Ontology based Drug-Drug Interaction Model

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Abstract— **The rapidly increasing amount of data in pharmacy industry provides new opportunities and challenges for large scale data mining and Semantic Web. To meet challenges, various types of data about drugs, patients, diseases, adverse effects of drugs, drug-drug interaction and so on must be effectively integrated. Ontologies are used to retrieve and manipulate the data and display information in very precise and organized way. There do not exist a system that can identify the advanced drug-drug interaction automatically. In this research paper, we have proposed a system that can provide the advanced level drug-drug interaction. In this research, we have proposed an ontology-driven system that can provide the information about drugs, diseases, advanced drug-drug interaction (DDI), drug types, disease types, ingredient types, mechanism of action type, pharmokinetics type, physiologic effect type and dose form type. We have observed that pharmacist/doctors are also interested in administration methods, adverse effects, DDI mechanism, DDI types, drug reaction frequency, drug ingredient, drug interaction level, reaction duration and side effects. Most of above domain knowledge is missing in existing DDI ontologies. We have developed an ADDI ontology that can capture above mentioned advanced details for drug-drug interaction. SPARQL queries are posed to compute and extract the results. Our proposed ontology based system can facilitate the doctors and pharmacists to identify the adverse effects of different drugs interaction and help the patients as well.**

Keywords-component; Drug-drug interaction, Ontology driven drug-drug interaction, Ontology, Semantic technologies in pharmacy

I. INTRODUCTION

Many organizations are exploring the benefits of using of Semantic Web (SW) technologies, in the hope to reduce the data extraction and integration cost. The rapidly increasing amount of data in pharmacy industry provides new opportunities and challenges for large scale data mining. Apart from quantity, the inherent diversity and heterogeneity of the data are significant barriers. Semantic Web standards have been shown to be successful in such environments to create coherence and integrate information "meaningfully" in a way that the data can be contextually understood, accurately interpreted and made actionable. There exist connection between patient and medication that a patient uses against any clinical problem. A patient could be suffering from multiple diseases and he might be taking multiple medicines to cure different diseases. In this phenomenon, two or more drugs may have some effects on the patient. Drug-drug interactions occur when a drug interacts, or interferes, with another drug. There is lack of automatic or computer based artifact that can intelligently analyze the adverse effects of drugs before it prescribed [1]. Drug-drug interaction in this particular case, lead to unsuitable condition. This unsuitable condition is due to two main reasons. First reason is the lack of patient history and second is drug-drug interaction. Our main focus of research is the second one. We provide an ontology based solution for detection of advanced drug-drug interaction. There are several types of drug-drug interaction. Few of them are antagonism, synergism, potentiation, and interaction with metabolism. i) Antagonism means one drug can minimize the effect of other drug by intervention into blood circulation and settlement in human cells. ii) Synergism tends to usage of two or more medicine for the cure of one targeted disease that might strengthen the process to recover with in outstanding tenure. This technique is quite effective and usable in different cases. iii) Potentiation is used as a catalyst to boost the effectiveness of other drug. This helps in urgent recovery of the patient while this might leave side effects due

to different scenarios of patient history. iv) Interaction with metabolism is a process which defines different channels like how drug can interact with body. Drug is interacted with body in two ways i) Pharmacokinetic and ii) Pharmacodynamics. Pharmacokinetic (PK) refers to approach that how medicine circulates and distributes in metabolism or other body parts after the usage. Pharmacodynamics is arena of studies which deals with the interaction with organism and parasites of human body and also leaves the effects of manipulation [1]. Every drug has adverse effects. But these adverse effects become more serious and dangerous when two or more drugs interact with each other. The main purpose of this research paper is to investigate the adverse effects of drug-drug interaction. Patients are treated by multiple doctors for different diseases at same time. Patient used multiple drugs without knowing the side effects. These side effects may appear immediately or after some time in the form of headache, stomach pain, vomiting, inner bleeding etc. In adverse cases, it may cause heart attack, kidney failure and temporary memory loses. The main objective of our research work is to detect the effects of drug-drug interaction in a better way and provide an ontology-driven interface that shows the effects of drugs. The system facilitates the doctors and pharmacists to identify the advanced DDI and also helps the patients.

In next section, we have provided the state of the art. Related work in the domain of drug-drug interaction, health domain, diseases and semantic web is explained. Existing ontologies in the domain of drug and diseases are provided as well. The methodology of research, scope of the research, objective, requirement elicitation, domain specific competency questions, ontology engineering and user interface are provided in section 3. Ontology design is provided in section 4. Last section provides SPARQL queries with results and concludes our work and provides some future directions.

II. RELATED WORK

Drug Interaction Ontology (DIO) is formal representation of pharmacological knowledge. In DIO, Drug-biomolecule has taken as primary block for knowledge. Drug-biomolecule interaction is represented in the form of symbols. DIO ontology symbolically represents the values of different interactions with the help of effect or, object and output. "The Drug Ontology (DrOn) has been developed to enable comparative effectiveness. DrON also provides the health services researchers to query the National Drug Codes that represent products by ingredient, by molecular disposition, by therapeutic disposition, and by physiological effect." The Drug Ontology (DrOn) is available at https://bioportal.bioontology.org/ontologies/DRON [3].

RxNorm simplifies the name of the clinical drug and this initiate a relationship between different medicine names, that might frequently used in the pharmacy software's i.e. First Databank, Micromedex, MediSpan, Gold Standard Drug Database, and Multum. According to the U.S National Library of Medicine (NLM), "RxNorm now includes the National Drug File - Reference Terminology (NDF-RT) from the Veterans Health Administration. NDF-RT is a terminology used to code clinical drug properties, including mechanism of action, physiologic effect, and therapeutic category." [4][5].

SNOMED CT is detailed description of ontology to define diversified clinical terms to be used for the boost of human health information system. It distinguishes the drug and information linked on different parameters. "SNOMED CT is considered to be the most comprehensive, multilingual clinical healthcare terminology in the world." It is available in RDF format at https://bioportal.bioontology.org/ontologies/SNOMEDCT [6].

According to the U.S National Library of Medicine, NDF-RT is used for modeling drug characteristics. In 2003, the Department of Veterans Affairs Veterans Health Administration (VHA) has started the construction of an Enterprise Reference Terminology (ERT). Their main goal was controlled medical terminologies that provide following benefits:

- When describe any medicine it contain minimum ambiguity.
- Human productivity should be maximized.
- Improve the performance of applications that are helpful in decision making.
- Manage information in machine based medical records.
- Patient information is displayed in a better way.
- They support evidence-based medicine.

It provides the formal content model of medication and assigns a unique identifier to each concept [7].

U.S National Library of Medicine (NLM) developed a tool RxNav, which provides the standard name of Drugs. Their database contains about 17000 drug names. It provides the graphical representation of drugs, ingredients and drug components. RxNav provides search facility like names and codes of drugs and components in the drug resources referenced by RxNorm. It provides keyword based intelligent search. Result is displayed in group, form, simplified and table view [8].

The Disease Ontology has been developed for human disease. The purpose of disease ontology is to provide the biomedical community with consistent, reusable and sustainable descriptions of human disease. Applications based in DOID helps in disease navigation and provide visual structure of disease. The disease ontology is available in RDF/XML format at https://bioportal.bioontology.org/ontologies/DOID. DOID ontology contains 9243 classes and 15 different types of properties [9].

Maria et al (2013), has proposed ontology called dug-drug Ontology called DINTO'. They claimed that they had proposed the first Drug Interaction Ontology (DINTO) that automatically arranges DDI related information. The main goal of DINTO is to form that basis for developing NLP (Natural process language) applications in the pharmacovigilance domain.

Maria et al (2013) describes that drug-drug interaction is based on the four factors i.e. age, diseases, genetic factor and drug related feature. On basis of above mentioned factors, following ways are proposed to minimize drug-drug interaction.

1. Co-Administration of the drugs.
2. Monitor the patient on early stages for the detection and adverse effect of DDI.
3. Dosage of the single or both interactions needs some time adjustment for the patient to be used.

Most of the tasks are done manually. No complete ontology based automated solution is provided to detect the drug-drug interaction [1].

Akihiko et al (2004), has developed an Ontology called DIO. Drug Interaction Ontology (DIO) was developed for formal representation of pharmacological knowledge. "DIO provides a fundamental framework for accumulation of reusable knowledge components in molecular pharmacology". DIO deals with the basic framework of reusable parts information in human molecules pharmacology. Authors of DIO claim the fast search of drug by the first name that is shown on interactive web browser. User might be able to select generic name after the result been displayed on the screen for further perusal [10]

Jingjing Liu et al (2011), says that "People regularly take multiple drugs in order to normalize serum levels of biomarkers such as cholesterol or glucose, or to reduce blood pressure. All drugs have side effects, which are sometimes debilitating or even life-threatening. When a person taking multiple drugs experiences a new symptom, it is not always clear which, if any, of the drugs or drug combinations are responsible." Authors work on automated based system which gathers all the reviews from the different online forums. Patients tend to post their experiences on forums after using the group of medicine. One of the problems with these types of forums is that anyone can post anything about a drug. Negative comments can be posted to misguide the patients or reviewers. The other problem with these types of forums is that they are limited to some medicines like statin in this case [11].

María et al (2013), has worked on DD corpus. Corpus is a collection of written texts in specific domain. They only focused to work on Pharmacokinetics and do not deal with second branch of the DDI 'Pharmacodynamics'. They have collected data manually from the databank for the manipulation. María et al (2013) has conducted a survey in seven differ countries and divide the results in 14 groups. This corpus is described in two different types of text i.e. med-line abstract and DDI drug bank. Med-line abstract has several advantages for authors and readers. It is to assist health professionals in selecting clinically relevant and methodologically valid journal articles. This way is to guide the author to summarize the content of their documents. Second, DDI Drug bank has been taken from the database. After their analysis they supported that there must be automatic tool which analyze and quantify the early detection of DDI. Mathias et al (2014), has described some initial steps for developing a basic domain ontology that allows tracing the cause of potential drug-drug interaction (PDDI) knowledge. They have developed an ontology Drug-drug Interaction Evidence Ontology (DIDEO). In their proposed ontology, they have had reused entities from the Drug Ontology (DRON). But unfortunately, the structure and ontology in some format is not publically available [1].

Huda Kafeel et al (2014), highlighted the issue of DDI and its effects on the patients. They claim that people of age group 4 - 85 years are infected due to drug-drug interaction. They enforce that, it is the duty of pharmacist, along with the prescriber to ensure that patients are aware of the risk of side effects of DDI. They have taken 1064 patients, out of them, 608 (60%) are normal one without any effect of DDI and 406 (40%) are effected by DDI. Level of effect had at least one interacting combination with 13% major, 17% moderate and 10% minor interactions. According to their research major level of interactions were found in prescription of patient's age between 16 - 49 years. This research motivates us to develop computer base system can detect advanced DDI [12].

III. METHODOLOGY

"Ontological Engineering refers to the set of activities that concern the ontology development process, the ontology life cycle, as well as the methodologies, tools and languages required for building ontology" [13]. Ontology must answer the following questions like why we need this ontology. Do we already have ontology in the particular domain? Can we reuse the existing ontology? Define classes and subclasses and relevant properties. Distinguish between object and data type properties. What type of competency questions are answered by the ontology? All these questions are answered at different stages in this research paper. The main objective of our research paper is to detect the effects of drug-drug interaction in a better way and provide an interface that shows the effects of drugs. The system facilitates the domain experts to identify the DDI and also helps the patients. Following are the steps that we take in the development of system for ontology based drug-drug interaction.

1. Analysis of Drug-Drug Interaction Schemas
2. Domain specific competency questions with the consultation of SMEs and literature
3. Requirement Elicitation
4. Development of data dictionary
   a. Identification of concepts in drug-drug interaction domain with the help of SMEs and literature
5. Ontology Engineering of Advanced DDI
6. Knowledgebase in OWL
7. Querying Function's Design & implementation (using SPARQL queries)
8. Test Results for Querying functions
9. Implementation

After discussion with SMEs and literature review, we have identified important interaction types like Antagonism, Synergism, Potentiation and Interaction with metabolism. As mentioned before existing ontologies and existing online tools like medscape.org and www.drugs.com do not provide sufficient information related to drug-drug interaction.

These tools do not provide information like interaction level, drug mechanism, DDI type, reaction duration, drug reaction frequency. To find out the necessary information Pharmacist needs to do further processing. Figure 1, shows the required "DDI Type" related schema.

After discussion with domain experts, we have identified following competency questions.

1. Detect drug-drug interaction.
2. Is there an interaction between Drug A and Drug B?
3. Is there effect of Drug A modified by Drug B?
4. Provide the list of drugs?
5. Provide the list of diseases?
6. Which drug is used to treat Disease {x, y and z}?
7. Do drug A has interaction with Drug {B, C, D…}?
8. What is interaction level between drug A and drug B?
9. What is administration method of drug A.?
10. What are adverse effects of drug A?
11. Is drug A suitable for child/female?
12. What is the dosage form of drug A?
13. Provide the drug reaction frequency of Drug A?
14. What are the ingredients of drug A?
15. What is reaction duration of drug A?
16. Provide the list of side effects of drug A.?

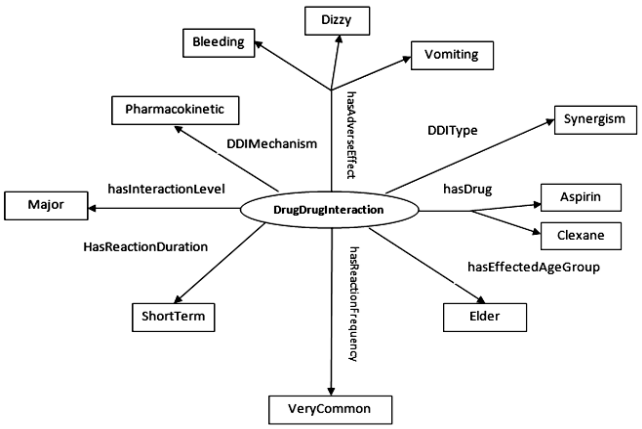

Figure 1. Drug-Drug Interaction Type Schema

Keeping all competency questions in mind, we have developed ADDI ontology. On the basis of analysis and discussion with domain experts, we have discovered that above problems can be resolved, if we have ontology that can identify the advanced drug-drug interaction including interaction level, mechanism of interaction, DDI type, side effects, adverse effects etc.

This research provides the ontology driven solution for advanced drug-drug interaction. Drug-drug interaction ontology contains information about dosage form, administrated methods, adverse effects, DDI mechanism (pharmacokinetic and pharmacodynamics).It also contains information about patient gender and his age groups as these factors are also important for advanced drug-drug interaction. Figure 2 shows the main classes and their relationship of ADDI ontology. Keeping all competency questions in mind, we have developed ADDI ontology. On the basis of analysis and discussion with domain experts, we have discovered that above problems can be resolved, if we have ontology that can identify the advanced drug-drug interaction including interaction level, mechanism of interaction, DDI type, side effects, adverse effects etc. This research provides the ontology driven solution for advanced drug-drug interaction. Drug-drug interaction ontology contains information about dosage form, administrated methods, adverse effects, DDI mechanism (pharmacokinetic and pharmacodynamics).It also contains information about patient gender and his age groups as these factors are also important for advanced drug-drug interaction.

IV. DESIGN

As we discussed in previous section that there is no any complete ontology that detect advanced DDI. Some ontologies are developed for drug-drug interaction like DIO, DINTO and etc but information provided in these ontologies is incomplete. Therefore we have proposed an advanced Drug-drug Interaction Ontology (ADDI Ontology).

In this section, we have proposed an advanced Drug-drug Interaction Ontology (ADDI Ontology). Our ontology can provide dosage form, administrated methods, adverse effects, DDI mechanism (pharmacokinetic and pharmacodynamics), DDI Types (Antagonism, Synergism, Potentiation, Interaction with metabolism), drug reaction frequency, drug ingredient, drug interaction level, reaction duration and undesirable effects that was not provided n the existing ontologies or systems. This section provides the design details of our proposed ADDI ontology.

A. Ontology Building

Different approaches are used to build an ontology, like one approach is create ontology from scratch, define all relevant classes, sub-classes, object type properties, data type properties, literal, define facets and load instance etc. The ontology development process requires manual efforts. Another approach is re-using any existing ontology and modify it according to your requirements. For advanced drug-drug interaction, we are not reusing existing ontologies but developed our own ontology from scratch. We have used Protégé ontology editor and OWL for the development of our drug-drug interaction ontology.

B. Knowledge Acquisition

The knowledge acquisition (KA) is classifying the knowledge that we represent in ontology. There are many different sources of knowledge where the domain knowledge can be extracted like domain experts, literature review, books and manuals. For advanced drug-drug interaction ontology, we have used multiple sources for knowledge acquisition like pharmacist, brainstorming, literature, books (as shown in figure 2), drug manuals, online resources and existing ontologies in the drugs domain.

C. Structure of ADDI Ontology

Advanced Drug-drug Interaction ontology (ADDI Ontology) has classes, subclass, object properties and data type properties. Classes, subclasses, object properties and

data type properties are inter-related. Classes and sub-classes are connected with each other through object properties and data type properties.

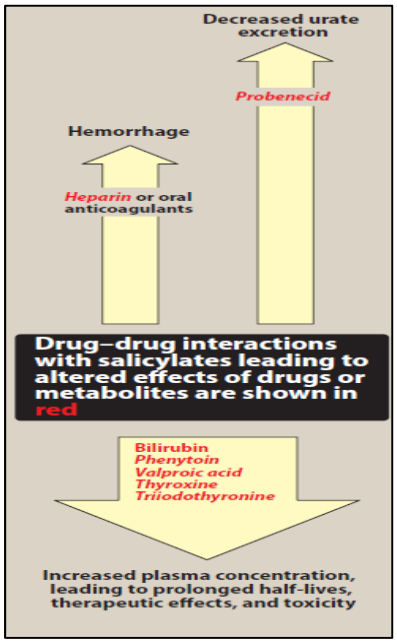

Figure 2. Drug-Drug interactions, adopted from [14]

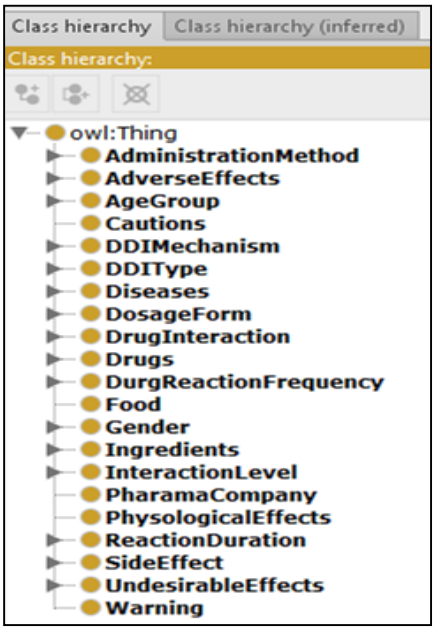

Figure 3. Classes from Advanced DDI ontology

Synonyms and other related information about any entity is also stored in the form of labels and descriptions.

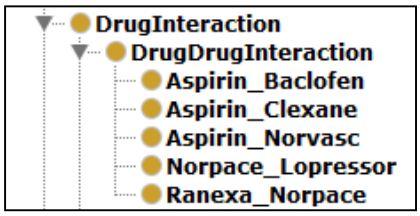

Figure 4. Sub-classes of drug-drug interaction class in ADDI ontology

D. OWL Classes and Subclasses

Classes represent abstract groups or collections of objects of domain ontology. These are used to group resources with same characteristics. Classes may be further divided into sub classes.. Fig 4 shows few sub-classes of our ADDI.\

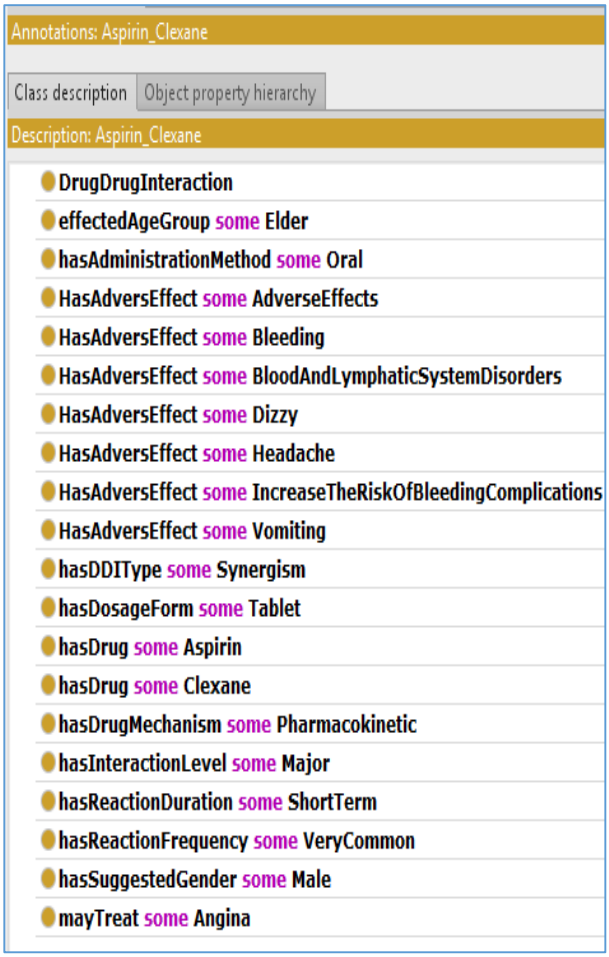

Figure 5. Aspirin and Clexane Interaction in ADDI ontology

E. OWL Data Type Properties

Relationships between classes and data are represented in the ontology through data type properties. owl:DatatypeProperty is a subclass of the RDF class rdf:Property. Data type properties contain value in the form of text, string or an integer attached to a single concept. Data type properties are linked with classes and data through domain and range.

F. OWL Object Type Properties

Object properties represent relationships between classes. owl:ObjectPropertyis a subclass of the RDF class rdf:Property. It contains domain and range of individuals. Main object properties of our DDI ontology are shown in Figure 8 shows of object type properties of ADDI ontology.

G. Drug-Drug Interaction

Drug interaction is an important part of our ontology. It represents all the important information about drug-drug interaction. Figure 7 shows interaction between

- Aspirin and Baclofen
- Aspirin and Clexane
- Aspirin and Norvasc
- Norpace and Lopressor
- Renexa and Norpace

Figure 7 shows the advanced level interaction between two drugs i.e. Renexa and Norpace.

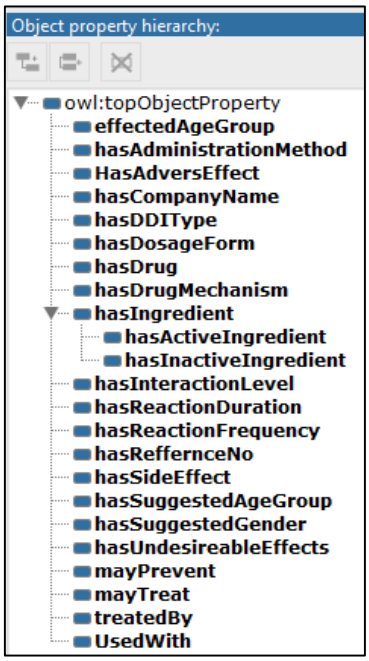

Figure 6. Object Type Properties of ADDI ontology

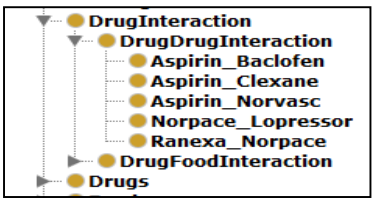

Figure 7. Drug-drug interaction from ADDI ontology

V. Conclusion and Future Work

Pharmacists need to address the problems caused due to drug-drug interaction (DDI). DDI can cause serious outcomes including severe drug reactions. There is always need to develop software's to early detect the DDI. Our ontology based advanced drug-drug interaction is a step to provide advanced DDI. In this research paper, we have developed an ontology that can detect advanced ADDI. Our ADDI ontology can provide information about drugs and diseases, advanced drug-drug interaction DDI, drug types, disease types, ingredient types, mechanism of action type, pharmokinetics type, and physiologic effect type. Doctors and pharmacists are interested in dosage form, administration methods, adverse effects, DDI mechanism (pharmacokinetic and pharmacodynamics), DDI types (Antagonism, Synergism, Potentiation, Interaction with metabolism), drug reaction frequency, drug ingredient, drug interaction level, reaction duration and side effects. Most of above domain knowledge is not machine readable and is missing in existing DDI ontologies and tools. ADDI ontology is developed in OWL and SPARQL is used extract the required information from the ontology. PHP RDF/API is utilized for the development of ontology based application. Our main contribution is to develop the schema part of advanced drug-drug interaction and then extraction of DDI related information from the ontology.

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