An ontology for drug-drug interactions

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Abstract
Drug-drug interactions form a significant risk group for adverse effects associated with pharmaceutical treatment. These interactions are often reported in the literature, however, they are sparsely represented in machine-readable resources, such as online databases, thesauri or ontologies. These knowledge sources play a pivotal role in Natural Language Processing (NLP) systems since they provide a knowledge representation about the world or a particular domain. While ontologies for drugs and their effects have proliferated in recent years, there is no ontology capable of describing and categorizing drug-drug interactions. Moreover, there is no artifact that represents all the possible mechanisms that can lead to a DDI. To fill this gap we propose DINTO, an ontology for drug-drug interactions and their mechanisms. In this paper we describe the classes, relationships and overall structure of DINTO. The ontology is free for use and available at https://code.google.com/p/dinto/

Keywords: Ontology, Drug-drug interactions, Text mining, Semantics, Pharmacology

1 Introduction

In recent years, ontologies have become important tools to support researchers in their efforts to remain up to date with the flood of emerging information. The domain of pharmacology has not been a stranger to the proliferation of ontologies and knowledge bases. RxNorm facilitates information exchange about medication among clinical systems [1], standardizing names for clinical drugs and for dose forms. SNOMED CT is the most comprehensive ontology of clinical terms for supporting health information systems [2], including different classifications of drugs and drug-related information. MeSH [3], a controlled vocabulary thesaurus for indexing MedLine articles, contains a large amount of pharmacological information, including pharmacological actions of drugs.

Drug-drug interactions (DDIs) are common adverse drug reactions having an important impact on patient safety and healthcare costs. Although there is a large number of drug databases and semi-structured resources (such as DrugBank [4], Stockley

[5] and Drug Interactions Facts [6]) with information about DDIs, these databases are incomplete and the consistency of their content is limited, so it is very difficult to assign a real clinical significance to each interaction. Ontologies allow the formal representation of the knowledge in a particular domain. However, although several ontologies exist for the pharmacology domain, none covers all classes related to drug-drug interactions. In fact, to the best of our knowledge, there are only three ontologies focusing in the representation of DDI information. The first one, DIO [7] (Drug Interaction Ontology), is a formal representation of drug pharmacological actions, depicted by drug-biomolecule interactions that are the underlying mechanism in some types of DDIs. The second one is the PK ontology [8] that was developed for the representation of drug pharmacokinetic information, and has been used to annotate pharmacokinetics studies of DDIs. The third one is the OWL version of the Drug Interaction Knowledge Base (DIKB) [9], an evidence taxonomy that, when combined with a set of inclusion criteria, enables drug experts to specify their confidence in a type of drug mechanism assertion. However, neither of these represents all the different DDI mechanisms, consequences and additional factors.

In this paper, we propose the first Drug Interaction Ontology (DINTO) that systematically organizes all DDI related information. This ontology represents all the possible mechanisms that can produce a DDI, including both types, pharmacodynamic and pharmacokinetic mechanisms. Our final purpose is that this ontology can be used as a basis for developing NLP applications in the pharmacovigilance domain. In this work we describe the classes, relations, structure and organization of this newly developed ontology. DINTO is available in OWL for download at https://code.google.com/p/dinto/.

2 Methods

To build DINTO we follow the methodology for ontology development METHONTOLOGY [10], further supplemented with specific tasks relating to embedding this ontology within the context of existing efforts, particularly those of the OBO Foundry [11].

2.1 Specification

We defined the ontological requirements for a comprehensive ontology that will represent all the information related to the domain of DDIs and that should be mapped to other ontologies. During this step we defined different competency questions (CQs) that will be used as a type of requirement specification and evaluation for the finished ontology.

2.2 Knowledge Acquisition

Prior to the present work, we created a manually annotated corpus, the DDI corpus [12]. This corpus was used in the initial stages of the ontology creation process, which

led to the identification of basic concepts in the DDI domain and relations between them.

Firstly, we used the UAM Corpus tool,[1] a free environment for linguistic annotation of text corpora. This tool enables the annotation of selected segments in the corpus, with various features or labels. The study of the annotated segments was used for identification of linguistic patterns in these texts. For example, in the analysis of annotated segments in the corpus labelled "pharmacodynamic effects of a drug" we identified five main ways a clinical consequence of a DDI can be described:

- The effect of a DDI is the effect of a drug: e.g. "*increase the adrenergic effect of*", "*reduced the action of*".
- The effect of a DDI refers to a negative effect of a drug: e.g. "*the adverse effect of*", "*the ototoxic potential of*".
- The effect of a DDI refers to the signs or symptoms, generally related to an adverse effect, without explicitly relating them with a drug: e.g. "*serious reactions such as rigidity, myoclonus, or autonomic instability*".
- The effect of the DDI provides information regarding some aspect of the DDI: e.g. "*additive CNS depressant effect*", "*observed an excessive reduction of blood pressure*".
- The effect is expressed through a modification in some analytical test result: e.g. "*increase in prothrombin time*".

Secondly, we conducted a keyword analysis with the freeware AntConC corpus analysis toolkit[2] and computed a concordance analysis of relevant terms. The outcome of this activity is a list of relevant concepts and their relationships with other concepts. For example, through this analysis we identified those terms used to described a modification or alteration (*increase*, *decrease*, *potentiation*, etc.) and analysed the concepts in the domain that are usually related with them. For example, the concept *enhanc** can be used with terms classified as "pharmacokinetic parameter", "pharmacokinetic process", "effect" or "toxicity"; however, the term *elevat** is only used in our corpus with terms classified as "concentration" and "pharmacokinetic parameter".
Another important source of information is provided by other ontologies that can potentially be re-used and imported to our ontology. We reviewed different ontologies that were identified as related to some aspect of DDIs. A brief description of the most prominent ontologies in this domain is provided in section 3.3 Related Ontologies.

2.3 Conceptualization

In the conceptualization of DINTO, the most important and challenging aspect was the construction of the basic schema that relates the pharmacodynamics and pharmacokinetics aspects of an individual drug and the DDI aspects, since creating specific boundaries between these domains is not possible. A simplified schema is illustrated

[1] http://www.wagsoft.com/CorpusTool/
[2] http://www.antlab.sci.waseda.ac.jp/

in Figure 1, which shows the integration between the pharmacokinetics and pharmacodynamics aspects of an individual drug and how they are related with a DDI.

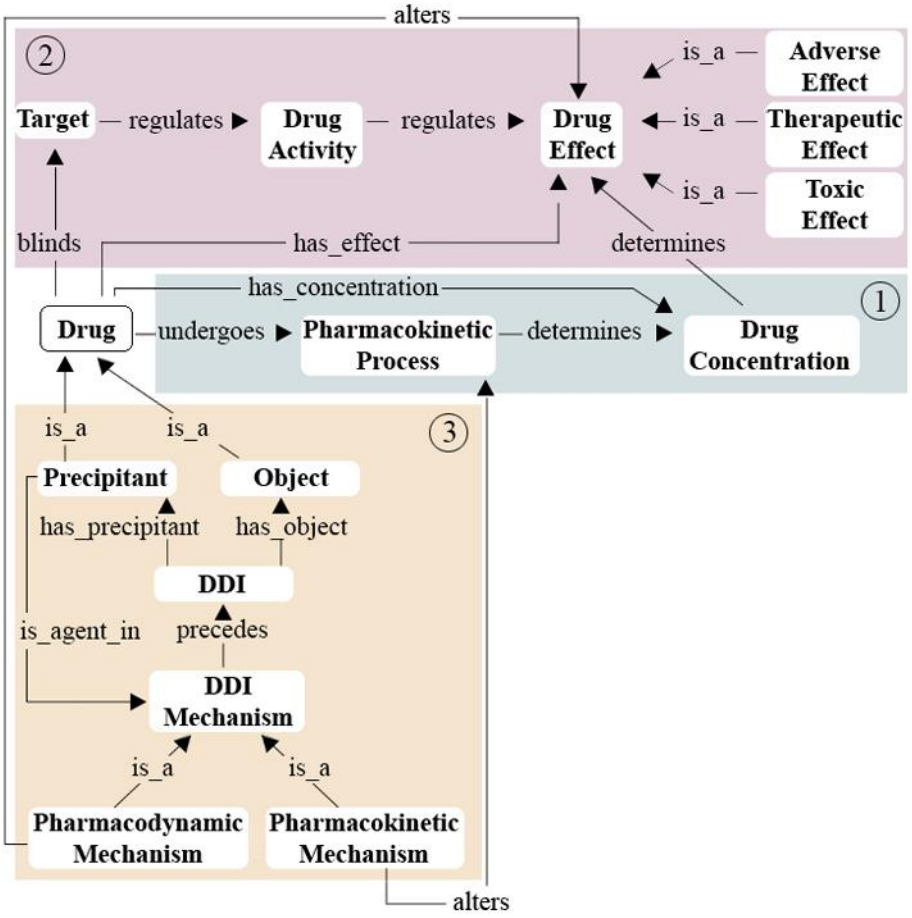

Fig. 1. Diagram for pharmacokinetic and pharmacodynamic aspects of a DDI.

In the schema, the pharmacokinetic information is shown in section 1, which represents how a drug undergoes different pharmacokinetic processes in the body (absorption, distribution, metabolism and excretion). These processes determine the concentration of the drug in the body (in the blood and in the different tissues). The concentration of the drug determines its effect.

The pharmacodynamic information is shown in section 2: a drug binds different proteins in the body. The target is the one that regulates (facilitates or impairs) the activity of the drug and this activity regulates (facilitates or impairs) the effect of the drug in the body. As is shown in the figure, a drug can have different effects (therapeutic, adverse or toxic).

Section 3 represents that a DDI is a process involving exactly two drugs, one of them is the Precipitant and the other one is the Object. A drug that is a precipitant has an *is_precipitant_in* relationship with a DDI; a drug that is an object has an *is_object_in* relationship with a DDI. The precipitant is the one that leads to the occurrence of the DDI, the one that triggers the mechanisms. Therefore, a drug is a precipitant, as well, if it has an *is_agent_in* relationship with a DDI Mechanism. On the other hand, the object is the victim in the interaction. Therefore, it will be a drug that has a relationhip *undergoes*, *has_concentration* or *has_effect* with an effect or concentration that is altered by a DDI Mechanism. There are two types of DDI mechanisms, pharmacokinetic mechanism and pharmacodynamic mechanism. The former one implies the alteration in a pharmacokinetic process of a drug, which, as is shown in the schema, will alter the concentration of the drug in the body and, consequently, its effects. The latter one affects to the target, leading to an alteration (an increase or a decrease) in the drug effect. There are different types of pharmacokinetic and pharmacodynamic mechanism. Some examples are described and represented in section 3.5 Use Cases.

2.4 Implementation

The implementation language is the Web Ontology Language 2 (OWL2) and we have used the Protégé ontology editing software[3].

2.5 Evaluation

We plan to evaluate the ontology in use for two different applications: prediction of DDIs on the basis of their mechanism, and text mining the pharmacological literature. However, for the time being our evaluation has consisted of two approaches: 1) classification scenario testing and 2) supporting or answering of previously established CQs. Additionally, we have invited peer review of the ontology.

The first one allows checking the consistency and expressivity of the ontology and the detection of errors through a manual iterative review of the inferred relationships and classifications. For this classification scenario testing, we have added individuals to the ontology with associated properties. Each one of these test sets represent a real DDI caused by a specific DDI mechanism. Through this method, we tested that performing classification has resulted in the individuals being detected as members of the correct target classes (instance checking) and that the inferred relationships are those expected.

With the second approach we check if the ontology satisfies the ontology requirements established in the specification step through the use of the created CQs. Table 1 shows a sample of them and their corresponding axioms as an example of how the ontology corresponds to the requirements of the competency questions (the examples are related to the interaction between Cyclosporin and Rosuvastatin explained in section 4.1 Use Case of a pharmacokinetic DDI).

[3] http://protege.stanford.edu/

Table 1. Competency Questions and corresponding axioms in the ontology that can be used to derive answers.

Question	Axiom	Example
Is there an interaction between DrugA and DrugB?	DDI *has_participant* Participant DDI *has_precipitant* Precipitant DDI *has_object* Object	CyclosporinRosuvastatin *is_a* DDI CyclosporinRosuvastatin *has_precipitant* Cyclosporin CyclosporinRosuvastatin *has_object* Rosuvastatin
Is the effect of DrugA modified by DrugB?	Precipitant *alters* Drug Effect	Cyclosporin *increases* Rhabdomyolisis Rhabdomyolisis *is_effect_of* Rosuvastatin
What is the mechanism of the interaction between DrugA and DrugB?	DDI *is_preceded_by* DDI Mechanism	CyclosporinRosuvastatin *is_preceded_by* OATP1B1 Inhibition OATP1B1 Inhibition *is_a* Pharmacokinetic Mechanism
Is there a PK interaction between DrugA and DrugB?	Pharmacokinetic DDI *is_preceded_by* Pharmacokinetic Mechanism	CyclosporinRosuvastatin *is_preceded_by* OATP1B1 Inhibition OATP1B1 Inhibition *is_a* Pharmacokinetic Mechanism

3 Structure of DINTO

The current version of the developed ontology DINTO is an OWL artifact containing 396 classes, 67 object properties and 3,317 axioms, prior to the import of other ontologies. In this section we describe the main classes in DINTO. Thereafter, we define the object properties and show an example of the use of chained properties in the ontology. Finally, a description of the related and imported ontologies is also provided.

3.1 Classes

The different classes in the ontology represent all the DDI-related knowledge. The information regarding DDIs and represented in the ontology can be divided into three main groups: drug-related information, DDI-related information, and information relevant to the domain but not specifically related to drugs or DDIs.

Drug related information refers to those classes that are not specific to DDIs and, therefore, are within the scope of other biomedical ontologies. These include:

- The drugs themselves: for example, norfloxacin or duloxetine. These are imported from the ChEBI Ontology[4] [13].
- The effects of the drugs: such as antihypertensive effect or nephrotoxic effect. The effect of a drug can be classified in DINTO in three main classes (see Figure 1): therapeutic effect (the intended use of the drug), adverse effect or toxic effect (undesirable effects of a drug). These will be taken from ChEBI and databases such as SIDER[5].
- The role or bioactivity of a drug: agonist, inhibitor, etc. These roles are specifically related with a protein included in the ontology. For example, the class "inhibitor" has as a child the class "CYP3A4 inhibitor".
- The pharmacokinetic processes that drugs undergo in the body: absorption, distribution, metabolism or excretion.
- The pharmacokinetic parameters describing these processes and the concentrations of drugs in the body: area under the curve or Cmax, for example.
- The drug related procedures intended to avoid or reduce the effects of the DDI: reduction in drug dose, separation of the administration of the drugs by a minimal interval of time, etc.
- The drug factors that can affect the effect and severity of a DDI: such as dosage or pharmaceutical form.

DDI related information refers to those classes specifically related to DDIs. They are shown within a yellow box in Figure 1:

- The DDIs themselves: the interaction between two drugs. Every DDI between two specific drugs is a class, such as Cyclosporin-Rosuvastatin DDI, that refers to the specific process in which cyclosporin interacts with rosuvastatin through a specific mechanism. For the time being, only the class DDI and the subclasses pharmacokinetic DDI (PkDDI) and pharmacodynamic DDI (PdDDI) have been created. In future work, specific DDIs will be created for each interacting pair.
- The mechanism of a DDI: such as the inhibition of the metabolic enzyme of one drug by another drug. Every DDI mechanism is a class that is defined on the basis of other entities and object properties. For example, the inhibition of the membrane transporter OATP1B1 is a class named "hepatocyte basolateral OATP1B1 inhibition". It is defined as a DDI mechanism that *has_agent* a precipitant that *inhibits* the transporter OATP1B1.
- The effect of a DDI: the consequence in the patient as a result of the interaction between two drugs.

The remaining classes are important in the DDI domain, but are not specifically related to drugs or DDIs.

- The sources of information that can describe a DDI: a controlled study, a case report.

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[4] To date, the imported file from ChEBI contains 3236 classes, all of them referring to drugs.

[5] http://sideeffects.embl.de/

- The target to which a drug binds: calcium channel, beta-adrenergic recptor, etc.
- Metabolic enzymes: such as CYP1A2 or UDP-glucuronosyltransferase.
- Transporters and drug efflux pumps: albumin, P-glycoprotein.
- Patient factors that can affect the effect and severity of a DDI: age, diseases or genetic factors.

All these classes are defined in natural language following Aristotelian principles, and OWL definitional axioms are captured where appropriate and possible. For example, the class precipitant is a subclass of the class drug and is defined as: "*A precipitant is a participant that alters the disposition and/or effects of another drug by triggering a DDI mechanism.*" The OWL definitional axiom for precipitant is:

('is agent in' some 'DDI mechanism') or
(drug and
(alters some 'pharmacokinetic process')

In combination with the object properties, these OWL definitions are responsible for the inference capabilities of DINTO.

3.2 Relationships

We follow the OBO community effort to standardize the relationships used in biomedical ontologies [14].

The current version of DINTO contains 67 object properties. These object properties are important for inferences, enabled by the explicit specification of domains and ranges for some of these object properties and from the creation of property chains between them. Through the use of chained properties we can represent ordered pharmacological events.

During the analysis of the DDI corpus, we identified multiple ways in which an interaction between two drugs can be expressed. Therefore, the relationship *interacts_with* in the ontology is one of the most complex. Moreover, it has multiple property chains. An example is shown in Figure 2.

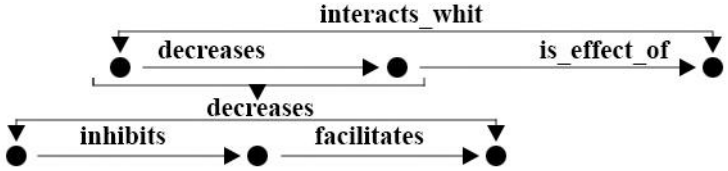

Fig. 2. Description of the relationship interacts_with

The object property *interacts_with* is a symmetric relationship that has domain and range "drug". It is a subproperty of the property chain:

$$decreases \circ is\_effect\_of \rightarrow interacts\_with$$

The relationship *is_effect_of* is defined as "*A relationship between an effect and the chemical that produces it*". It has "drug effect" as domain and "drug" as range.
The relationship *decreases* is a subproperty of the relationship *alters* and sibling to the relationship *increases*. *Decreases* is defined in DINTO as "*A relationship between an entity x (process or continuant) and an entity y, which bears a quality that is decreased by x, leading to a change that is decreased compare to normal or previous value*". Therefore, it can have as domain or range any entity (continuant or process). In the same way as interacts_*with*, decreases is a subproperty of different chained properties. For example:

$$blocks \circ facilitates \rightarrow decreases$$

The relationship *blocks* is defined as "*A relationship between a drug x and a receptor or ion channel (y), where (x) 'binds to but does not activate (y) thereby blocking the actions of endogenous or exogenous (y)-agonists.*'". It has domain "drug" and range "protein".

The relationship *facilitates* is a subproperty of the relationship *regulates* and sibling to the relationship *impaires*. The definition of *facilitates* is "*A relationship between an entity x (continuant or process) and a process y, which occurrence depends directly or is heavily dependent on x*". It has as domain any entity and as range the union of the classes "physiological effect" and "pharmacokinetic process".

3.3 Related Ontologies

An analysis of related ontologies was performed. The following ontologies were identified as useful knowledge sources, and subsets from them were integrated into DINTO.

- Basic Formal Ontology[6]: We follow BFO's definitions for upper level classes such as Process and Disposition in our work.
- OBO Ontology Metadata[7]: The OBO ontology metadata project standardises annotation properties for common annotation types such as definition, synonym and so on. We import the ontology-metadata.owl (a subset of the IAO[8]).
- Relation Ontology [14]: RO is a collection of relations intended primarily for standardization across ontologies in the OBO Foundry and wider OBO library. We map our relations to RO where appropriate.
- Semanticscience Integrated Ontology[9]: We map our relations to SIO where no appropriate RO mapping is available.
- Chemical Entities of Biological Interest [13]: ChEBI includes many drugs and their biological roles, and we use it as a source for terminology and role relationships.

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6 http://www.ifomis.org/bfo
7 https://code.google.com/p/information-artifact-ontology/wiki/OntologyMetadata
8 http://code.google.com/p/information-artifact-ontology/
9 https://code.google.com/p/semanticscience/wiki/SIO

- Functional Therapeutic Classification System[10]: FTC sorts over a thousand approved drugs based on their mode of action. The FTC features over 20'000 categories defining the pharmacology of therapeutic agents.
- PK Ontology [8]: This ontology is used as a source for terminology, definitions and units in this area.
- Drug Interaction Ontology [7]: We use DIO as a model for relating DDI mechanisms to their locations.
- DIKB [9]: We map our *has_object* and *has_precipitant* relationships with their equivalents in DIKB.

4 Use Cases

In this section we explain two use cases for the ontology, representing the two main types of mechanism.
DINTO has been designed to represent all possible mechanisms that can lead to a DDI. The ontology provides the general pharmacological principles of the domain. Based on this general knowledge it is possible to establish specific DDIs between specific pairs of drugs. Every DDI mechanism is manually conceptualized and incorporated into the basic schema (Figure 1). To check the consistency of this general conceptualization, a specific real example in the DDI domain is selected for every DDI mechanism. A test set of individuals is created in the ontology and the minimal number of relationships between them is explicitly established. Through the use of a reasoner (such as Fact++), we check the consistency and review that the classification of entities as well as the inferred object properties are the expected ones and consistent with the literature.
In this paper we described two of these examples, one for a pharmacokinetic DDI and one for a pharmacodynamic DDI.

4.1 Use case of a pharmacokinetic DDI

Different membrane transporters are important in the pharmacokinetics of drugs, since they can affect the drug disposition, its therapeutic efficacy and its adverse drug reactions. They are very important, as well, as a mechanism for pharmacokinetic DDIs. For example, the drug rosuvastatin is transported into the hepatocyte, where it is metabolized and inactivated, through the transporter OATP1B1. Several drugs inhibit the activity of this protein, which may result in lower hepatic intracellular and higher blood concentrations of OATP1B1 substrates. For instance, an increase in the area under the curve (AUC) of rosuvastatin has been described when co-administered with the OATP1B1 inhibitor cyclosporine [15].
The first example is represented in Figure 3. The drug “Cyclosporine” inhibits the activity of the protein “OAT1B1”. This protein is related, as we said, with the pharmacokinetics of the drug “Rosuvastatin” in the way that is shown in the figure. There-

[10] https://www.ebi.ac.uk/chembl/ftc/data/

fore, “Cyclosporine” is classified as a “Precipitant” (the one that triggers the DDI) and “Cyclosporine” is classified as “Object” (the one that is victim in the DDI). Moreover, the ontology classifies the pharmacokinetic process “Rosuvastatin Metabolism” as “Decreased Metabolism”, whereas the concentration and effects of rosuvastatin are classified as “Increased Concentration” and “Increased Effect”. It is inferred in this example that “Cyclosporine” *decreases* the metabolism of “Rosuvastatin” and that “Cyclosporine” *increases* its concentration and its effect. Moreover, the symmetric interaction *interacts_with* between both drugs is inferred as well.

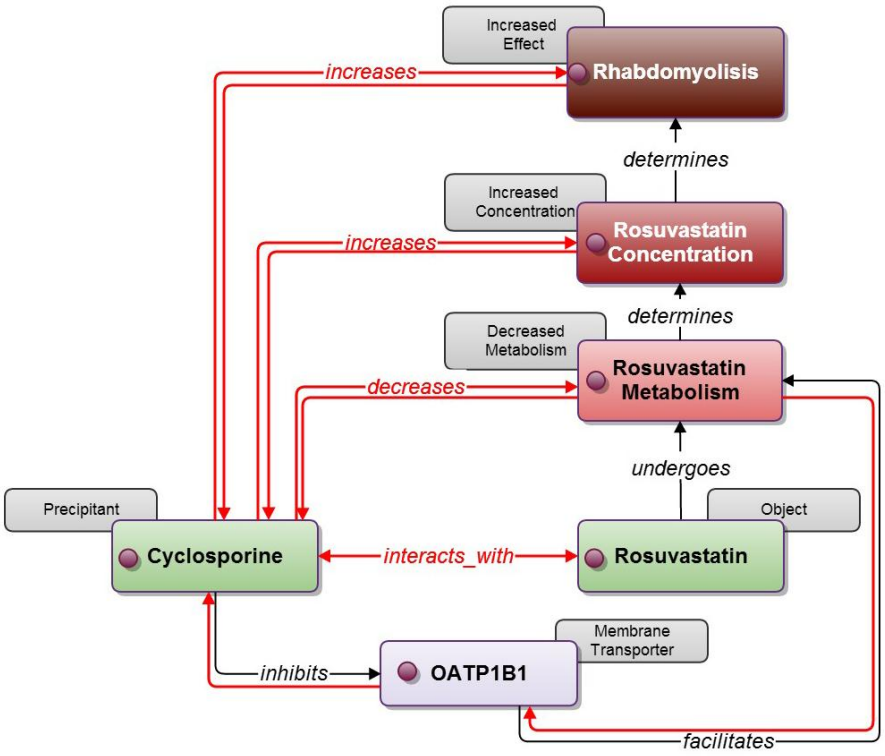

Fig. 3. DDI between Cyclosporin and Rosuvastatin. Black arrows are the established relationships; red arrows are the inferred relationships and grey boxes are the inferred classifications for the individuals.

Figure 4 shows how the same relationships are inferred when we use a different test set and preliminary relationships to represent the same example. In this case, we create an individual representing the DDI, “Cyclosporine-Rosuvastatin DDI”, as well as the mechanism, “OATP1B1 inhibition”. As it is shown in the figure, the DDI is classified as a pharmacokinetic DDI just in basis of the mechanism by which is preceded.

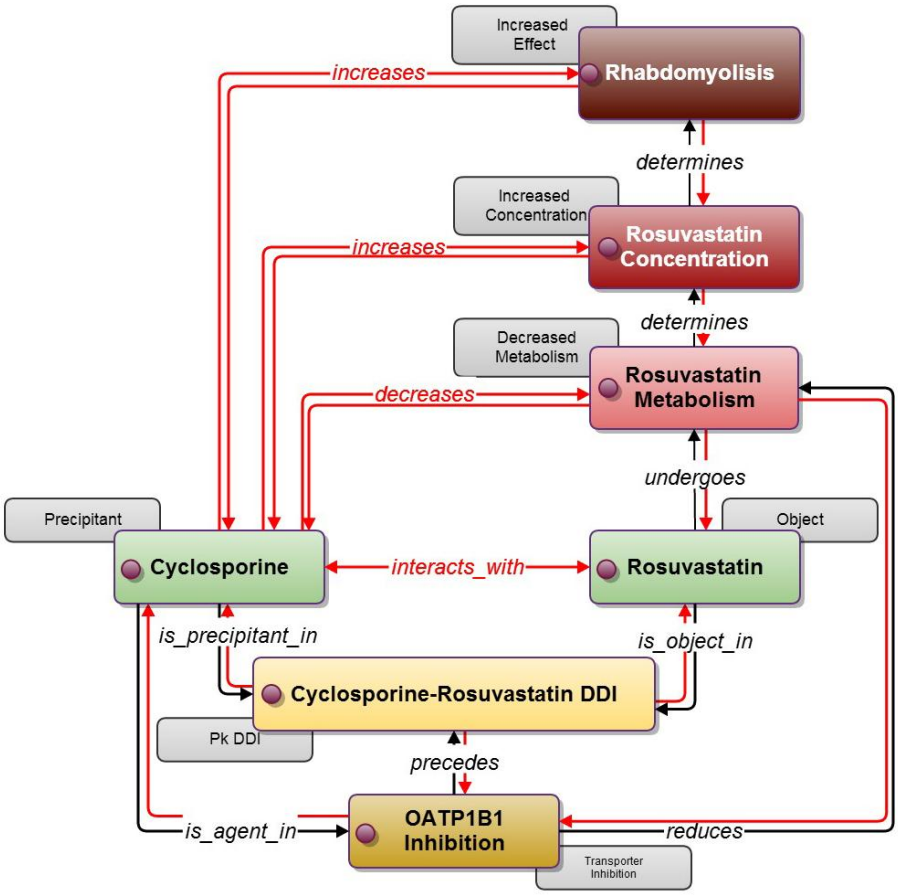

Fig. 4. DDI between Cyclosporin and Rosuvastatin. Black arrows are the established relationships; red arrows are the inferred relationships and grey boxes are the inferred classifications for the individuals.

4.2 Use case of a pharmacodynamic DDI

Drugs binding the same target but presenting different activities can be involved in a DDI by an antagonistic mechanism. This is the case of the opioid receptor antagonist naloxone, which binds to the receptor without triggering a response, and different opioid agonists, such as propoxyphene, in which their activity is determined by these receptors. In cases of overdosage of propoxyphene, an increase in the undesirable effects such as central nervous system depression can be observed. Naloxone is used

as an antidote in these cases, since the interaction between these two drugs will lead to a decrease in the effects of the agonist [15].
In Figure 4 we show the test set created for this example. Since "Propoxyphene" *activates* the "Opioid Receptor" and this *facilitates* the effects of this drug, the introduction of another drug, "Naloxone", which *blocks* the activity of the receptor will lead to a decrease in the effects of the former one. As is shown in the figure, the ontology infers these *decreases* relationships as well as the *interacts_with* relationship.

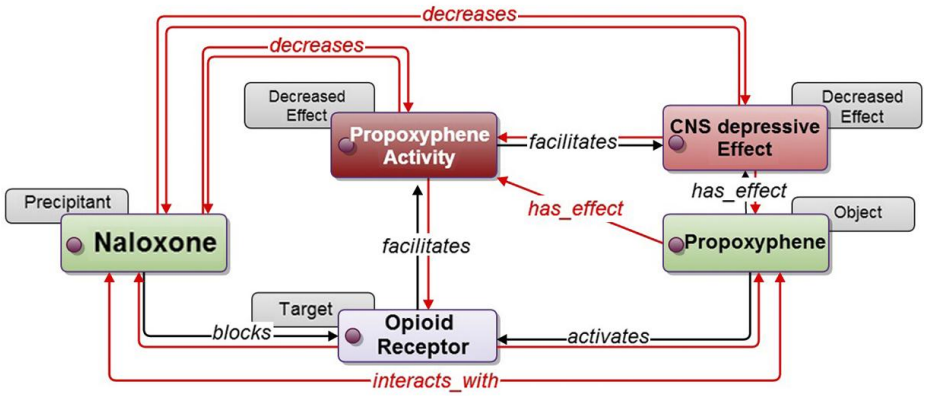

Fig. 5. DDI between Naloxone and Propoxyphene. Black arrows are the established relationships; red arrows are the inferred relationships and grey boxes are the inferred classifications for the individuals.

5 Conclusion

In this paper we have described a comprehensive ontology that represents all the information related to the domain of DDIs and their mechanisms. A DDI is a process involving two drugs, which occurs as the consequence of another process (called the mechanism), which is triggered by one of the drugs. As a result, the concentrations or effects of the second drug are altered. The consequence for a specific patient will depend on different factors. These include patient related factors, such as the age, diseases, or genetic factors, and drug related factors, for example, mode of action, toxicity, dosage or administration mechanism route. The clinical relevance or significance of a DDI is related to the type and magnitude of the effect, and is defined by several different factors [6]. These include the documentation about the DDI, including the types of studies, the subjects where it has been observed, the onset of apparition of the effects and its severity.

Depending on all these aspects, different procedures allow to prevent or reduce the undesirable effect of a DDI, such as avoiding the co-administration of both drugs, monitoring the patient for the early detection of an effect due to the DDI, or the adjustment of the dosage of one or both interacting drugs.

An important aspect in DINTO is the classification of drugs into different groups. Authors describing DDIs usually refer to a DDI as an interaction between an individual drug and a group of drugs or between two groups of drugs [16], [17]. During the analysis of the DDI Corpus it was observed that, usually, the selected characteristic for the group of drugs described suggests relevant information about some aspect of the DDI, such as its effect. Therefore, the inclusion of different classifications of drugs will be fundamental to the improvement of DINTO. Some interesting classifications for this purpose are the previously mentioned FTC or the ongoing project ADRM [18], which will allow the classification of drugs according to their adverse effects.

We are working to follow the OBO Foundry principles. All the entities in the ontology have numerical identifiers. In future work we plan to map to BFO as our upper ontology. The relevant information found in the related ontologies and included in our conceptual models will be imported. Finally, we will evaluate the ontology for prediction of DDIs on the basis of their mechanisms and for the application of text mining from pharmacological texts, although we anticipate that it may find additional use amongst domain experts once it is further developed.

The ontology described in this work is available at https://code.google.com/p/dinto/.

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