighbors. Given a prediction property, $r = \text{has_response}$ we know the domain $D(\text{has_response}) = \text{Treatment}$ and range $R(\text{has_response}) = \text{Response}$. Figure 1a shows entities of type Treatment and entities of type Response for the domain and range of the property has_response, respectively. The EDB comprises all the ground facts defined by the ego networks: $\text{ego}(T1), \text{ego}(T2), \text{ego}(\text{low_effect})$, and $\text{ego}(\text{effective})$, and their neighbors $\alpha(N(T1)), \alpha(N(T2)), \alpha(N(\text{low_effect})), \text{and } \alpha(N(\text{effective}))$, where entities $T1$ and $T2$ belong to class Treatment, and low_effect and effective belong to the class Response.

An example of EDB is the set of facts \{interacts_with(D1, D2), interacts_with(D2, D4)\}, where the property interacts_with $\in L$ and the entities \{D1, D2, D4\} $\subseteq V$. The predicate interacts_with represents interactions between two drugs. Let $P(1)$ be a Datalog program (IDB) containing the following clauses:

\begin{align*}
\text{rule1} & \quad \text{interactsWith}(A, X) \Rightarrow \text{inferredInteraction}(A, X). \\
\text{rule2} & \quad \text{inferredInteraction}(B, X), \text{interactsWith}(A, B) \Rightarrow \text{inferredInteraction}(A, X).
\end{align*}

The predicate inferredInteraction(A, X) is an IDB predicate, and interactsWith(A, X) is an EDB predicate. Rule rule2 states that exist an inferred interaction between drug A and X, if there is another drug B which interacts with A with the predicate interacts_with, and there is an inferred_interaction from B to X. The evaluation results of rule2 is \{inferred_interaction(D1, D4)\}, shown in Figure 1c with a red arrow.

KGE is a machine learning model that learns vector representation (i.e., KG embeddings) in a low dimensional continuous vector space for entities $v \in V$ and relations $e \in E$ in a $K^G$. The KGE model exploits the $K^G$ structure to predict new relations in $E$. The KGE model resorts to a scoring function $\phi$ to estimate the plausibility of the vector representation of a triple, where higher $\phi$ values yield higher plausibility [17]. Link prediction is performed by identifying which vector representation of an entity provides the best values of the scoring function $\phi$, these entities are added to the incomplete triples as heads or tails. If $\text{prediction} = \text{tail}$, then the link prediction task is the process of finding $t$ as the best scoring tail for the incomplete triple $\langle h, r, ? \rangle$:

\[
\arg\max \limits_{t \in V} \phi(h, r, t).
\]

If $\text{prediction} = \text{head}$, it can be defined analogously. The state of the art of KGE methods may be negatively impacted by the data sparsity issue, i.e., ground facts that can be used as positive samples to guide KGE training.
represent only a minor portion. The proposed deductive database system for abstract target prediction alleviates the data sparsity issue by enhancing links in the ego network $\text{ego}(v)$, which are managed as new ground facts.

Suppose the abstract target prediction is defined for the current knowledge graph $KG$ presented in Figure 1a where the prediction property is $r = \text{has\_response}$, and the prediction corresponds to the tail, i.e., $\text{prediction} = \text{tail}$. The link prediction task predicts incomplete triples $\langle h, r, ? \rangle$, where the head $h$ represents entities of class $\text{Treatment}$, i.e., entities $h \in V$ such that $I(h) = \text{Treatment}$, and the relation is $r = \text{has\_response}$.

2.1. Motivating Example

Fig. 3. Motivating Example. Figure 3a shows two polypharmacy oncological treatments, $T1$ and $T2$, represented in RDF. The drugs $DB00193$, $DB00642$, and $DB00958$ are part of $T1$, and the drug-drug interactions are represented by the property $\text{InteractsWith}$. The therapeutic response of $T1$ is annotated as $\text{low\_effect}$ by the property $\text{has\_response}$, while the therapeutic response of $T2$ is unknown. Figure 3b depicts the ideal RDF graph, where a symbolic system generates a new DDI between $DB00193$ and $DB00958$. Ideally, a sub-symbolic system detects that both treatments are similar and predicts the effectiveness of $T2$ as low effective.

We motivate our work in healthcare, specifically for predicting polypharmacy treatment response. Polypharmacy is the concurrent use of multiple drugs in treatments, and it is a standard procedure to treat severe diseases, e.g., lung cancer. Polypharmacy is a topic of concern due to the increasing number of unknown drug-drug interactions (DDIs) that may affect the response to medical treatment. Pharmacokinetics is a type of DDIs, i.e., the course of a drug in the body. Pharmacokinetics DDIs alter a drug’s absorption, distribution, metabolism, or excretion. For example, an increase in absorption will increase the object drug’s bioavailability and vice versa. If a DDI affects the object’s drug distribution, the drug transport by plasma proteins is altered. Moreover, a drug’s therapeutic efficacy and toxicity are affected when a pharmacokinetics DDI alters the object’s drug metabolism. Lastly, if the excretion of an object drug is reduced, the drug’s elimination half-life will be increased. Notice that the pharmacokinetic interactions can be encoded in a symbolic system.

Figure 3a shows two polypharmacy oncological treatments encoded in RDF. We extract the known DDIs between the drugs of these treatments from DrugBank. However, polypharmacy therapies produce unforeseen DDIs due to drug interactions in the treatment. Since DDIs affect the effectiveness of a treatment, there is a great interest in uncovering these DDIs. Figure 3b depicts an ideal RDF graph where all the existing relations are explicitly encoded.
represented. Dotted red arrows represent DDI between the drugs DB00193 and DB00958 that are generated as the result of DDIs among drugs in the treatment. A Datalog program represents the rules that state when these DDIs are produced between the drugs administrated in a treatment. The extensional database corresponds to facts representing explicit relationships; in our case, these facts are extracted from DrugBank. The intensional database corresponds to intensional rules that define all the combinations of DDIs that may produce new DDIs; they allow for deducing implicit DDIs in a treatment. The DDI between DB00193 and DB00958 increases the information of treatments T1 and T2, enabling both treatments to share more relationships. Then, a sub-symbolic system, i.e., a knowledge graph embedding model, can explore these enhanced relationships and make a more accurate prediction of the treatment response by employing the deduced DDIs. For example, the geometric model TransH places T1 and T2 nearby in the embedding space after deducing DDIs and predicts the therapeutic response of T2. As a result, this neuro-symbolic system enhances treatment information by identifying drug combinations whose interactions may affect treatment effectiveness. We propose an approach that resorts to symbolic reasoning implemented by a Datalog system and stage-of-the-art KGE models; it deduces DDIs within a treatment. Then, the KGE model embeds all the knowledge in the graph and predicts treatment responses. Although we depict the method in the context of treatment effectiveness, this approach is domain-agnostic and could be applied to any other link prediction task.

3. Proposed Symbolic and Sub-symbolic System

3.1. Problem Statement

Given an actual knowledge graph \( KG = (V, E, L, C, I, D, R, ego, N, \alpha) \) and its corresponding ideal knowledge graph \( KG' = (V, E', L, C, I, D, R, ego, N, \alpha) \). Given an abstract target prediction over an actual knowledge graph \( KG, \tau = (KG, r, pred, DS, KGE) \), we tackle the problem of predicting relationships over \( KG' \).

Given a relation, \( e \in \Delta(E_{\text{comp}}, E) \) (i.e., the set of missing edges in \( KG \)), the problem of predicting relationships consists of determining whether \( e \in E' \), i.e., if a relation \( e \) corresponds to an existing relation in the ideal knowledge graph \( KG' \). We are interested in whether \( e \) belongs to the ideal \( KG' \), i.e., find a set \( E_e \) that belongs to the ideal \( KG' \).

\[
\arg\max_{E_e \subseteq E_{\text{comp}}} |E_e \cap E'|.
\]

3.2. Proposed Solution

Our proposed solution resorts to a symbolic system implemented by a deductive database to enhance the predictive precision of the link prediction task solved by knowledge graph embedding models. The approach assumes that a link prediction problem is defined in terms of an abstract target prediction \( \tau = (KG, r, pred, DS, KGE) \) over a knowledge graph \( KG = (V, E, L, C, I, D, R, ego, N, \alpha) \).

**A Symbolic System:** Deductive system \( DS \) corresponds to the deductive databases where the EDB comprises ground facts of the form: \( p(s, o) \), where the triple \( (s, p, o) \in ego(v) \cup \alpha(N(v)) \), \( I(v) \in \{C_1, C_2\} \), \( C_1 = D(r) \), and \( C_2 = R(r) \). The variables \( C_1 \) and \( C_2 \) represent the domain and range of the property \( r \), respectively. The IDB contains rules that allow deducing new relationships in the ego network \( ego(v) \). The computational method executed to empower the ego networks \( ego(v) \) is built on the results of deductive databases to compute the minimal model of the deductive database[16]. The minimal model corresponds to the instantiations of IDB predicates. This minimal model is defined in terms of the fixed-point assignment \( \sigma_{\text{ego}}(\cdot) \), that deduces relationships between entities \( v_i \) and \( v_j \) in the neighbors \( N(\cdot) \). The minimal model for \( DS \) can be computed in polynomial time in the overall size of the ego network \( ego(v) \) and the neighbors \( \alpha(N(v)) \) for all the entities \( v \) where \( I(v) \in \{C_1, C_2\} \), \( C_1 = D(r) \), and \( C_2 = R(r) \).

**A Sub-symbolic System:** A model to learn Knowledge Graph Embeddings solves the abstract target prediction \( \tau \) over \( KG \) for the relation \( r \) and the prediction head or tail. The sub-symbolic system predicts incomplete triples of the way \( \{h, r, ?\} \) if \( \text{prediction} = \text{tail} \) and \( \{?, r, t\} \) if \( \text{prediction} = \text{head} \).

The Integration of Symbolic and Sub-symbolic Systems: The ego network \( ego(v) \) and the edges between their
### 3.3. The Symbolic and Sub-symbolic System Architecture

Figure 4 depicts the architecture that implements the proposed approach. The architecture receives a knowledge graph $K_G = \{V,E,L,C,I,D,R,ego,N,a\}$ and an abstract target prediction $\tau = \langle K_G, r, prediction, DS, KGE \rangle$, where $K_G$ is the knowledge graph, $r$ is a property, $prediction$ represents the head or tail of triples to predict, $DS$ is the deductive system, and $KGE$ is the knowledge graph embedding. The architecture returns a learned model of embeddings. These embeddings are used to solve the target prediction task defined by $\tau$.

The architecture is composed of two main steps. First, the relationships implicitly defined by the deductive system are deduced by means of a Datalog program. Second, once $K_G$ is augmented with new deduced relationships, $KGE$ learns a latent representation of entities and properties of $K_G$ in a low-dimensional space. The architecture is agnostic of the method to learn the embeddings. Moreover, our approach is domain-agnostic. For example, it can be applied in the context of Industry 4.0 to discover relations between standards and thus solve interoperability issues between standardization frameworks [18, 19].

### 3.4. Abstract Target Prediction Task. Running Example

Albeit illustrated in the context of treatment response, the proposed method is domain-agnostic. It only requires the definition of the deductive system to enhance the relationships in the ego network of the entities $v$ where $I(v) \in \{C_1, C_2\}$, $C_1 = D(r)$, and $C_2 = R(r)$. The variables $C_1$ and $C_2$ represent the domain and range of the property $r$, respectively. Figure 5 illustrates the proposed steps to enhance the predictive performance by knowledge graph embedding models. The $K_G$ shown in Figure 5(A) is the same as in Figure 1a. Assuming we receive as input the abstract target prediction $\tau = \langle K_G, r, prediction, DS, KGE \rangle$, where the $K_G$ is represented in Figure 5(A), the property is $r = has\_response$, the $prediction = tail$, $DS$ is the deductive system, and $KGE$ is the KGE algorithm. The EDB of the $DS$ comprises all the ground facts of the form: $p(s,o)$, where the triple $(s, p, o) \in \text{ego}(v) \cup \alpha(N(v))$, $I(v) \in \{C_1, C_2\}$, $C_1 = D(has\_response)$, and $C_2 = R(has\_response)$. Then, the domain and range of the property $r = has\_response$ are $\text{Treatment}$ and $\text{Response}$, respectively. In addition, the entity type for $v$ in ego network is $\text{Treatment or Response}$. The entities $\text{low\_effect}$ and $\text{effective}$ are of type $\text{Response}$, and $T1$ and $T2$ are entities of type $\text{Treatment}$. 

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Fig. 4. **Approach.** The input is a knowledge graph ($K_G$), an abstract target prediction $\tau$, and a deductive system, and returns a KGE model. The symbolic system is implemented by a deductive system $DS(EDB, IDB)$ that deduces new relationships in the ego network $ego(v)$ and between their neighbors $\alpha(N(v))$. Then, the sub-symbolic system implemented by a KGE model employs the $K_G$ with the deduced new relationships to predict incomplete triples. $KGE$ solves the abstract target prediction $\tau$ for the relation $r$ and the prediction head or tail.
The EDB comprises all the ground facts defined by the ego networks: $ego(T_1), ego(T_2), ego(low_effect)$, and $ego(effective)$, and their neighbors $\alpha(N(T_1)), \alpha(N(T_2)), \alpha(N(low_effect))$, and $\alpha(N(effective))$. Figure 5(B) shows the ego networks $ego(T_1)$ and $ego(T_2)$ with the set of edges between pairs of entities in the set of neighbors of entity $T_1$ and $T_2$ defined by $\alpha(N(T_1))$ and $\alpha(N(T_2))$, respectively. Then, $DS$ deduces new relationships enhancing the links in the $ego(T_1)$ and $ego(T_2)$; red arrows represent the deduced relationships. Considering the Datalog program $P(1)$ as the IDB for $DS$, the facts $inferred_interaction(D1, D4), inferred_interaction(D3, D4), inferred_interaction(D5, D4), and inferred_interaction(D5, D2)$ are deduced enhancing the ego network.

The SPARQL query in Listing 1 extracts the ego network $ego(T_1)$ and the set of edges between pairs of entities in the set of neighbors of entity $T_1$ defined as $\alpha(N(T_1))$. Listing 1 illustrates a CONSTRUCT query that returns RDF triples in the form of subject, predicate, and object and represents the ground facts of the EDB. The predicate represents the ground predicated in the EDB, the subject represents the first term of the ground predicated, and the object represents the second term.

**Listing 1: SPARQL query to ground the extensional predicate interacts_with(A, B)**

```
PREFIX ex: <http://example/vocab/>
CONSTRUCT { ?A <interacts_with> ?B } WHERE {
}
```
The input to our use case contains 548 polypharmacy cancer treatments $T$, extracted from lung cancer clinical records, with the therapeutic response from each of them and the known Drug-Drug Interactions. The therapeutic response or disease progression is because of a complete therapeutic response or stable disease. A treatment means a partial treatment means a partial treatment with an effective therapeutic response. In that treatment, $P1$ received treatment on 10.07.2020 with an effective therapeutic response. In that treatment, $P1$ was treated with a combination of chemotherapy drugs and one non-oncological drug. Drug-Drug Interactions with the effect and the impact are reported.

The P4-LUCAT consortium\(^2\) collected heterogeneous data sources that comprise clinical records, drugs, and scientific publications and built a knowledge graph that provides an integrated view of these data. The KG is built with the aim of personalized medicine for Lung Cancer treatments. The treatments are extracted from Electronic Health Records (EHRs) from the Hospital Universitario Puerta del Hierro of Majadahonda of Madrid (HUPHM). Furthermore, the DDIs are extracted from DrugBank, in the approved category. The interactions’ type and effect are extracted using named entity and linking methods implemented by Sakor et al. [20]. These methods have also been used to extract DDIs in covid-19 and lung cancer treatments [21, 22]. Table 1 contains a summary of the number of extracted using named entity and linking methods implemented by Sakor et al. [20]. These methods have also been used to extract DDIs in covid-19 and lung cancer treatments [21, 22]. Table 1 contains a summary of the number of treatments and the responses: low-effect or effective.

### 4.1. Treatment Knowledge Graph Creation

As a proof concept, we apply our neuro-symbolic approach to address the problem of predicting polypharmacy treatment effectiveness. We have implemented a deductive system on top of a Treatment Knowledge Graph ($\mathcal{KG}$). The technique aims to identify the combination of drugs whose interactions may affect the treatment’s effectiveness. Then, the problem of predicting treatment effectiveness is modeled as a problem of link prediction between treatments and the responses: low-effect or effective.

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2. https://p4-lucat.eu/
Table 1

<table>
<thead>
<tr>
<th>Knowledge Graph for Lung Cancer</th>
<th>Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Patients</td>
<td>1'242</td>
</tr>
<tr>
<td>Lung Cancer Drug</td>
<td>45</td>
</tr>
<tr>
<td>Chemotherapy Drug</td>
<td>7</td>
</tr>
<tr>
<td>Immunotherapy Drug</td>
<td>3</td>
</tr>
<tr>
<td>Antiangiogenic Drug</td>
<td>2</td>
</tr>
<tr>
<td>Tki Drug</td>
<td>5</td>
</tr>
<tr>
<td>Non Oncological Drug</td>
<td>41</td>
</tr>
<tr>
<td>Oncological Surgery</td>
<td>9</td>
</tr>
<tr>
<td>Tumor Stage</td>
<td>6</td>
</tr>
<tr>
<td>Publications</td>
<td>178'265</td>
</tr>
<tr>
<td>Drugs</td>
<td>8'453</td>
</tr>
<tr>
<td>Drug-Drug Interactions</td>
<td>1'550'586</td>
</tr>
</tbody>
</table>

Fig. 6. Representation of a patient in the Lung Cancer Knowledge Graph.

cording to the data extracted from the clinical records. Figure 7a shows the treatment response distribution, where there are 149 effective treatments and 399 low-effect treatments. Figure 7b and 7c present the histogram for the class effective and low-effect, respectively. We can observe that there are treatments with nine and ten drugs in both treatments’ response classes. Also, the most low-effect treatments are composed of more drugs than effective treatments. The rate of drugs between five and ten can be explained by the fact that in patients with multiple comorbidities, multiple drugs are prescribed to treat the disease.

For each treatment, \( t_i \in T \), the DDIs and their effect are known from DrugBank [23]. Then, the treatments, the treatment response, the drugs, DDIs, and DDI effects for each treatment are managed in \( KG \). Figure 8 shows a portion of \( KG \). The node colors correspond to the type of entity, and the edges represent relationships among the drugs grouped in a treatment. The polypharmacy treatment knowledge graph \( KG = (V, E, L, C, I, D, R, ego, N, \alpha) \) is defined as follows:

- The types Drug, Treatment, DDI, Effect of DDI, and Treatment Response belong to Classes.
- Drugs, Treatments, DDIs, Effect of DDI, and Treatment Response are represented as instances of V.
Fig. 7. Descriptive analysis of the treatment responses.

Fig. 8. Portion of Treatment Knowledge Graph $KG$. The $treatment1$ is composed by three drugs represented by the nodes, $drug:DB00642$, $drug:DB00193$, and $drug:DB00958$. The $treatment2$ also contains three drugs and shares $drug:DB00958$ with $treatment1$. The blue node $ddi:DB00958DB06186$ represents a DDI in the $treatment2$ where the $drug:DB00958$ is the precipitant, and $drug:DB06186$ is the object drug. The effect of this DDI is represented by the yellow node $ex:excretion$ and the impact by the node $ex:decrease$. Then, the treatment $treatment2$ has a low effective response represented by the property $ex:has_response$.

- Edges in $E$ that belong to $V \times V$ represent relations about drugs into a treatment.

4.2. Symbolic System. Deductive Database

Let $\tau = (KG, r, prediction, DS, KGE)$ be the input abstract target prediction, where $KG$ is the polypharmacy treatment knowledge graph, $r = has\_response$, $prediction = tail$, $DS$ the deductive database system, and $KGE$ the knowledge graph embedding algorithm. The IDB of the $DS$ comprises a set of rules to deduce new DDIs in treatments. A DDI is deduced when a set of drugs are taken together and is represented as a relation in the minimal model of the deductive database $DS$. The extensional database corresponds to statements about interactions between drugs stated in $KG$. The ground predicates included in the EDB are the following; they are extracted from
the KG by executing SPARQL queries:

```sparql
PREFIX tkg: <http://research.tib.eu/lung-cancer/vocab/>
PREFIX tkge: <http://research.tib.eu/lung-cancer/entity/>
CONSTRUCT {?E <rule1> ?I} WHERE {
  ?ddi a tkge:DDI .
  FILTER((?E in (tkge:serum, tkge:absorption) && ?I="increase") || (?E in (tkge:metabolism, tkge:excretion) && ?I="decrease"))
}
```

Listing 3: SPARQL query to ground the extensional predicate \( \text{rule}_1(E, I) \)

```sparql
PREFIX tkg: <http://research.tib.eu/lung-cancer/vocab/>
PREFIX tkge: <http://research.tib.eu/lung-cancer/entity/>
CONSTRUCT {?E <rule2> ?I} WHERE {
  ?ddi a tkge:DDI .
  FILTER((?E in (tkge:serum, tkge:absorption) && ?I="increase") || (?E in (tkge:metabolism, tkge:excretion) && ?I="decrease"))
}
```

Listing 4: SPARQL query to ground the extensional predicate \( \text{rule}_2(E, I) \)

The facts included in the ground predicates \( \text{precipitant}, \text{object}, \text{effect}, \text{and impact} \) from the EDB are extracted using the CONSTRUCT query of Listing 5. The EDB contains thousands of facts for those predicates; therefore, only a few ground facts are presented.

The above-mentioned \( \text{rule}_1 \) identifies the combinations of effect and impact that alter the toxicity of an object drug, while \( \text{rule}_2 \) determines the combinations of effect and impact that alter the effectiveness of an object drug. The predicates \( \text{rule}_1 \) and \( \text{rule}_2 \) represent the effect and impact of pharmacokinetic DDIs. The intensional database (a.k.a. \( \text{IDB} \)) comprises Horn rules that state when a new DDI can be deduced as a result of the combination of the treatment’s drug. These rules are negation free; thus, the interpretation of the deductive database corresponds to the minimal model of the \( \text{EDB} \) and \( \text{IDB} \). The intensional database relies on the fact that pharmacokinetic DDIs cause the concentration of one of the interacting drugs (a.k.a. object) to be altered when combined with the other drug (a.k.a. precipitant). Thus, the absorption, distribution, metabolism, or excretion rate of the object drug is affected. Whenever the object drug absorption is decreased (resp. increased), the bioavailability of the drug is also affected. Furthermore, any alteration in the metabolism or excretion of the object drug has consequences on the therapeutic efficacy and toxicity of the drug. The following Datalog rules state the effect of pharmacokinetic DDIs:

\[
\text{precipitant}(ID, A), \text{object}(ID, B), \text{effect}(ID, E), \text{impact}(ID, I) \Rightarrow
\]

Furthermore, any alteration in the metabolism or excretion of the object drug has consequences on the therapeutic efficacy and toxicity of the drug. The following Datalog rules state the effect of pharmacokinetic DDIs:
PREFIX tkg: <http://research.tib.eu/lung-cancer/vocab/>
PREFIX tkge: <http://research.tib.eu/lung-cancer/entity/>

  ?ddi <impact> ?I } WHERE {
  ?ddi a tkge:DDI .
  ?ddi tkge:impact ?I }

Listing 5: SPARQL query to extract the ground the extensional predicates precipitant(ddi,A), object(ddi,B),
effect(ddi,E), and impact(ddi,I)

\[
\text{ddi}(A, E, I, B). \quad (1)
\]
\[
\text{inferred}\_\text{ddi}(A, E, I, B). \quad (2)
\]
\[
\text{inferred}\_\text{ddi}(A, E_2, I_2, B), \text{ddi}(B, E, I, C), \text{rule}_1(E, I), \text{rule}_1(E_2, I_2), (A \neq C) \Rightarrow 
\text{inferred}\_\text{ddi}(A, E, I, C). \quad (3)
\]
\[
\text{inferred}\_\text{ddi}(A, E_2, I_2, B), \text{ddi}(B, E, I, C), \text{rule}_2(E, I), \text{rule}_2(E_2, I_2), (A \neq C) \Rightarrow 
\text{inferred}\_\text{ddi}(A, E, I, C). \quad (4)
\]

Rule (2) states the base case of the \textit{IDB}. The predicate symbol \textit{ddi} represents the DDIs with their effect and impact in \textit{KG}. Precipitant drug \textit{A} generates effect \textit{E} (e.g., absorption, excretion, metabolism, serum concentration) with impact \textit{I} (e.g., increase or decrease) in object drug \textit{B}. The predicate symbol \textit{inferred}\_\textit{ddi} expresses a deduced DDI, where the first term is the precipitant drug, the second and third terms represent the value of the property effect and impact of the DDIs deduced, and the last term is the object drug. Rule (3) and (4) define the effects of combining drugs that interact in a polypharmacy treatment and comprises the clauses to deduce relationships encoded in \textit{KG}. The head predicate \textit{inferred}\_\textit{ddi} becomes valid when the predicate symbols in the body of the rule are also valid. The DDIs deduced from the Rule (3) increase the toxicity of the object drug, and the DDIs deduced from Rule (4) alter the effectiveness of the object drug. Those deduced DDIs are aggregated to the \textit{KG}; they represent valuable insights into each treatment. Each DDI deduced, which is part of the minimal model of the \textit{IDB} predicate \textit{inferred}\_\textit{ddi}(A,E,I,C), is inserted into the \textit{KG} using the query shown in Listing 6. From the motivating example, we can observe that by applying the DDI deductive system to the treatment \textit{T1} in Figure 3a, a new DDI is deduced in Figure 3b; it represents a new triple enhancing the treatment information, reducing thus, data sparsity.

PREFIX tkg: <http://research.tib.eu/lung-cancer/vocab/>

INSERT DATA {
  <ddi> tkg:precipitant <A> .
  <ddi> tkg:object <C> .
  <ddi> tkg:effect <E> .
  <ddi> tkg:impact <I>
}

Listing 6: SPARQL query to insert the deduced DDI from the intensional predicate \textit{inferred}\_\textit{ddi}(A,E,I,C)
4.3. Sub-Symbolic System. Knowledge Graph Embedding Model

Once the deductive system DS deduces new DDIs, the Knowledge Graph Embedding algorithm KGE is applied to learn a latent representation of the entities in a low-dimensional space. The DS increases the relationships in the ego networks ego(v) such as I(v) ∈ {C1, C2}, C1 = D(has_response), and C2 = R(has_response). The DS minimizes the data sparsity issues by augmenting the description of the treatments with newly deduced DDIs. Then, KGE is able to improve the entities’ representation in the embedding space. Thus, the scoring function φ(h, r, t) of the KGE is improved, and the link prediction task infers missing links that correspond to triples (h, r, ?), where I(h) = D(r) and r = has_response. Thus, h are entities of class Treatment, and entities in the object position t are of class Response. Symbolic and sub-symbolic systems are highly complementary to each other. Sub-symbolic AI systems are able to solve complex problems that humans cannot analyze to draw conclusions or make predictions. Sub-symbolic methods are generally robust to data noise, while symbolic systems are vulnerable to data noise, which contrasts with the strength of sub-symbolic approaches.

5. Experimental Study

We empirically assess the impact of the DDIs encoded in KG on our approach’s behavior. In particular, this work explores the following research questions: **RQ1** Can the problem of predicting treatment effectiveness be effectively modeled as a problem of link prediction? **RQ2** Can the symbolic system for an abstract target prediction improve the link prediction performance of the KGE models? **RQ3** Can knowledge encoded in drug-drug interactions enhance the accuracy of the predictive task?

5.1. Experiment Setup

We empirically evaluate the effectiveness of our approach to capture knowledge encoded in KG and predict polypharmacy treatment response.

5.1.1. Benchmarks

We conduct our evaluation over three Knowledge Graphs represented in Figure 9. KG\textsubscript{basic} is the Knowledge Graph which only contains for each polypharmacy treatment the DDIs and their effect extracted from Drugbank.
The second Knowledge Graph, $\mathcal{KG}_2$, includes not only the DDIs extracted from DrugBank, but also the ones deduced by Deductive Database $DS$, i.e., it contains new deduced DDIs and their effects. Lastly, the third Knowledge Graph, $\mathcal{KG}_{random}$ is created from $\mathcal{KG}_{basic}$; it also includes the same number of links included in $\mathcal{KG}_2$ but these links are randomly generated, i.e., they correspond to false or true relationships. We aim to validate whether the links discovered by our DDI Deductive System improve the prediction of treatment responses.

### 5.1.2. Knowledge Graph Embedding Models

We utilize eleven models to compute latent representations, e.g., vectors, of entities and relations in the three KGs and then employ them to infer new facts. In particular, we utilize three main families of models:

- Tensor Decomposition models such as HolE and RESCAL.
- Geometric models such as RotatE, QuatE, and the Trans* family models TransE, TransH, TransD, TransR.
- Deep Learning models such as UM, SE and ERLMP.

The symbolic-sub-symbolic system proposed is implemented in eleven embedding models from different families [17]. Holographic embeddings (HolE) [24] computes circular correlation, denoted by $\star$ in Table 2, between the embeddings of head and tail entities. RESCAL [25] is an algorithm of relational learning based on a tensor factorization, where it models entities as vectors and relations as matrices. In RESCAL, the relation matrices $W_i$ contain weights $w_{i,j}$ between the $i$-th factor of $h$ and $j$-th factor of $t$. RotatE [26] represents each relation as a rotation from the head entity to the tail entity in the complex latent space. The rotation $r$ is applied to $h$ by operating a Hadamard product (denoted by $\circ$ in Table 2). QuatE [27] operates on the quaternion space and learns hypercomplex valued embeddings (quaternion embeddings) to represent entities and relations. TransE [28] proposes a geometric interpretation of the latent space and interprets relation vectors as translations in vector space, $h + r \approx t$. TransE can naturally model 1-n, n-1 and n-m relationships. Suppose a relation $r$ with cardinality 1-n, $(h, r, t_1), (h, r, t_2)$ then the model fits the embeddings in order to ensure $h + r \approx t_1$ and $h + r \approx t_2$, i.e., $t_1 \approx t_2$. Translation on hyperplanes (TransH) [29] is an extension of TransE that aims to overcome the limitations of TransE. TransH interprets a relation as a translating operation on a hyperplane. Furthermore, each relation $r$ is represented by the hyperplane’s norm vector ($w_r$) and the translation vector ($d_r$) on the hyperplane. The variables $h_\perp$ and $t_\perp$ denote a projection of head vector $h$ and tail vector $t$ to the hyperplane $w_r$. TransD [30] represents entities and relations in distinct vector spaces and learns embeddings by translation between projected entities. $h_r = h \star M_r$ where $M_r$ corresponds to a projection matrix $M_r \in \mathbb{R}^{d \times k}$ that projects entities from the entity space to the relation space; further $r \in \mathbb{R}^d$. TransD [31] employs separate projection vectors for each entity and relation. In score function of TransD the variables $h_\perp$ and $t_\perp$ are defined as, $h_{\perp} = M_p h$ and $t_{\perp} = M_t t$, where $M_p, M_t \in \mathbb{R}^{m \times n}$ are two mapping matrices defined as follows: $M_p = r_p h_p + I_{m \times n}$ and $M_t = r_t p + I_{m \times n}$. The subscript $p$ means the projection vectors, and $I_{m \times n}$ denotes the identity matrix of size $m \times n$. The Unstructured Model (UM) [32] is a simplified version of TransE where it does not consider differences in relations and only models entities as embeddings. This model can be beneficial in KGs.
containing only a single relationship type. Structured Embedding (SE) [33] model defines two matrices $M_{r,1}$ and $M_{r,2}$ to project head and tail entities for each relation. SE can discern between the subject and object roles of an entity since it employs different projections for the embeddings of the head and tail entities. ERMLP [34] is a model based on a multi-layer perceptron and uses a single hidden layer. In the score function, the variable $W \in \mathbb{R}^{k \times 3d}$ represents the weight matrix of the hidden layer, the variable $w \in \mathbb{R}^{d}$ represents the weights of the output layer, and $g$ is the activation function. In Table 2, the variable $k$ corresponds to the number of neurons in the hidden layer.

The PyKEEN (Python KnowlEdge EmbeddiNgs) framework [35] is used to learn the embeddings. The hyper-parameters utilized to train the model are epoch number 200 and training loops: stochastic local closed world assumption (sLCWA). The negative sampling techniques used are Uniform negative sampling and Bernoulli negative sampling. The embedding dimensions and the rest of the parameters are set by default. To assure statistical robustness, we apply 5-fold cross-validation. For evaluating the performance of embeddings methods, we measure the metrics: \[ \text{Precision} = \frac{TP}{TP + FP}, \text{Recall} = \frac{TP}{TP + FN}, \text{F1-Score} = \frac{2 \cdot \text{Precision} \cdot \text{Recall}}{\text{Precision} + \text{Recall}}. \]

5.3. Implementations

The pipeline for predicting polypharmacy treatment response has been implemented in Python 3.9. Experiments were executed using 12 CPUs Intel® Xeon(R) W-2133 at 3.60GHz, 64 GB RAM, and 1 GPU GeForce GTX 1080 Ti/PCIe/SSE2 with 12 GB VRAM. We used the library pyDataLog\textsuperscript{3} to develop the Deductive System and the library PyKEEN\textsuperscript{4}, to learn the embeddings.

5.2. Metrics to Characterize the Benchmarks

Table 3 shows the statistics of the three KGs. We considered the metrics, Number of Triples ($T$), Entities ($E$), and Relations ($R$) to measure the size in KG. The metrics Relation entropy ($RE$) and Entity entropy ($EE$) are considered to measure diversity and Relational density ($RD$) and Entity density ($ED$) to measure sparsity in the KG.

The metrics $RE$ and $EE$ measure the distribution of relationships and entities in the KG, respectively. Higher values of $RE$ mean that all possible relations are equally probable, and lower values mean one or more relations have a high probability. The values of the metric $RE$ means that all possible relations in $KG$ are more equally probable than all possible relations in $KG_{basic}$ and $KG_{random}$. The three KGs have a higher $EE$ value than $RE$ as they use a small set of manually defined relations but contain many entities. The metrics $RD$ and $ED$ measure the sparsity of entities and relationships in the KG, respectively. We measure sparsity as information density, where $RD$ means average triples per relation and $ED$ is the average triples per entity. $KG_{basic}$ has the lower average triples per relation and entity while $KG$ and $KG_{random}$ have the higher average triples per entity. The metrics evaluated in Table 3 are defined in the paper [36], implemented by us and available at the GitHub repository\textsuperscript{5}.

5.3. Impact of Capturing Symbolic Knowledge

Figure 10 shows the behavior of the scoring function for the entities predicted by TransH and RotatE embedding models. For the purpose of brevity, we only show the score value results for two embedding models. The evaluation material is available \textsuperscript{6}. We can notice how $DS$ for the prediction property $r = has\_response$ is impacting

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\textsuperscript{3}https://sites.google.com/site/pydatalog/home
\textsuperscript{5}https://github.com/SDM-TIB/Statistics_KnowledgeGraph
\textsuperscript{6}https://github.com/arivasm/Neuro-Symbolic_Treatment-Response.git
Fig. 10. Score value of the predicted entities. The green line represents the cut-off at the percentile 27 for effective treatments and 73 for low-effect treatments for the three KGs.

the KGE models. Figure 10a to 10c and Figure 10g to 10i show the score values of the entities predicted on the link prediction task given the predicate \( \text{ex:has}_\text{response} \) and object \( \text{effective} \) by the \( \text{TransH} \) and \( \text{RotatE} \) models, respectively. Figure 10d to 10f and Figure 10j to 10l report on the score values of the entities predicted given the predicate \( \text{ex:has}_\text{response} \) and object \( \text{low-effect} \) by the \( \text{TransH} \) and \( \text{RotatE} \) models, respectively. We can observe
that the models have different behaviors for each KG. The vertical line in each plot represents the cut-off in a specific percentile. The percentile used for each KG was based on the percentage of links to the entity effective and low-effect in the KG, e.g., the percentile for the effective treatments is 27, because the amount of links to treatment response (effective and low-effect) is 548 and 149 are effective treatments (100 * 149/548). The portion of entities predicted, delimited by the vertical line, is evaluated in terms of precision, recall, and f1-score.

5.4. Evaluating the performance of our integrated Symbolic-Sub-symbolic System

The selected portions of entities predicted are measured precision, recall, and f1-score on average because of cross-validation. Figure 11 and Figure 12 show the evaluation of the Link Prediction task through Uniform negative sampling and Bernoulli negative sampling, respectively. Uniform sampling randomly chooses the candidate entity based on a uniform probability between all possible entities. Bernoulli sampling corrupts the head with probability $p$ and the tail with $1 - p$, where $p$ is an average number of unique tail entities per unique head entities given a relation $r$. The relation with cardinally $1-n$ has a higher probability of corrupting the head, and relations $n-1$ have a higher probability of corrupting the tail. Figure 11 and 12 show the results of the three benchmarks. Each plot depicts the results of a metric for each embedding model and KG. The best performing embedding model in the three metrics is TransH. The KGE models have all better performance in $KG$ regarding the three metrics evaluated in both negative sampling techniques. In addition, the worst performance is observed in $KG_{random}$. The DS minimizes the data sparsity issue with meaningful relationships and enhances the predictive performance of KGE models. These results suggest that the deduced DDI by the Deductive System DS are meaningful to the treatment responses. More importantly, they put the crucial role of the deduced relations into perspective.

5.5. Discussion

The techniques proposed in this paper rely on known relations between entities to predict novel links in the KG. During the experimental study, we observed that these techniques could improve the prediction of treatment...
Fig. 13. **Boxplot of Cosine Similarity.** The boxplot illustrates the distribution of cosine similarity values between treatments in the x-axis with a list of treatments. We observe the five treatments in the x-axis are more similar to the treatments in KG than in KG_{basic}.

effectiveness. Figure 13 shows a box plot of cosine similarity. Considering the KGE model with better performance TransH, we computed the cosine similarity between the embedding entities of type treatment. Five treatments with a low-effect response are selected, and TransH in KG_{basic} misclassifies them, but TransH in KG predicts them correctly. Next, all the treatments with a low-effect response are selected. Thus, the cosine similarity is computed between the selected treatment and the list of treatments with the same response. The first box contains the result of TransH in KG_{basic}; this box contains the similarity values between the treatment and the list of treatments with the same response that treatment355 y the list of treatment with the same response that treatment355. The second box depicts the result of TransH in KG for the same treatment in the first box. We can observe that the five treatments are more similar to the list of treatments in KG than in KG_{basic}. The first quartile, median, and third quartile values in the boxplot are higher in KG than in KG_{basic}. Therefore, these outcomes put in evidence the quality of the deduced links in KG and their impact on the accuracy of the KGE models in the resolution of the task of predicting treatment effectiveness.

Fig. 14. **The distribution of DDIs by treatment for each KG.** Figure 14a shows the density of treatments by DDIs for the treatment response effective in KG_{basic}, KG, and KG_{random}. Figure 14b shows the density of treatments by DDIs for the treatment response low-effect.

Figure 14 shows the distribution of DDIs by treatment in KG_{basic}, KG, and KG_{random}. The x-axis represents the count of DDIs in treatment, and the y-axis represents the density of treatments in the KG with a specific x value. We utilized the Kernel Density Estimation (KDE) function to compute the probability density of the count of DDIs.
in each KG. We can observe for both treatment response effective and low-effect that KG have less density for treatments with five or fewer DDIs than the other two KGs and more density for treatments with more than five DDIs than the rest of the KGs. Furthermore, most treatments with effective response contain less than five DDIs while treatments with low-effect response contain more than five DDIs. These outcomes put into evidence the crucial role that implicit DDIs have on a treatment’s response and the need to deduce them using symbolic systems.

**Analysis of deduced DDI by Treatment classes:** Figure 15 exhibits the distribution of DDIs by treatment response in both KG\textsubscript{basic} and KG. The DDI Deductive System deduces new DDIs in 23.1% of treatments with low-effect responses, while only 10.7% of treatments with effective responses deduce new DDIs. This analysis indicates that the DDI Deductive System deduces more than twice the number of DDIs in low-effect response treatments than in effective response treatments.

**Fig. 15. Distribution of DDIs by treatment response.**

6. Related Work

6.1. Neuro-Symbolic Artificial Intelligence

Neuro-Symbolic Artificial Intelligence is a highly active area that has been studied for decades [2]. Neuro-symbolic AI focuses on integrating symbolic and sub-symbolic systems. Several approaches employ translation algorithms from a symbolic representation to a sub-symbolic representation and vice versa [1]. The aim is to provide a neuro-symbolic implementation of logic, a logical characterization of a neuro-system, or a hybrid learning system that contributes features of symbolic and sub-symbolic systems [2, 5]. Real applications are possible in areas with social relevance and high economic impacts, such as bioinformatics, robotics, fraud prevention, and the semantic web [1]. Methods utilized in neuro-symbolic integration in some of the aforementioned applications include translation algorithms between logic and networks. Also, the community has focused on studying the systems empirically through case studies and real-world applications. An example of a neuro-symbolic system in the field of bioinformatics is the Connectionist Inductive Learning and Logic Programming (CILP) [8]. In the field of vision-based tasks, such as semantic image labeling, high-performance systems have been produced. Karpathy et al. [9] propose an approach introduced for the recognition and labeling tasks for the content of different regions of the images; it combines Convolutional Neural Networks over the image regions together with bidirectional Recurrent Neural Networks over sentences. Once this mapping of images and sentences in the embedding space has been established, a structured objective is introduced that aligns the two modalities through multimodal embedding. The emerging system performs better than classical approaches, where tasks involving semantic descriptions are associated with databases that contain background knowledge, and computer image processing approaches are based on rule-based techniques.
Despite the progress of Neuro-Symbolic Artificial Intelligence, the scope and applicability of symbolic processing are limited. Furthermore, these systems do not examine polynomial overload when integrating both paradigms. Our work leverages the symbolic system, independent of the application domain, and improves the predictive precision of KGE models. Moreover, in our approach, the deductive database is addressed to an abstract target prediction which renders the computational complexity polynomial-time. Thus, we show the positive impact on the overall performance of a predictive model implemented using KGEs considering a deductive system.

6.2. Knowledge Graph Embedding in Biomedical field

Knowledge graphs are becoming increasingly important in the biomedical field. Discovering new and reliable facts from existing knowledge using KGE is a cutting-edge method. KG allows a variety of additional information to be added to aid reasoning and obtain better predictions.

Zhu et al. [37] develop a process for constructing and reasoning multimodal Specific Disease Knowledge Graphs (SDKG). SDKG is based on five cancers and six non-cancer diseases. The principal purpose is to discover reliable knowledge and provide a pre-trained universal model in that specific disease field. The model is built in three parts: structure embedding (S) with TransE, TransD, and ConvKB, category embedding (C), and description embedding (D) with BioBERT to convert description annotations into vectors. The best results are obtained when description embedding is combined with structure embedding, specifically with the ConvKB embedding model. Karim et al. [38] propose a new machine-learning approach for predicting DDIs based on multiple data sources. They integrated drug-related information such as diseases, pathways, proteins, enzymes, and chemical structures from different sources into a KG. Then different embedding techniques are used to create a dense vector representation for each entity in the KG. These representations are introduced in traditional machine learning classifiers and a neural network architecture based on a convolutional LSTM (Conv-LSTM), which was modified to predict DDIs. The results show that the combination of KGE and Conv-LSTM performs state-of-the-art results.

The above-mentioned research aims to discover reliable knowledge based on knowledge graphs using KGE models. However, they are limited by the data sparsity issue of the KGE models and the lack of symbolic reasoning. We overcome this limitation by integrating a Neuro-Symbolic AI system, enabling expressive reasoning and robust learning to improve the predictive performance of KGE models.

6.3. Polypharmacy side effect prediction and Drug-Drug Interactions prediction

In recent years, there has been a growing interest in Pharmacovigilance. Extensive research has been conducted to predict potential DDI. One approach to predicting potential DDI is based on similarity [39–42], with the core idea of predicting the existence of a DDI by comparing candidate drug pairs with known interacting drug pairs. These approaches define a wide variety of drug similarity measures for comparison. The known DDIs that are very similar to a candidate pair provide evidence for the presence of a DDI between the candidate pair drugs. Sridhar et al. [39] propose a probabilistic approach for inferring unknown DDIs from a network of multiple drug-based similarities and known DDIs. They used the probabilistic programming framework Probabilistic Soft Logic. This symbolic approach predicts three types of interactions [39], CYP-related interactions (CRDs), where both drugs are metabolized by the same CYP enzyme, NCRDs, where no CYP is shared between the drugs and general DDI from Drugbank. Furthermore, they considered seven drug-drug similarities. Thus, they found five novels DDIs validated by external sources. A framework to predict DDIs is presented in [42]; they exploit information from multiple linked data sources to create various drug similarity measures. Then, they build a large-scale and distributed linear regression learning model to predict DDIs. They evaluate their model to predict the existence of drug interactions, considering the DDIs as symmetric. A neural network-based method for drug-drug interaction prediction is proposed in [43]. They use various drug data sources in order to compute multiple drug similarities. They computed drug similarity based on drug substructure, target, side effect, off-label side effect, pathway, transporter, and indication data. The proposed method first performs similarity selection and then integrates the selected similarities with a nonlinear similarity fusion method to obtain high-level features. Thus, they represent each drug by a feature vector and are used as input to the neural network to predict DDIs.
Other approaches focus on predicting DDIs and their effects [44–47]. Beyond knowing that a pair of drugs interact, it is essential to know the effect of DDI in polypharmacy treatments. In [45], propose a novel deep learning model to predict DDIs and their effects. They use additional features based on structural similarity profiles (SSP), Gene Ontology term similarity profiles (GSP), and target gene similarity profiles (TSP) to increase the classification accuracy. The proposed model uses an auto-encoder to reduce the dimension of the resulting vector from the combination of SSP, TSP, and GSP. The benchmark used has 1597 drugs and 188’258 DDIs with 106 different types. The model works as a multi-label classification model where the deep feed-forward network has an output layer of size 106, representing the number of DDI types. The results show that the model obtains equal or better results in 101 out of 106 DDI types than baseline methods. Also, they demonstrate how adding the features GSP and TSP increases the accuracy of DDIs prediction. Marinka Zitnik et al. [44] present Decagon, an approach for predicting the side effects of drug pairs. The approach develops a new convolutional graph neural network for link prediction. They construct a multi-modal graph of protein-protein interactions, drug-protein target interactions, and the DDI side effects. The graph encoder model produces embeddings for each node in the graph. They proposed a new model that assigns separate processing channels for each relation type and returns an embedding for each node in the graph. Then, the Decagon decoder for polypharmacy side effects relation types takes pairs of embeddings and produces a score. Thus, Decagon can predict the side effect of a pair of drugs.

All the approaches mentioned above are limited to predicting DDIs and their effects between pairs of drugs. However, in our view, the interactions and their effects need to be considered as a whole and not in pairs in polypharmacy treatments. Our symbolic system resorts to a set of rules that state the implicit definition of new DDIs generated as a result of the combination of multiple drugs in treatment. Since cancer treatment schemes are usually composed of more than one drug, and patients may have several co-existing diseases requiring additional medications, it is of significant relevance the deduction of DDIs holistically in a given treatment.

7. Conclusions and Future Work

This paper addresses the problem of Neuro-Symbolic AI integration, enabling expressive reasoning and robust learning to discover relationships over knowledge graphs. We have presented an approach that integrates symbolic-sub-symbolic systems to enhance the predictive performance of abstract target prediction in KGE models. The symbolic system is implemented by a deductive database defined for an abstract target prediction over a KG. The proposed solution builds the ego networks of the head and tail of the abstract target prediction to deduce new relationships in the ego network; it is able to enhance the ego networks of the abstract target prediction and effectively predict treatment effectiveness. Further, the sub-symbolic system implemented by a KGE model enhances the predictive performance of the abstract target prediction and completes the KG. The performance of the proposed approach is assessed in a knowledge graph for lung cancer to discover treatment effectiveness. Predicting treatment effectiveness is effectively modeled as a problem of link prediction, and exploiting DDI Deductive System improves existing embedding models by performing the treatment prediction task. Results of a 5-fold cross-validation process demonstrate that our approach, integrating neuro-symbolic systems, improves the eleven KGE models evaluated. The presented approach using the symbolic system’s reasoning can enhance the ego networks of the abstract target prediction and effectively predict treatment effectiveness. Thus, our work broadens the repertoire of Neuro-Symbolic AI systems for discovering relationships over a KG. As for future work, we envision having a more fine-grained description of the DDIs and a descriptive profile of the patients and improving the model.

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References


