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DINTO: Using OWL Ontologies and SWRL Rules to Infer Drug–Drug Interactions and Their Mechanisms

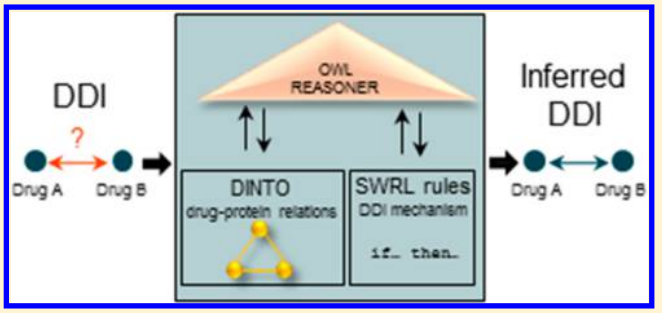
María Herrero-Zazo,*[,†] Isabel Segura-Bedmar,[†] Janna Hastings,[‡] and Paloma Martínez[†]

[†]Department of Computer Science, Universidad Carlos III de Madrid, Leganés 28911, Madrid, Spain

[‡]Cheminformatics and Metabolism, European Bioinformatics Institute (EMBL-EBI), Hinxton, CB10 1SD, U.K.

Supporting Information

ABSTRACT: The early detection of drug–drug interactions (DDIs) is limited by the diffuse spread of DDI information in heterogeneous sources. Computational methods promise to play a key role in the identification and explanation of DDIs on a large scale. However, such methods rely on the availability of computable representations describing the relevant domain knowledge. Current modeling efforts have focused on partial and shallow representations of the DDI domain, failing to adequately support computational inference and discovery applications. In this paper, we describe a comprehensive ontology for DDI knowledge (DINTO), which is the first formal representation of different types of DDIs and their mechanisms and its application in the prediction of DDIs. This project has been developed using currently available semantic web technologies, standards, and tools, and we have demonstrated that the combination of drug-related facts in DINTO and Semantic Web Rule Language (SWRL) rules can be used to infer DDIs and their different mechanisms on a large scale. The ontology is available from https://code.google.com/p/dinto/.



INTRODUCTION

Early detection of drug–drug interactions (DDIs) is crucial to ensure patient safety and to avoid increases in healthcare costs.[1] There are different databases supporting healthcare professionals in the detection of DDIs. However, their quality is very uneven, the consistency of their content is limited,[2] and they do not scale sufficiently in accordance with the growth in pharmacovigilance literature.[3] In addition, large amounts of valuable information are hidden in published articles, scientific journals, books, and technical reports.[4] Thus, the large number of DDI information sources has overwhelmed most healthcare professionals, and it is no longer possible to remain up to date on everything published about DDIs.

Computational methods can play a key role in the identification, explanation, and prediction of DDIs on a large scale, since they can be used to collect, analyze, and manipulate large amounts of biological and pharmacological data.[5] However, these methods rely on the availability of computable representations of DDI knowledge, which describe the general domain knowledge and can be understood and exploited by information systems.[6]

During the last years, different research groups have attempted the formal representation of the DDI domain. However, these efforts have been carried out independently and focus on partial[7−9]—detailed representations of one specific aspect of the domain—or shallow[10,11]—global representation trying to include all relevant aspects, but with a low level of detail—representations of the domain. For example, while the Drug Interactions Ontology (DIO) focuses on the representation of the drug–biomolecule interactions leading to certain types of DDIs,[9] the model created by Mille et al. attempted a global representation of the domain, including concepts such as "DDI effect" or "mechanism", but excluding the description of the different processes leading to DDIs.[10] These models have been implemented using different formalisms or languages, such as first order logic (FOL),[7] the eXtensible Markup Language (XML),[10] or the World Wide Web Consortium (W3C) standard Web Ontology Language (OWL).[9,11,12] Reuse and integration of these different formalisms in a unique framework is a challenging task. As a consequence, there is a lack of a comprehensive representation of the DDI domain suitable for computational applications.

In spite of these issues, these projects have established several proof-of-concepts of the role and usefulness that formal representations of the DDI domain can have in different applications, and specifically on natural language processing (NLP) of pharmacological texts[10,12,13] and prediction of DDIs.[8,14,15] For example, Rubrichi and Quaglini[11] used a representation of the DDI domain to annotate a set of documents for the training and testing of an information extraction (IE) system, while the Pharmacodynamics Ontology representation framework was used to predict DDIs occurring via a pharmacodynamic mechanism.[8] Both NLP of pharmacological texts and prediction of DDIs are relevant and promising

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research areas for the management of DDIs and have attracted a great deal of attention in recent years.

On the one hand, NLP techniques can be used to retrieve and extract DDI information from text, supporting researchers and healthcare professionals in searching DDI information. The last SemEval-2013 DDIExtraction challenge[16]—aimed to promote the development of IE techniques for the detection of DDIs from texts—demonstrated the growing interest of the NLP community on this field, showing important advances since the previous edition in 2011.[17]

On the other hand, computational inference of DDIs might be applied to the development of clinical decision support systems (CDDS)[18] or signal detection in pharmacovigilance.[19] Different approaches have been proposed: (i) extrapolation of in vitro data to the in vivo situation;[20] (ii) similarity-based methods[21] and adverse drug reactions (ADR) data mining;[22] (iii) text mining of scientific literature;[23,24] and (iv) pharmacological knowledge representation and reasoning.

The last approach relies on a formal representation of the DDI domain that, in combination with a reasoning engine, can be used to infer DDIs. It can be divided into two main subtypes: those using semantic networks and those based on description logics (DLs) representations and/or rules. Semantic networks represent drugs as nodes and interactions between drugs as edges, and have been used to infer DDIs between other drugs through reasoning.[25,26] Recently, there is an increasing interest in more expressive representation formalisms capable of supporting additional inferences, which have proven to be useful to predict DDIs on the basis of their underlying mechanisms.[8,14,15,24,27] However, none of the existing projects have dealt with the inference of DDIs occurring by different mechanisms within the same framework. DDIs are broadly classified into two main groups with respect to their mechanisms: pharmacokinetic (PK) and pharmacodynamic (PD) DDIs. A PK DDI occurs when one drug affects the levels of another drug in the body, while a PD DDI occurs when one drug alters the effects of another drug without altering its concentration. While only one project dealt with the representation and prediction of PD DDIs,[8] the remaining projects focused on PK DDIs[14,15,24,27] and specifically on metabolism-related DDIs.

Moreover, the number of predicted DDIs has ranged from a couple of pairs[14] to less than 1000,[24] while commonly used DDI information compendia include over 2500 DDIs.[28] The reason for this low coverage is that these projects require not only a formal representation of the domain but additionally the following: (i) the storage of large amounts of structured information; (ii) a formal and highly expressive representation of complex processes; and (iii) powerful inference capabilities to apply machine reasoning to large amounts of semantic data. Semantic web technologies, and specifically ontological engineering, can provide the techniques and tools necessary to overcome these issues.[29] The semantic web has been postulated as the solution for data integration over disparate biomedical domains,[30] supported by standards such as OWL[31] and its extension SWRL.[32−34]

In this framework, we propose the creation of a comprehensive ontology for drug−drug interactions knowledge, DINTO, a resource designed to be used by the computational community working on applications within the DDI domain. In this paper, we describe the ontology and evaluate its performance in inferring different types of DDIs in a unique representational framework. Indeed, an important contribution of our work is that we address the representation of different types of mechanisms leading to both PK and PD DDIs, instead of focusing on a specific DDI mechanism. Moreover, for the entire application we exclusively harness the resources and tools of the semantic web and the ontology engineering field, providing, in addition, a novel framework for the assessment of their current usefulness and limitations in this type of project.

METHODS

Drug−Drug Interactions Ontology: DINTO. DINTO is a comprehensive ontology that systematically organizes all DDI related knowledge and the first formal representation that includes a wide range of DDI mechanisms, including both PD and PK mechanism types. It has been developed following the Neon methodology for ontology development[35] and the principles recommended by the OBO Foundry,[36] a collaborative effort for the integrated development and maintenance of biomedical ontologies. The main resource used to capture the knowledge of the domain has been the DDI corpus, a set of annotated texts from different sources describing DDIs.[37] DINTO has been created to be useful in several applications, and has been applied to different NLP tasks.[38]

The conceptual model (CM) in DINTO has been constructed using an iterative process to include all relevant entities and processes (represented as classes) and the relationships (object properties) that form the DDI domain. Figure 1 shows a simplified version of the CM, which has been implemented using the Web Ontology Language 2 (OWL 2)[31] using the Protégé tool.[39]

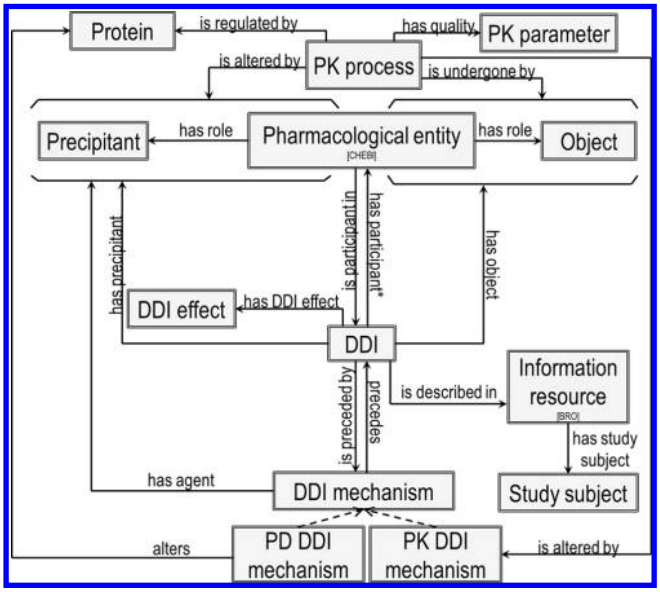

Figure 1. Summarized version of the conceptual model in DINTO.

The main premise that has driven the development of this ontology is the reuse of relevant information currently available in other ontologies or information resources. Pharmacological entities or drugs have been imported from the ChEBI ontology,[40] an ontology for small chemical entities that includes many drugs and their biological roles. The different relationships between them and proteins, such as '*inhibits*' or '*metabolizes*', have been imported from the database DrugBank, which combines chemical and pharmaceutical information for

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approximately 4900 pharmacological substances.[41] Besides relationships between drugs and proteins, this database includes information about DDIs and their mechanisms, which have also been imported to DINTO. In addition to this, the last version of the ontology DINTO 1.2 includes also adverse drug reactions (ADRs) imported from the Ontology of Adverse Events (OAE)[42] and their relationships to drugs from the database SIDER.[43]

DDIs are represented in two different ways in our ontology: classes and relationships between classes. For example, the interaction between the pharmacological entities '*desvenlafaxine*' and '*amitryptyline*' is represented as the class '*desvenlafaxine/amitriptyline DDI*', which represents the process that occurs when the two drugs interact. On the other hand, both classes '*desvenlafaxine*' and '*amitryptyline*' are related through the symmetric relationship '*may interact with*', which represents the possible interaction of '*amitryptyline*' with '*desvenlafaxine*' and vice versa. In addition to specific DDIs between pharmacological entities, the ontology includes a classification of DDIs on the basis of their clinical relevance, type of consequence or effect, and preceding mechanisms (Figure 2).

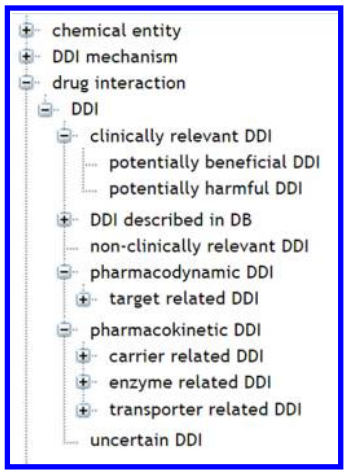

Figure 2. Different types of DDIs in DINTO (viewed in the BioPortal website).[44]

The last one is especially important, since it allows the classification of DDIs on the basis of their mechanism. In this way, the relations between different types of DDIs and their mechanisms are represented in DINTO through OWL definitional axioms. They establish that classes preceded by a PD DDI mechanism belong to the class '*pharmacodynamic DDI*', while classes preceded by a PK DDI mechanism are '*pharmacokinetic DDI*' classes. In other words, any individual of the '*pharmacodynamic DDI*' class is equivalent to (≡) any individual that has a '*is preceded by*' relationship with at least one (*some*) individual of the class '*pharmacodynamic DDI mechanism*'.

'*pharmacodynamic DDI*' ≡ '*is preceded by*'*some* '*pharmacodynamic DDI mechanism*'

'*pharmacokinetic DDI*' ≡ '*is preceded by*'*some* '*pharmacokinetic DDI mechanism*'

In a similar way, a more accurate classification of DDIs, following the hierarchies shown in Figure 3, is represented in the ontology.

The last released version (DINTO 1.2) includes 28 178 classes (of which 11 555 are DDIs and 8786 are pharmacological entities) and 161 properties of which 73 are object properties or relationships between classes (e.g., '*may interact with*'), 17 are datatype properties, or relationships between a class and data value (e.g., '*has concentration*'), and 71 are annotation properties that provide additional information for classes or other properties (e.g., '*synonym*'). From the total number of classes, 11732 have a definition in natural language, while 11 587 include OWL definitional axioms.

To ensure the quality of the ontology, we have performed a technical evaluation by checking its adherence to a set of predefined criteria, standards, or requirements adopted from the three main research efforts defining the desirable characteristics for reusable and high quality ontologies.[36,45,46] Their recommendations have been summarized in a template used as a guide during the development of DINTO and as a checklist for the evaluation of the final ontology, as it is shown in Supporting Information 1.

Rules for Inference of DDIs. To infer DDIs on the basis of their pharmacological mechanisms, it is necessary to represent the biological processes leading to their occurrence. These are complex processes requiring a formal and expressive representation.

A first approach consisted in the creation of different property chains describing the relationship '*may interact with*'. Property chains are a feature in OWL 2 used to infer a single property based on the existence of several other properties. Through the use of these chained properties, we could represent ordered pharmacological events.[47] However, in our prior work, the examples we used represented only two drugs per event at the individual level. The extension of this approach to a version including a larger number of individuals and their relationships led to incorrect inferences. We identified two main reasons for this.

First, drug−protein relationships, such as that '*ciprofloxacin*' '*inhibits*' the activity of '*CYP450 3A4*', are imported from the database DrugBank into DINTO and used in property chains. However, drugs can have several relationships with the same protein. For example, the pharmacological entity '*droperidol*' imports the relationships '*has pharmacological target*' and '*blocks*' with the protein entity '*alpha-1a adrenergic receptor*'. Therefore, the property chain '*has pharmacological target*' and '*blocks*' → '*may interact with*' led to the inference that '*droperidol*' may interact with itself.

Second, we observed that the type of DDI, such as '*enzymatic inhibition DDI*', was inferred when one of the two drugs involved in the DDI has a relationship '*inhibits*' with some enzyme, without requiring the other interacting drug to have any relationship with the same enzyme. Therefore, property chains provide limited expressivity to represent the concomitant circumstances leading to DDIs. As a result, we concluded that the inference of DDIs between multiple entities by representing pharmacological mechanisms as property chains is not appropriate.

As an alternative, we decide to create rules representing DDI mechanisms and use them to infer new '*may interact with*' relationships. Boyce et al.[7] demonstrated that a set of rules in first-order logic could represent how one drug alters the metabolism of another drug. The same PK DDI mechanism was represented by Tari et al.[24] and Moitra et al.[27] using the logic programming language ASP.[48] However, logic programming has not been designed as an ontology language for direct

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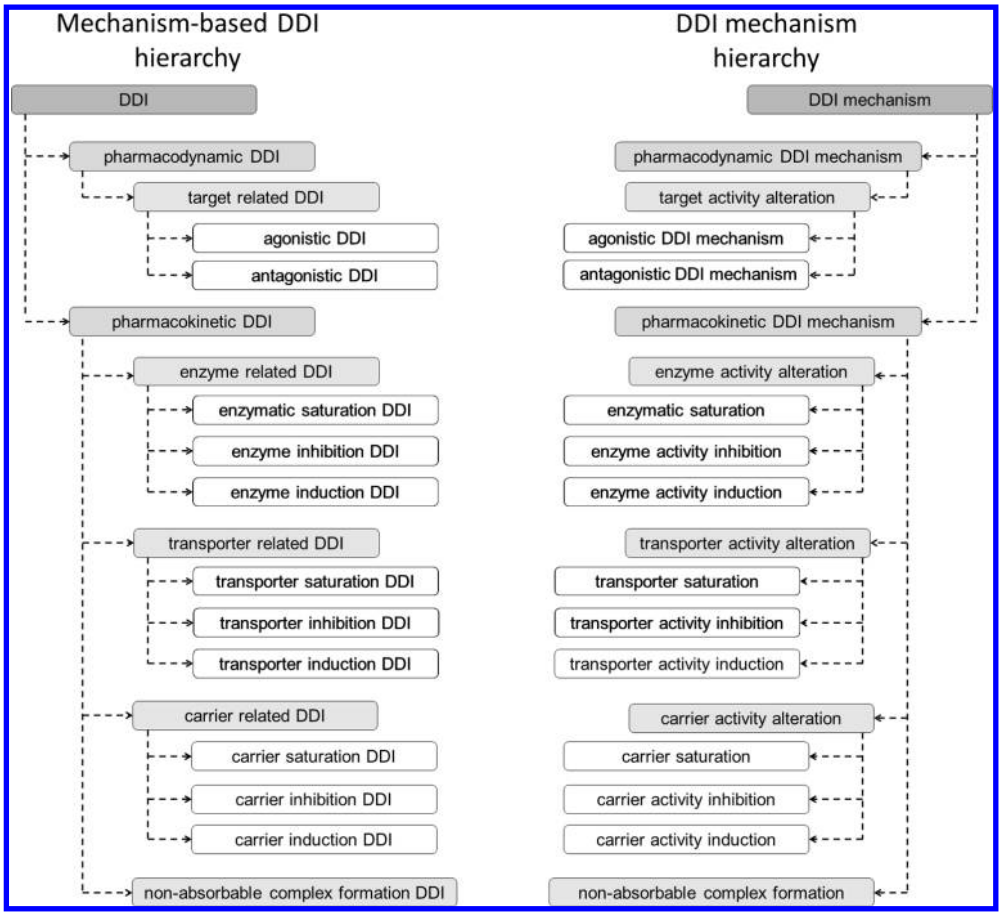

Figure 3. DDI and DDI mechanism hierarchies in DINTO.

interchange of knowledge, which hinders interoperability with the remainder of the semantic web and ontologies.[49] In contrast, in our approach we use SWRL, an expressive OWL-based rule language.

SWRL rules are written as antecedent-consequent pairs. For example, the rule below establishes that if one pharmacological entity (*?other_y*) inhibits the activity of an enzyme (*?z*), which metabolizes another pharmacological entity (*?y*), then there is an interaction between the two pharmacological entities *?other_y* and *?y*. Since SWRL adopts OWL's open world assumption (OWA)—or the assumption that what is not known to be true is unknown but not necessarily false[50]—it is not straightforward to assume that two individuals are automatically distinct if they have different names. Therefore, it is necessary to include the *differentFrom* atom, which determines that the variables *?other_y* and *?y* do not refer to the same underlying individual.

```
inhibits(?other_y, ?z), metabolizes(?z, ?y), DifferentFrom (?other_y, ?y)
-> 'may interact with'(?other_y, ?y)
```

In this project, we have created two main groups of SWRL rules representing protein-related DDI mechanisms. The first one formalizes different types of DDI mechanisms, including both PD and PK mechanisms, in a set of rules inferring new '*may interact with*' relationships. The rule used as example above belongs to this group. The second group of rules assigns a specific type to a DDI on the basis of its mechanism, represented through drug−protein relationships, including the different target, enzyme, carrier, or transporter-related DDIs, and their subtypes (Figure 3). An example of one of these rules describing an interaction occurring by antagonism between two drugs is represented below.

```
'has participant'(?x, ?other_y), 'has participant'(?x, ?y), 'is inhibited
by'(?z, ?y), activates(?other_y, ?z), DifferentFrom (?y, ?other_y) ->
'antagonistic DDI'(?x)
```

Although DDIs occurring by the alteration in the activity of a protein involved in the pharmacokinetics or pharmacodynamics of the interacting drugs are most commonly described in the literature, there are other mechanisms that can lead to severe DDIs. For example, coadministration of two different drugs that prolong the QT interval, such as amiodarone and disopyramide, can lead to additive effects and finally produce a ventricular tachycardia known as *torsade de pointes*.[28] To represent this type of mechanism caused by the addition of an ADR, we create the SWRL rule shown below.

```
'pharmacological entity'(?y), 'pharmacological entity'(?other_y), 'adverse
effect'(?e), 'has effect'(?y, ?e), 'has effect'(?other_y, ?e),
DifferentFrom (?other_y, ?y) -> 'may interact with'(?y, ?ohter_y)
```

In this rule we have included a more exhaustive representation of the domain—by establishing the class to which each individual belongs—to study if this information could be added to the rules while still obtaining correct inferences. In this way, variables *?y* and *?other_y* are described to belong to the '*pharmacological entity*' class, while *?e* is defined as an '*adverse effect*'. This information is not necessary to obtain the inferences in the experiments described in this paper,

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Table 1. Classification of DDIs on the Basis of Their Asserted Mechanisms

type of DDI	description	no.
PK DDI	DDI classified to occur through any pharmacokinetic mechanism	5711
PD DDI	DDI classified to occur through any pharmacodynamic mechanism	1101
PK DDI + PD DDI	DDI classified to occur through both pharmacokinetic and pharmacodynamic mechanisms	659
enzyme related DDI	DDI classified to occur as a consequence of the alteration of the activity of an enzyme	5283
transporter related DDI	DDI classified to occur as a consequence of the alteration of the activity of a transporter	1673
nonabsorbable complex formation DDI	DDI classified to occur as a consequence of the formation of nonabsorbable complexes	128
enzyme related + transporter related DDI	DDI classified to occur as a consequence of both the alteration of the activity of an enzyme and the alteration of the activity of a transporter	1367
enzyme related + target related DDI	DDI classified to occur as a consequence of both the alteration of the activity of an enzyme and the alteration of the activity of a target	631
enzyme related + transporter related + target related DDI	DDI classified to occur as a consequence of the alteration of the activity of an enzyme, the alteration of the activity of a transporter, and the alteration of the activity of a target	140
transporter related + target related DDI	DDI classified to occur as a consequence of both the alteration of the activity of a transporter and the alteration of the activity of a target	166
unclassified DDI	DDI that has not been classified on the basis of its known mechanisms	6061

because in the reduced versions described below the relationships define each concept. For example, the relationship '*inhibits*' is established only between a '*pharmacological entity*' and a '*protein entity*' in DINTO. Therefore, in the assertion 'inhibits(?other_y, ?z)" *?other_y* is a '*pharmacological entity*' and *?z* is a '*protein entity*'. Therefore, we could obtain the desired inferences keeping the rules as simple as possible. However, this information could be useful in the future, when the CM in DINTO will become more complex, and the same relationship could be established between different entity types.

INFERENCE EXPERIMENTS

In this section, we describe four experiments performed to evaluate the inference capabilities of DINTO alone and in combination with SWRL rules. In the first experiment (*IExp1*), we analyze how a reasoner classifies known DDIs by using only explicit information about their mechanisms. The aim is to check if the information explicitly represented in the ontology is consistent, and if the relationships established between DDIs and their mechanisms allows for their correct classification. However, inferences that are more complex rely on the formal representation of DDI mechanisms. Therefore, in the second experiment (*IExp2*) we validate if the combination of the first set of SWRL rules and drug−protein relationships in DINTO can be used to infer new DDIs. In the third experiment (*IExp3*) we combine the second set of rules to infer both, DDIs and their mechanisms. With this third experiment, we validate if the formal representation of DDI mechanisms by means of drug−protein relationships can be used to identify automatically the underlying mechanism of a DDI. Finally, in the fourth experiment (*IExp4*) we use the relationships between drugs and their known adverse effects and a SWRL rule to infer DDIs due to the addition of ADRs.

To accomplish the machine reasoning tasks, we aimed to use publicly available ontology reasoner engines, including FacT++,[51] Pellet,[52] and HermiT.[53] These three support the features of OWL 2, although only Pellet and HermiT support SWRL rules. However, the performance of these reasoner engines is compromised in the case of very large and complex ontologies,[54] and as of yet unfortunately, none of them is able to process the whole version of DINTO. Therefore, we adopt different strategies to simplify the ontology while maintaining the information that is necessary to retrieve the desired inferences. In the end, we found that only HermiT 1.3.8 can perform reasoning on the reduced version of DINTO combined with the inference rules.

***IEXP1*: Classification of DDIs on the Basis of Their Asserted Mechanisms.** The objective of this experiment is to evaluate if the ontology is consistent when classifying DDIs imported from DrugBank on the basis of their asserted (or explicitly represented) mechanisms as PK or PD DDIs.

DINTO includes a total of 11 555 classes representing DDIs that have been imported from the database DrugBank. Information about their mechanisms ('*target activity alteration*', '*enzyme activity alteration*', '*transporter activity alteration*,' or '*nonabsorbable complex formation*') has been also imported when it is provided by the original source. Therefore, the OWL definitional axioms relating DDIs and their mechanisms included in the ontology allow the classification of different types of DDIs based on this information.

To perform this reasoning task, we reduce the size of the ontology while maintaining all the DDIs imported from DrugBank and their mechanisms. This reduced version of DINTO includes only the top classes '*DDI mechanism*' and '*drug interaction*' and their subclasses. When leveraging a reasoner, we obtain an inferred classification of DDIs on the basis of their asserted mechanisms.

We use the reasoner engines HermiT 1.3.8 and FacT ++ to classify the ontology, which detect any inconsistency. A total of 1101 DDI classes are classified as PD DDIs, while 5711 are classified as PK DDIs. It is important to note that some DDIs are described in DrugBank to be preceded by both a PK DDI mechanism and a PD DDI mechanism. For example, the interaction between '*didanosine*' and '*zalcitabine*' is preceded by a '*target activity alteration*' and a '*transporter activity alteration*'. Therefore, the class '*didanosine/zalcitabine DDI*' is classified as both PD and PK DDI. This information is correct from a pharmacological perspective since, although most DDIs are frequently assigned a type PK DDI or PD DDI, there are cases where both mechanisms can lead to the occurrence of DDIs.[28] In the same way, a DDI can be classified at the same time as two different subtypes of PK DDIs (e.g., '*transporter related DDI*' and '*enzyme related DDI*'). Finally, 128 DDIs are classified as '*nonabsorbable complex formation DDI*' while 6061 DDIs, for which any asserted mechanism is described in DrugBank, have not been classified. These results are shown in Table 1.

***IEXP2*: Inference of New DDIs Due to a Protein-Related Mechanism.** The aim of this experiment is to test if

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the information included in DINTO in the form of drug−protein relationships can be combined with SWRL rules to infer new DDIs. To do this, we create a reduced version of the ontology containing only 426 pharmacological entities (corresponding to those mentioned in the DDI corpus), and 752 protein entities having at least one relationship with any of the included drugs. Inferences from SWRL rules are made in the ABox, that is, using assertions at the individual level. Therefore, the second step is to automatically create individuals for every class—'*pharmacological entity*' and '*protein entity*' subclasses—and the corresponding relationships among them. Due to the OWA, we asserted that all the individuals are distinct from one another using the functionality provided by Protégé. In the final step, we import the 59 SWRL rules into this reduced version of DINTO and execute the reasoner.

A total of 21 560 '*may interact with*' relationships between two pharmacological entities are inferred, which are automatically imported to the corresponding class level leading to 10 780 new DDI classes of the type '*drugA/drugB DDI*'. To evaluate the results of this experiment, we compare the inferred DDIs (from now on named the inferred set *I*) with all those DDIs described in DrugBank involving some of the 426 drugs included in the ontology (the asserted set *A*). Therefore, the *I* set consists of 10 780 inferred DDIs, while the *A* set includes 2245 asserted DDIs. There is a total of 656 DDIs common to both sets, which means that the 29% of the DDIs in DrugBank have been inferred in DINTO. These results are summarized in Table 2.

Table 2. Number of DDIs in the Inferred (*I*) and Asserted (*A*) Sets for 426 Drugs

type of DDIs according to the description source (DINTO or DrugBank)	no.
DDIs inferred in DINTO (*I* set)	10 780
DDIs described in DrugBank (*A* set)	2245
DDIs inferred in DINTO but not described in DrugBank	10 124
DDIs described in DrugBank but not inferred in DINTO	1589
DDIs inferred in DINTO and described in DrugBank (coincidences)	**656**

We compare, as well, coincidences between the drugs involved on the DDIs in the *I* and *A* sets. From the 426 drugs included in the experiment, only 219 participate in at least one inferred DDI, while only 309 drugs are involved in at least one asserted DDI. Specifically, there are 172 common to both sets. Therefore, we can consider them as drugs correctly described to participate in at least one DDI (*true positive drugs*). Furthermore, there are 70 drugs that are not included in either of the two sets. They represent those drugs for which any interaction has been incorrectly inferred (*true negative drugs*). Finally, 47 drugs are involved in at least one inferred DDI only, while 137 drugs participate in at least one asserted DDI only. The former can be considered as false positives—i.e., drugs for which at least one DDI has been incorrectly inferred—and the latter as false negative drugs—i.e., drugs for which at least one DDI has not been correctly inferred (Table 3).

For a detailed analysis of such a large number of inferences, we focus our evaluation on those DDIs involving the same drugs in both sets. In this case, the new inferred set *I2*, generated by considering the subset of *I*, consists of 7039 inferred DDIs, while the new asserted set *A2* consists of 815 asserted DDIs. The number of common DDIs in both sets is

Table 3. Comparison of the Number of Drugs in the Inferred (*I*) and Asserted (*A*) Sets

coincidence of drugs	interpretation	no.	%
drugs coincident in both sets (*true positives*)	drugs correctly described to participate in at least one DDI	**172**	40.38
drugs not present in any of the sets (*true negatives*)	drugs for which any interaction has been incorrectly inferred	70	16.43
drugs only in the inferred set *I* (*false positives*)	drugs for which at least one DDI has been incorrectly inferred	47	11.03
drugs only in the asserted set *A* (*false negatives*)	drugs for which at least one DDI has not been correctly inferred	137	32.16
total		**426**	100

the same (656 DDIs), meaning that 80% of the DDIs in *A2* have been correctly inferred. The remaining 20% represents the *false negative DDIs*, or those DDIs in *A2* that have not been inferred by our method (159 DDIs). On the contrary, those inferred DDIs that are not included in *A2* represent the *false positive DDIs* (Table 4).

Table 4. Number of DDIs in the Inferred (*I2*) and Asserted (*A2*) Sets for 172 Common Drugs

type of DDIs according to their description source (DINTO or DrugBank)	no.
DDIs inferred in DINTO (*I2*)	7039
DDIs described in DrugBank (*A2*)	815
DDIs inferred in DINTO but not described in DrugBank	6383
DDIs described in DrugBank but not inferred in DINTO	159
DDIs inferred in DINTO and described in DrugBank (coincidences)	**656**

To perform a qualitative analysis of these results, we randomly select and review 15 *false positive DDIs* and 10 *false negative DDIs*. Evidence supporting all the false positives is found, meaning that there is an underlying DDI mechanism, such as for example, that one of the drugs inhibits one or more of the metabolizing enzymes of the other drug. Regarding *false negatives*, we identify they correspond to DDIs occurring through mechanisms that cannot be represented on the basis of currently known drug−protein relationships, such as non-absorbable complex formation or additive ADR effects.

***IEXP3*: Inference of DDI Mechanisms.** In this experiment, we combine the information represented in the ontology with a second set of SWRL rules to infer both DDIs and their underlying mechanisms. First, we randomly select 93 DDIs imported to DINTO from DrugBank. This number ensures the correct performance of the experiment, while enabling the following manual review of the results. Then, we create a version of the ontology containing only those drugs involved in some of these DDIs (a total of 146 pharmacological entities), their related proteins, and the mentioned 93 DDIs. After that, we create the corresponding individuals and the relationships among them. Then, we delete the OWL definitional axioms describing the relationship between a DDI and its asserted mechanism, ensuring that the inferences are obtained only through the SWRL rules. We combine the reduced version of the ontology and the file containing the 59 SWRL rules before executing the reasoner HermiT 1.3.8.

Inferences obtained in this experiment are compared with the mechanism-based classification asserted in the DrugBank data set. The database uses data on drug−target, drug−enzyme, and

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drug−transporter associations to establish the "possible base DDI mechanism" for some of the DDIs.[55] This information is imported to DINTO as classes and relationships, and used, as shown in *IExp2*, to classify DDIs as '*target related DDI*', '*enzyme related DDI*', '*transporter related DDI*', or '*nonabsorbable mechanism formation DDI*'. Drug-carrier associations are not included for any DDI in the original source, and therefore, none of the DDIs imported from DrugBank are classified as '*carrier related DDI*'. In contrast to these five possible classifications of drugs in DrugBank, our 59 SWRL rules representing DDI mechanisms lead to 15 different possible classifications, with different levels of granularity (Figure 3).

We compare the inferred classification of the 93 DDIs with the classification of DDIs on the basis of DrugBank mechanisms. Due to the different granularity of both classifications, we consider that a DDI has compatible mechanisms in both sets if there is an exact coincidence in the type of protein(s) involved (target, enzyme, transporter, or carrier).

As shown in Table 5, most inferences correspond to this case (77%). During the analysis of these results, we observe that there are ten DDIs for which none mechanism is inferred. They correspond in DrugBank to DDIs occurring by '*nonabsorbable complex formation*' mechanisms, which, as mentioned before, is not included in our SWRL rules.

Table 5. Classification of DDIs on the Basis of Their Asserted (Known) Mechanisms

classification of DDIs in *IExp3*	no.	%
DDIs with compatible mechanisms in DrugBank and DINTO	72	77.42
DDIs with additional mechanisms in the *A* set (DrugBank)	7	7.53
DDIs with additional mechanisms in the *I* set (DINTO)	3	3.22
DDIs with any coincident mechanism in both sets	1	1.08
DDIs classified in DrugBank to occur via *nonabsorbable complex formation*	10	10.75

For other seven DDIs, DrugBank establishes an additional mechanism that is not inferred in DINTO. All of them have in common that both interacting drugs have a relationship '*induces*' or '*inhibits*' with the same protein and, as a consequence, a DDI is established between them in DrugBank. However, SWRL rules describing these patterns have not been created in DINTO since, from a pharmacological point of view, it would not be correct to infer that this situation leads to a DDI. For example, the two drugs '*midodrine*' and '*dexamethasone*' inhibit the activity of the enzyme '*Cytochrome P450 2D6*' (CYP2D6). From this information, DrugBank establishes that there could be a possible enzyme-based interaction between them. However, this assumption is incorrect, since this interaction can occur only if this enzyme is involved in the metabolism or activity of one of the two drugs—or their metabolites. If this is not the case, both drugs alter the activity of the enzyme, but their activities or concentrations are not modified. Since no other relationship is described in DrugBank between CYP2D6 and the drugs, we cannot establish that this is the mechanism of interaction between them. Therefore, a DDI should not be established when the information available is only that two drugs induce and/or inhibit the same protein.

In contrast to this, there are three DDIs with an additional mechanism in the inferred set in comparison with the asserted set, due to their classification as '*carrier related DDI*'. Finally, there is one DDI without any coincident mechanism in both sets. In this case, both previously mentioned reasons for discrepancy are involved. The complete list of DDIs and their inferred and asserted classifications are available in Supporting Information 2.

***IEXP4*: Inference of New DDIs by the Addition of an ADR.** Previous experiments focus on the inference of DDIs due to the alteration of the activity of a protein involved in the pharmacokinetics or pharmacodynamics of the interacting drugs. In contrast, the aim of this experiment is to test if the information included in DINTO in the form of drug−ADR relationships can be combined with a SWRL rule to infer new DDIs. To do this, we create a reduced version of the ontology and select 11 severe ADRs (3 affecting the hematopoietic system; 3 affecting the cardiovascular system; 3 affecting the central nervous system; 1 affecting musculoskeletal and connective tissue; and 1 affecting multiple systems). We select then three drugs related to at least one of the selected ADRs, leading to a final number of 33 drugs included in the reduced version (Supporting Information 3). As in previous experiments, we create individuals for every class and the corresponding relationships among them, and import the SWRL rule created to infer new '*may interact with*' relationships. The reasoner HermiT classifies the reduced version in less than 50 s, and we obtain a total of 436 new DDIs.

In contrast to previous experiments, we cannot automatically compare the inferred results and the DDIs included in DrugBank because they are not labeled to occur by the addition of an ADR in this—or another—database. We perform a manual comparison to the database DrugBank and the DDI compendium Stockley's Drug Interaction[28] to manually check if the inferred DDIs are described to interact by the addition of an ADR. Results show that the number of DDIs specifically described to occur by the inferred mechanism is 16 for the database and nine for the compendium. It is important to note that the global number of coincidences is higher in both sources, especially in Stockley's. However, most of them are described to occur via a PK mechanism, and not by the addition of an ADR. Previous studies observed that most information about DDIs refers to PK DDIs, in part because these PK studies are usually performed as a requirement for the authorization of a new drug in the market.[56] However, some DDIs occur not by a single mechanism, but often by two or more mechanisms acting in concert.[28] For example, it has been observed that extrapyramidal symptoms might be developed when patients in treatment with fluoxetine are prescribed risperidone or other antipsychotics. The reasons are not understood, but most of them appear to be an exaggeration of the side-effects of the other drugs caused by fluoxetine, perhaps due to inhibition of their metabolism, or possibly additive with the effects of fluoxetine.[28] Although in this case the information source mentions the possible contribution of both mechanisms, it is not possible to know the real impact of the mechanisms inferred in this experiment in the occurrence of the DDIs.

DISCUSSION AND CONCLUSIONS

In this study, we have demonstrated that the use of the semantic web standard languages OWL and SWRL support the formal representation of complex pharmacological knowledge. In addition, we have demonstrated that the combination of drug-related facts in our ontology and inference rules representing different DDI mechanisms can be used to infer DDIs and their mechanisms in a larger scale than previous projects.[8,14,15,24,27]

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DDIs and their underlying mechanisms are complex pharmacological processes, and their conceptualization and implementation require an expressive representation language. Despite the richness of OWL's set of relational properties, its expressivity does not allow the expression of all possibilities for object relationships.[54] Indeed, we have observed that the use of advanced OWL 2 features, such as property chains, is not adequate for the consistent representation of this knowledge. However, this limitation can be overcome by the combination of an OWL ontology with inference rules. In this work, we have demonstrated that the standard language SWRL is adequate to represent different types and subtypes of DDI mechanisms in a unique framework, while, in contrast to programming languages used by former efforts,[24,27] ensuring interoperability between ontologies.

Moreover, these rules have been successfully applied to the inference of DDIs. Previous work in this domain had concluded that OWL-DL was not suitable for the detection of DDIs, and that it should be used only for ontology consistency checking.[57] However, in this paper we have shown that DLs formalisms can be successfully used for the inference of DDIs by means of combining drug-related facts as an OWL ontology and DDI mechanisms as SWRL rules.

The bottleneck in this process has been, however, the limited performance of ontology reasoning engines with very large and complex ontologies. None of the most popular OWL reasoners could process a whole version of DINTO. Therefore, following prior experiences of similar projects,[54] we had to reduce the size and complexity of our ontology. Reasoner engines are very important tools in semantic web technologies and ontological engineering, because they support not only ontology consistency checking, but also the inference and extraction of new knowledge.[58] Therefore, there has been much interest in the development of new and better reasoning engines. Many of them are publicly available, and there are different plugins that can be used to incorporate them into ontology editors such as Protégé. Moreover, some available reasoner engines have proven to be useful with very large ontologies, such as SNOMED CT.[59] For all these reasons, we chose reasoning engines that implement APIs in Protegé platform as the best option to perform our inference experiments based on DINTO. However, in spite of their benefits, the performance of these tools with ontologies containing a large number of individuals remains difficult.[58] Since inferences from SWRL rules are made at the individual level, our ontology became challenging for available reasoners, which represented the main limitation in this study. However, ontology technology is progressing rapidly and is an active area of ongoing research in recent years.[60,61] Indeed, since 2012 developers and users of OWL reasoners have the opportunity to compare and promote their systems in the annual OWL Reasoner Evaluation (ORE) workshop,[62] where they present new or enhanced systems and use them in a competition for the processing of challenging ontologies. To contribute to the development of robust and scalable reasoner engines, we have submitted DINTO as one of these challenging ontologies for the ORE 2015 edition.

In spite of this limitation, we have achieved the largest coverage for drugs included in a DDI inference experiment. The closest project, which combined NLP with formal knowledge representation and reasoning,[24] could test the inference system on a smaller number of drugs (295 drugs against the 426 included in our experiment). The main reason for the low coverage of the other projects is that they relied on manual curation to identify, gather, and structure the drug-related facts required as basic information to infer the DDIs. Although expert manual curation provides high quality information, this activity is both cost-intensive and time-consuming. Moreover, new pharmacological information is discovered and published every day in the scientific literature, which makes keeping a knowledge base up to date with this information a difficult task. To overcome these issues, we have designed a CM for DINTO that reuses and integrates information currently available in public information resources, such as pharmacological entities and their roles from the ChEBI ontology, ADRs from the OAE, drug−protein relationships and DDIs from the database DrugBank, drug−ADR relationships from the SIDER database, among many others.[63] With this approach, the development and evolution of the ontology is driven by the conjunction of both the requirements of the final application and the information available to be imported into the ontology. These resources are created, maintained, and updated by expert teams that review the scientific literature as the source of their information. Therefore, reusing them is the best way to include and integrate large amounts of pharmacological data in a unique representation framework, avoiding duplicate work within the limitations of manual curation procedures. To the best of our knowledge, there is no other ontology or information resource that combines DDI-related information from such a disparate number of resources, representing them in a unique representation framework and in a comprehensive way, as it is in DINTO. However, ontologies need to be updated, too. Since the information resources integrated in DINTO are differently updated (e.g., the ChEBI ontology is updated monthly, while DrugBank or SIDER have been updated every three years, approximately), we plan to release an annual updated version of DINTO, which will include the latest available versions of every information resource included in the ontology. With this strategy, we will provide an updated information resource that includes a large amount of pharmacological data curated by different expert teams.

The inference experiments performed in this study show that DINTO is a correct and comprehensive ontology for the DDI domain. While other ontologies have focused on the separate representation of PK[14,15,27] and PD[8] DDI mechanisms, DINTO is the first resource representing both of these in the same framework. Moreover, previous work has addressed only the representation of one specific subtype of PK DDIs: the alteration in drug metabolism. In contrast to this, we have represented different subtypes of PK and PD DDI mechanisms, leading to the most detailed formal description of these processes yet available.

Evaluation of the inferences obtained in the experiments has been performed against DDIs included in the database DrugBank. However, this database, or any other DDI information source, cannot be considered a gold-standard of "true DDIs".[8] The large number of possible DDIs, with different degrees of significance or influenced by drug or patient-related facts, makes it not feasible to manually collect all of them in a single information source. Indeed, important differences have been found in the coverage for DDIs among different information sources.[2] As a consequence, it is not possible to know if the '*false positive DDIs*' inferred in DINTO are not included in DrugBank because (i) they are interacting pairs but have not been included yet in the database, (ii) they are interacting pairs but the interaction between them has not

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been described in the scientific literature, or (iii) they are not interacting pairs of drugs. In spite of this, the other main reason for the high number of *false positives* is that our SWRL rules have been modeled to infer DDIs on the basis of different mechanisms, but independently of other related facts such as their significance or level of documentation. Therefore, for any pair of drugs for which an underlying DDI mechanism exists, no matter if it would lead to a clinically relevant DDI or a nonclinically relevant or unobservable DDI, the interaction is inferred. Inclusion of drug-related facts, such as protein affinity or therapeutic index information, could be useful to avoid inferring nonclinically relevant DDIs.

In contrast to this, there are other DDIs that could not be predicted by our SWRL rules. Most of these are DDIs for which their mechanisms cannot be explained by known drug−protein or drug-ADR relationships, including DDIs occurring by means of the physicochemical binding of the two drugs in the gastrointestinal tract or DDIs for which the underlying mechanism is not known or understood yet.

The analysis of these results is useful to identify further information that should be included in our ontology and to provide guidelines to refine our inference rules. For this purpose, in our future work we will include in the ontology information regarding the therapeutic index of drugs[7] or drug bioactivity data,[64] as well as information about physicochemical properties of drugs or new discoveries about drug−protein relationships.

■ ASSOCIATED CONTENT

Supporting Information

SI 1: Template used as a guide during the development of DINTO and as a checklist for the evaluation of the final ontology. SI 2: Results from *IExp3*, showing the inferred and asserted DDI mechanisms for 93 DDIs. SI 3: Results From *IExp4*, showing the drugs and the ADRs included in the experiments, and the number of inferred DDIs. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jcim.5b00119.

■ AUTHOR INFORMATION

Corresponding Author

*Tel.: +34 91 624 59 61. E-mail: mhzazo@pa.uc3m.es.

Notes

The authors declare no competing financial interest.

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