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Title: Conceptual Models of Drug-Drug Interactions: A Summary of Recent Efforts

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Abstract: Conceptual modeling elicits and describes general knowledge in a particular domain and is a fundamental step in the development of knowledge-based systems. However, different conceptual models (CMs) could represent the same domain because they result from human intellectual activity with different objectives. Analyzing previous related efforts is crucial when conceptualizing a domain to avoid duplication, increase interoperability and ensure scientific conformity. Our domain of interest is drug-drug interactions (DDIs), and here we review 15 studies that have attempted total or partial representation of the DDI domain. Direct comparison of these different conceptualizations is complex because CMs are usually not provided, differ considerably from each other or are described with diverse formalisms at different abstraction levels. Therefore, to compare these CMs, we represent all of them in a common representation framework. Here, we compare the scope, content, final implementation and applications of CMs of the DDI domain. We aim to identify which aspects of DDIs have been conceptualized, characterize how this information has been

modeled by different research groups, describe how each CM has been translated and illustrate the applications generated from the final models.

Keywords: Drug-drug interactions; Conceptual modeling; Knowledge representation; Ontology; Natural language processing; Computational inference

Highlights:

- We present a review of drug-drug interactions knowledge representations.
- We have identified 29 relevant documents describing 15 models or resources.
- Most of the models were created for natural language processing or DDI inference.
- To compare the models, we represent them in a common framework using UML diagrams.

Abbreviations:

ADR – Adverse drug reaction

ASP – Answer set programming

BRO – Biomedical Resource Ontology

ChEBI – The ontology for Chemical Entities of Biological Interest

CDSS – Clinical decision support system

CM – Conceptual model

DDI – Drug-drug interaction

DEI – Drug-Enzyme Interactions

DIDEO – Drug-drug Interaction and Drug-drug Interaction Evidence Ontology

DIKB – Drug Interactions Knowledge Base

DINTO – Drug-Drug Interactions Ontology

DIO – Drug Interaction Ontology

DL – Description logic

FOL – First order logic

GO – Gene Ontology

GRAIL – Galen Representation and Integration Language

IE – Information extraction

M-PADS – Multidisciplinary Psychoactive Drug Selection advisor system

NDF-RT – National Drug File-Reference Terminology

NER – Named entity recognition

NLP – Natural language processing

OAE – The Ontology of Adverse Events

OI – Ontology of Interactions

OWL – Web Ontology Language

PD – Pharmacodynamics

PDDI – Potential drug-drug interaction

PDO – The Pharmacodynamics Ontology

PK − Pharmacokinetic

PKO –Pharmacokinetics Ontology

PPO – Pharmaceutical Product Ontology

RDF – Resource Description Framework

RE – Relation extraction

SADL – Semantic Application Design Language

SIDER – Side Effect Resource

SOPHARM – Suggested Ontology for Pharmacogenomics

SPC – Summary of Product Characteristics

SWRL – Semantic Web Rule Language

UML − Unified Modeling Language

VHA – Veterans Health Administration

XML - Extensible Markup Language

1. INTRODUCTION

Knowledge representation is an essential activity in knowledge engineering. Particular knowledge about a domain (e.g., *the patient presents a sudden rise in temperature (39 °C) and neck stiffness and is a suspected case of meningitis*) requires prior general knowledge of how concrete objects are related in the world (e.g., *A disease presents signs and symptoms. The identification of signs and symptoms is used to diagnose the disease. A suspected case of meningococcal meningitis is defined as any person with sudden onset of fever (>38.5 °C) and at least one of the following signs: neck stiffness, altered consciousness or other meningeal signs*). Conceptual modeling elicits and describes the general knowledge of a particular domain. The sets of objects and facts in a particular domain constitute its conceptualization, and its formal description, which sometimes includes a graphical notation, is the conceptual model (CM) [1]. Usually, the design of a CM relies on the perspectives of experts in that specific domain. However, different CMs can represent the same domain because they result from human intellectual activity with different objectives. These CMs are abstract models that can be translated into different description languages and interpretable schemata such as ontologies, relational databases or XML schemata.

Because of the growing success of the Semantic Web, ontologies have become one of the most popular formalisms for knowledge representation. Indeed, the most comprehensive repository of biomedical ontologies, BioPortal,[1] doubled the number of collected ontologies from ~200 to more than 400 in the last six years [2]. The enormous complexity of the biological, medical and pharmaceutical domains compels authors to create individual ontologies with more exhaustive descriptions of specific areas within a broader domain.

[1] http://bioportal.bioontology.org/

Further, various applications such as the coding and indexing of medical records [3], semantic annotation of biomedical documents [4], data integration from the Semantic Web and Linked Data [5] or data analysis and discovery applications [6] may require different conceptualizations of the same domain.

Thus, some research groups initially develop their own independent conceptualizations *de novo*, which can lead to multiple isolated CMs that represent different or even overlapping aspects of the same domain. To avoid such duplication, the OBO Foundry,[2] a collaborative effort to develop and maintain biomedical ontologies, recommends collaboration to 1) avoid duplication of work, 2) increase interoperability and 3) ensure that ontology content is both scientifically sound and meets community needs [7].

The medical and pharmacological domains are active areas of knowledge-based systems research [8]. Representation of drug-drug interactions (DDIs), a serious type of adverse drug reaction (ADR) that occurs when one drug affects the levels or effects of another drug [9], is an important effort in these domains. DDIs pose serious risks to patients' safety and increase healthcare costs [10,11], so their early apprehension is vital in clinical settings [12]. Various research groups have proposed diverse computational approaches that rely on CMs or other formal representations of the domain to improve prediction or management of DDIs. Here, we review the aspects of DDIs that have been conceptualized, characterize how this information has been modeled by different research groups, describe how the different CMs have been finally implemented and illustrate the applications generated from the final CMs.

2. METHODS

2.1. Literature search

[2] http://www.obofoundry.org/

We have searched the bibliographic databases for the medical (MedLine through the PubMed search engine[3]), computational (IEEE Xplore[4] and ACM Digital[5]) and general (Web of Knowledge, [6] Scopus[7] and Google Scholar[8]) domains, considering only documents published in English from January 2000 through May 2016. We aimed to identify original research describing a partial or complete conceptualization of the DDI domain. Therefore we included only scientific articles, conference proceedings communications or dissertations, and excluded other document types such as abstracts, reviews, books or book chapters that usually only compile previously published information.

Our query was *("drug-drug interaction" AND "conceptual model") OR ("drug-drug interaction" AND "knowledge representation") OR ("drug-drug interaction" AND "formal representation") OR ("drug-drug interaction knowledge" AND model*).* After removing duplicates and inappropriate document types, we examined the titles and abstracts of the remaining papers, and finally selected 91 documents for full-text review. The summary of the search methodology and results is shown in Fig. 1.

[3] PubMed: http://www.ncbi.nlm.nih.gov/pubmed
[4] IEEE Xplore: http://ieeexplore.ieee.org/Xplore/home.jsp
[5] ACM Digital: http://dl.acm.org/
[6] Web of Knowledge: https://webofknowledge.com/
[7] Scopus: https://www.scopus.com/
[8] Google Scholar: www.google.co.uk/scholar

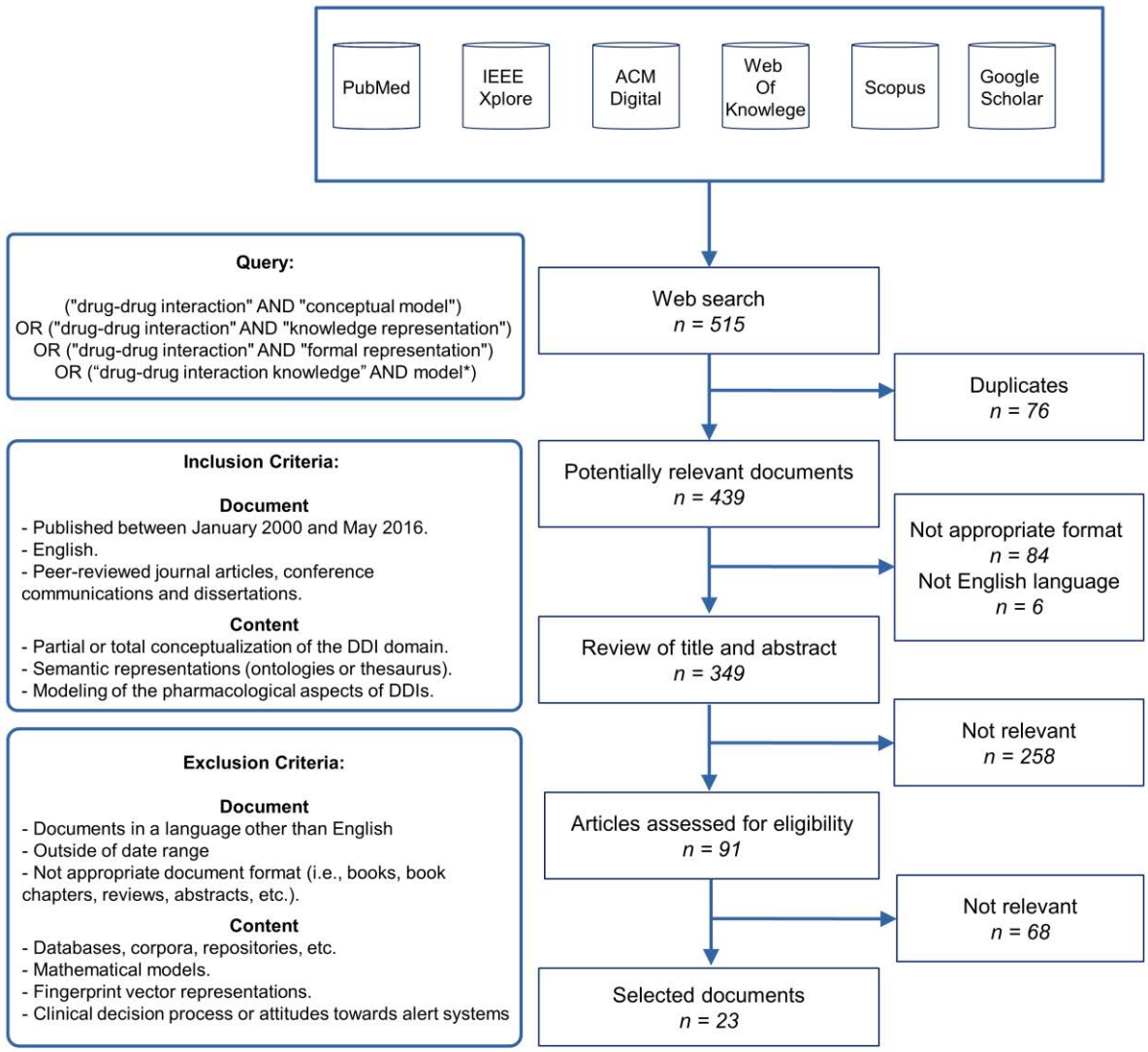

Figure 1. Flow chart of the literature search

We included works describing partial or total conceptualization of the DDI domain, including the underlying mechanisms (e.g., drug-protein interactions), if the final model was specifically applied to the identification or representation of DDIs. Works describing databases, corpora, or DDI repositories were excluded if their CMs were not described. Formal semantic representations of the domain as ontologies or thesauri were included, while mathematical modeling of pharmacological processes and fingerprint vector representations of drugs or proteins were excluded. Finally, representations of clinical decision processes, or responses to and attitudes towards alert systems were not considered. We selected a final total

of 23 documents that describe 15 different projects that required total or partial representation of the DDI domain (Table 1).

Table 1. Summary of current conceptual models in the DDI domain

CM[a]	Year	Known evaluation scenario or application[c]	Implementation[d]
PPO	2008	Pharmaceutical information integration	OWL
Khan et al.	2012	Prediction of DDIs	RDF
NDF-RT	2002[b]	Support of computerized systems	DL, OWL
OI	2014	Prediction of DDIs	-
Mille et al.	2007	NLP: encoding of text	XML
Rubrichi et al.	2012	NLP: annotation of text, information extraction and ontology population	OWL
DIO	2004	Prediction of pharmacokinetic DDIs	OWL
DIKB	2005	Prediction of pharmacokinetic DDIs Dynamic enhancement of drug product labeling	FOL OWL
Moitra et al.	2014	Prediction of pharmacokinetic DDIs	SADL/OWL
DEI	2016	Prediction of pharmacokinetic DDIs	OWL
PKO	2013	NLP: annotation of text	OWL
M-PADS	2001	Prediction of pharmacodynamic DDIs	GRAIL
PDO	2013	Prediction of pharmacodynamic DDIs	-
DIDEO	2014	Supporting the integration of DDI evidence and knowledge claims	OWL
DINTO	2013	NLP: NER and RE Prediction of pharmacokinetic and pharmacodynamic DDIs	OWL

[a] *Conceptual models − PPO: Pharmaceutical Product Ontology; NDF-RT: National Drug File-Reference Terminology; OI: Ontology of Interactions; DIO; Drug Interaction Ontology; DIKB; Drug Interactions Knowledge Base; DEI: Drug-Enzyme Interactions; PKO: Pharmacokinetics Ontology; M-PADS: Multidisciplinary Psychoactive Drug Selection advisor system; PDO: Pharmacodynamics Ontology; DIDEO: Drug-drug Interaction and Drug-drug Interaction Evidence Ontology; DINTO: Drug-Drug Interactions Ontology.*
[b] *Date of the earliest reference used in this review.*
[c] *Applications − NLP: Natural Language Processing; NER: Named Entity Recognition; RE: Relation Extraction.*
[d] *Implementation languages − OWL: Web Ontology Language; RDF: Resource Description Framework; DL: Description Logic; XML: Extensible Markup Language; FOL: First Order Logic; SADL: Semantic Application Design Language; GRAIL: Galen Representation and Integration Language.*

2.2. Creation of a common representation framework

Comparison of conceptualizations is difficult because CMs are usually not provided and those included in publications can differ considerably. Furthermore, the final implemented models are complex artifacts, such as sets of rules in first order logic (FOL) or Ontology Web Language (OWL) ontologies, and are therefore difficult to compare. So to compare the different models, we first depict all of the CMs in Unified Modeling Language (UML) class

diagrams, a standard modeling language that can be applied to diverse independent domains [13]. Although not all of the resources described in this review were originally intended for representation as UML diagrams, and some of the models might lose some expressivity because of this representation, UML is a powerful tool for defining CMs that conserves their overall aim and main concepts. The CMs are shown in the Supplementary Material and a more detailed description of the process is described in our previous work [14].

3. MODELING APPROACHES IN THE DDI DOMAIN

The conceptualizations identified here have addressed representation of the DDI domain in very different ways depending on their final purposes. The simplest representation merely indicates an interaction between two drugs, but does not provide any additional information, as in the **Pharmaceutical Product Ontology (PPO)**, an ontology for the integration of pharmaceutical knowledge [15] that combines an OWL-implemented model (Fig. S1) with a SWRL (Semantic Web Rule Language) inference rule to allow the corresponding drug products that contain two interacting active ingredients to inherit the DDIs for those ingredients. Similarly, **Khan et al**. [16] have presented a model in which a DDI is represented as a contraindication between two drugs, or between a drug and a disease or condition. This model also includes the patient factors age and gender, which are relevant to DDIs (Fig. S2). The model is implemented as an ontology for the example domain, insomnia, in the Resource Description Framework (RDF) language[9] as part of a hybrid system combining machine learning, structured knowledge representation and logic-based inference for medical decision support.

Instead of representing a DDI as a relationship between two drugs, the **NDF-RT** [17] (the National Drug File Reference Terminology of the U.S. Veterans Health Administration

[9] RDF: https://www.w3.org/RDF/

(VHA) medication terminology) represents it as a class related to exactly two active ingredients, with an attribute 'Severity' that is assigned one of the values '*Significant*' or '*Critical*' (Fig. S3). The NDF-RT is used for modeling drug characteristics and, until 2014, included DDIs [18,19]. It was used throughout the computerized patient record system of the VHA system to generate alerts if an interacting drug combination were prescribed [20,21].

Another more informative model is presented by Piovesan et al. [22] for the representation of computer-interpretable guidelines in the medical domain. They have created an **Ontology of Interactions** (**OI**) to merge and identify incompatible actions that can occur under two sets of guidelines, such as the combination of drugs that may interact (Fig S4). A simple algorithm is used to analyze the information in the ontology to identify potential DDIs.

Mille et al. [23] have also created a simple CM intended to represent the entire DDI domain (Fig. S5) to generate a structured DDI knowledge base for clinical decision support systems (CDSS). The CM is used to create an XML schema for encoding or markup of textual documents. This CM represents a DDI as the central concept related to other concepts. The model encompasses most of the important questions related to the DDI domain, such as: *how does the interaction occur?* ('Mechanism'); *which drugs interact?* ('Partner'); *what is the consequence of the DDI?* ('Consequence'); *which factors can increase the risk of the DDI?* ('Risk Factor'; 'Risk Association'); and *which factors or actions can decrease the risk of the DDI?* ('Precaution of Use'; 'Limitation'). Although this model broadly covers the DDI domain, it does not provide deeper descriptions of the answers to these questions.

Combining some of the characteristics of the models described above, the model created by **Rubrichi et al.** [24] explicitly represents the concept of DDI as a class (Fig. S6) and, as does

the CM of Mille et al., describes some of the most important aspects of DDIs, such as: *what is the consequence of the DDI?* ('Interaction Effect'); *which factors can increase the risk of the DDI?* ('Intake Route'; 'Posology'; 'Personal Conditions'); and *which actions can decrease the risk of the DDI?* ('Recovering Action'). However, the 'Mechanism' by which the interaction occurs is not represented. Inclusion of the mechanism is crucial to prevent, predict and manage (e.g., by selecting an alternative drug metabolized by a different enzyme) possible DDIs. The model is implemented as an ontology for the extraction of drug-related information from texts and ontology population [25].

The five models described so far attempted a general representation of the DDI domain, but did not dive into representation of the different mechanisms that lead to DDIs. DDIs are usually classified into two main groups based on their mechanisms: pharmacokinetic (PK) or pharmacodynamic (PD) DDIs [9]. A PK DDI occurs when one drug affects the absorption, distribution, metabolism or excretion of another drug, and thus its concentration leading to an increase in side or toxic effects or a decrease in therapeutic effects. In contrast, a PD DDI occurs when one drug modifies the effects of another drug without affecting its concentration, such as when the drugs act on the same target, leading to similar or distinct responses, or act through different pathways to produce similar or distinct effects. The models discussed below each focus on the representation of either PK or PD DDI mechanisms.

The Drug Interaction Ontology (DIO) was developed to formally represent pharmacological actions depicted by drug-biomolecule, but not drug-drug interactions, and focuses specifically on PK processes. Although the concept of DDI is not represented in this ontology, drug-biomolecule interaction information can be exploited by a system to predict DDIs. This ontology was created for knowledge sharing and functional usage and has been

applied for prediction of PK DDIs [26,27]. The conceptualization implemented as the DIO provides a detailed description of PK processes and their localization within the organism.

The Drug Interaction Knowledge Base (DIKB) is a knowledge representation system designed to predict DDIs based on their underlying mechanisms and the evidence supporting the drug-related facts [28,29]. These predictions are enabled by the formal representation of mechanisms that lead to DDIs, which are modeled as a set of rules in FOL [30] with an OWL DL evidence taxonomy for confidence assignment [31,32]. Although the authors studied the formal representation of different types of PK mechanisms in earlier efforts [28], they later developed representations only of metabolic inhibition [30]. This CM (Fig. S9) focuses on the relationships between the principal actors in a DDI that occurs due to inhibition of the enzymatic metabolism of a drug: the precipitant drug, the object drug and the metabolic enzyme. Two drug characteristics that determine the incidence and significance of DDIs are also included ('Narrow therapeutic index' and 'Sensitive substrate'). The inclusion of these features focuses the model on DDIs that could potentially be more relevant in the clinical domain. These classes, relationships and attributes are combined in a rule-based theory of how drugs interact based on these mechanisms. The evidence taxonomy is closely related to the FOL model (as shown in Fig. S9). It includes different types of evidence information sources, but also includes pharmacological features and molecular interactions related to DDIs. Here, we refer to both the FOL model and the evidence taxonomy as the DIKB model. Using the rule-based theory and information from a manually curated database of drug-related facts, including structured information about specific drugs, metabolites, metabolic enzymes and the relationships between them, a machine-reasoning system able to predict interactions between individual pairs of drugs was developed [32] and has also been used to dynamically enhance drug product labels [33].

Moitra et al. [34] described a semantic model of PK DDIs that occur through metabolism-related mechanisms that reused some concepts from the DIKB. It uses the Semantic Application Design Language (SADL), which can be automatically translated into an OWL model [35] to make inferences regarding PK DDIs using Answer Set Programming (ASP). The novel aspects of this model (Fig. S10) are that 1) it considers the combined effect of altering more than one enzyme activity in the same DDI; 2) the authors perform quantitative reasoning by including a 'reaction rate' between a drug and an enzyme; and 3) this allows estimation of the 'impact' of a DDI due to potential variation in drug concentrations.

Zhang et al. [36] have created an OWL ontology for **Drug-Enzyme Interactions (DEI)** as part of a hybrid approach that combines machine learning for relation extraction (RE) with reasoning to infer potential PK DDI that occur *via* metabolic-related mechanisms. This ontology includes only two classes: 'Drug' and 'Enzyme' and their possible relationships (Fig. S11). The ontology is populated with drugs, enzymes and their interrelationships extracted from texts, and potential DDIs are then inferred using property chains.

The final model we review for PK DDIs is the **Pharmacokinetic Ontology (PKO),** which represents PK-related information [37]. Although the final ontology integrates information from different resources, modeling efforts focus on the representation of different types of *in vitro* or *in vivo* PK DDI studies or experiments on drug interactions that affect some of the PK parameters of the interacting drugs (Fig. S12). The final ontology imports other ontological resources, such as the ChEBI ontology [38] or SOPHARM [39].

So far, we have described CM representing PK DDIs. However, there have been fewer attempts to represent PD DDIs. Van Hyfte et al. [40] created a formal knowledge framework to support rational selection of psychoactive drugs. Their **Multidisciplinary Psychoactive Drug Selection advisor system (M-PADS)**, implemented using the Galen Representation and Integration Language (GRAIL) [41], represents a DDI between two drug products and uses a generic formal inference rule to infer PD DDIs (Fig. S13). Although simple, this model represents important pharmacodynamic concepts including 'Pharmacological Action' mediated by a 'Receptor', its consequent 'Pathophysiological State' and a 'Therapeutic Unwanted Effect' to represent the concept of ADR.

The **Pharmacodynamics Ontology (PDO)** is another model for the development of machine reasoning systems for detecting PD DDIs [42]. As in the **DIO**, specific information regarding DDIs is not included in this model, but the descriptions of pharmacological processes can be used to predict interactions between specific pairs of drugs. This model focuses on the representation of the pharmacodynamics (biochemical or physiological effects) of drugs (Fig. S14). The suitability of this model to predict PD DDIs has been tested with drugs related to the noradrenaline signal transduction process.

Finally, two recent efforts, **The Potential Drug-drug Interaction and Potential Drug-drug Interaction Evidence Ontology (DIDEO)** and the **Drug-drug Interactions Ontology (DINTO)** attempt a global yet detailed representation of the DDI domain.

The uncertainty associated with drug information was one of the main challenges for representing and using knowledge of drug-mechanisms in the DIKB project. To overcome this issue, an effort to create a new ontology, **DIDEO**, for representing DDI evidence and

knowledge claims [43] is in progress. The innovative aspect of this ontology is the representation of 'Information Content Entities' (journal articles, data, graphics, or other pieces of information) that describe some aspect of a DDI and that are necessary to collect and organize evidence about DDIs. The authors have defined a potential DDI (PDDI) as an information content entity that specifies the possibility of occurrence of a DDI [44]. Here, we review the latest available version.[10] The resulting CM (Fig. S15) focuses on pharmacological aspects rather than information aspects. The current model includes the concepts 'DDI' and 'DDI effect' and related information such as DDI mechanism, molecular processes or PK parameters, which are information content entities that will be linked to their corresponding pharmacological definitions in the future. This ontology reuses information from numerous other ontologies including the ChEBI ontology [38] and the Gene Ontology (GO) [45].

The final model described here is **DINTO** [46], a comprehensive ontology that systematically organizes all DDI-related knowledge. DINTO is the first formal representation comprising a wide range of DDI mechanisms, including both PD and PK mechanisms. It was conceived as a robust resource useful for different applications, and has been evaluated in different scenarios: natural language processing (NLP) [47] and inference of DDIs and their mechanisms [46]. DINTO incorporates information from different related ontologies including pharmacological substances from the ChEBI ontology and ADRs from the Ontology of Adverse Events (OAE) [48]. DINTO also imports information from databases and incorporates proteins, drug-protein relationships and DDIs from the DrugBank database [49] and drug-ADR relationships from SIDER [50]. This CM was created by iterative analysis of previous efforts (Fig. S16), and thus includes most of the concepts represented in the CMs discussed above (see Table S1). This model exhaustively represents individual drugs

[10] Development version 2016-02-13

(e.g., ‘Paracetamol’), proteins (e.g., ‘CYP-3A4’) and DDIs (e.g., ‘Abiraterone/Carbamazepine DDI’). Moreover, different mechanisms are represented as SWRL rules that are then combined with the drug-protein and drug-ADR relationship information to allow large-scale prediction of PK and PD DDIs.

4. COMPARISON OF DDI KNOWLEDGE MODELING APPROACHES

Next, we compare the different conceptualizations and analyze the representation of the most relevant concepts in the DDI domain. Table S2 summarizes and compares the contents included in the 15 models.

4.1. Representation of Drugs and Drug Classes

Most of the CMs reviewed here represent the concept ‘Drug’ as an active ingredient (or a specific molecule with some pharmacological activity, such as *paracetamol*) and agree that a DDI occurs between two active ingredients. The exceptions are **M-PADS** and **DIDEO**, wherein the participants in a DDI are drug products (or the commercial unit of a medicine such as a pack of 20 tablets of *paracetamol*). Six of the models (**PPO**, **NDF-RT**, **Rubrichi et al.**, **PKO, M-PADS** and **PDO**) represent an active ingredient as a component of a clinical drug (i.e., the unitary dose of a medicine such as a tablet of *paracetamol*) or a drug product, while an active ingredient in the **DIDEO** is a ‘Role’, or a particular behaviour exhibited by a material that describes its activity [51]. Some models include only one class, ‘Drug’, and do not specify whether it represents an active ingredient or drug product, but the examples in **Khan et al.**, **OI**, **Moitra et al.** and **DEI** refer to active ingredients. In contrast, the **PPO** specifies that a drug product is an active ingredient.

The concept ‘Drug Class’ (that groups active ingredients together according to a relevant characteristic e.g., *analgesics*) is also represented in very different ways in each CM. **Mille et al.** represent drug class as an attribute ‘type’ of an ‘Active Ingredient’ (e.g., the active

ingredient *paracetamol* would have type *analgesic*), while **Rubrichi et al.** establish a 'Clinical Drug' or 'Drug Product' as part of 'Drug Class'. Although **Khan et al.** define a 'Drug Class' as subclass of 'Drug', in the **OI**, drugs can be organized through a multi-level hierarchy of abstraction from drug categories to specific drugs. Similarly, the **NDF-RT** relates drug classes and clinical drugs hierarchically (e.g., *acetylcysteine 20% inhalation solution* is a subclass of the *mucolytics* drug class) and a clinical drug is related to an active ingredient class through the relationship '*has ingredient*' (e.g., *acetylcysteine 20% inhalation solution* '*has ingredient*' *acetylcysteine*). The **M-PDAS** includes the concepts drug and drug product, but also includes a class 'Drug Therapy' that could represent drug classes. The **PKO** adopts the model from SOPHARM and represents an 'Active Ingredient' as a subclass of at least one 'Drug Class' that is a descendant of the top-level class 'Drug'. The **DIDEO** includes several hierarchies to classify drug classes by chemical structure imported from ChEBI, while the **DINTO** follows a different classification in ChEBI and imports all of the different roles and their relationships with active ingredients *via* the relationship '*has role*'.

4.2. Description of Drug Metabolites and Proteins

Besides drugs, other object entities are relevant in the DDI domain. Drug metabolites are represented in some of the models that describe the metabolism of drugs (**DIO**, **DIKB**, **DIDEO** and **DINTO**). Proteins are also important objects in the DDI domain as they are involved in both PD and PK mechanisms of most DDIs. The **DIO** represents three different types of proteins: 'Enzymes', 'Transporters' and 'Albumins', whereas the **M-PDAS** represents only the class 'Receptor', while only 'Enzymes' are represented in the **DEI** and **DIDEO**. **Moitra et al.** include two enzyme subclasses: 'Cytochrome P450' and 'UGT', as does the **DIKB**, which also includes specific cytochrome P450 isoenzymes. The **PKO** also represents 'Metabolizing Enzymes', 'Transporters' and 'Targets'. Finally, the **DINTO**

includes five protein types: ‘Enzyme’, ‘Transporter’, ‘Carrier’, ‘Target’ and ‘Receptor’, as well as subclasses that represent individual proteins and their relationships to specific drugs.

4.3. Representation of DDIs

The concept of a DDI is not explicitly represented in all of the CMs described here. The **NDF-RT**, **OI**, **Mille et al.**, **Rubrichi et al.**, **DIKB**, **DIDEO** and **DINTO** represent DDIs as a class, while the **PPO**, **Khan et al.**, **DEI** and **M-PADS** represent them as a relationship. The CM in the **OI** includes a class ‘Drug Interaction’ that occurs between active ingredients as a subclass of ‘Drug Category Interaction’, which involves at least one drug class as interacting entity. The **M-PADS** also represents DDIs at different levels of granularity, as drug classes, drug products, or active ingredients. In the CM in **Khan et al.**, a drug might interact with another drug but also with a ‘Disease’ or a ‘Condition’.

Despite the differences among CMs, a DDI is usually represented as a relationship between exactly two entities. Thus, interactions occur in the **DIKB** model between precipitant and object drugs. The **NDF-RT** and **Mille et al.** specify that an interaction occurs between two drugs, while in the **DINTO** it involves exactly two pharmacological entities with either ‘Object’ or ‘Precipitant’ roles. In contrast, the CM developed by **Rubrichi et al.** asserts that interactions could occur between two drugs, between a drug and a group of drugs, between a drug and a diagnostic test or between a drug and another substance. The **DIDEO** establishes the exception that participating entities in a DDI are drug products, and without specifying an exact number of participants. The DDI is further described through relationships with other classes (e.g., ‘DDI Mechanism’) or data properties (e.g., ‘Documentation Level’). Table S1 summarizes the concepts directly linked to the concept DDI.

4.4. Representation of DDI-related Processes

Processes and qualities are important concepts that should also be represented in the DDI domain. We have identified four main types of processes or qualities that have been included in some of the models described above: the effect of a DDI, the DDI mechanism, factors that can increase the risk or severity of the DDI, and actions to avoid or mitigate a DDI.

The consequences of a DDI are represented in six of the models (**DIKB**, **DINTO**, **DIDEO, OI**, **Mille et al.** and **Rubrichi et al.**). The four latter models represent DDI consequences at a high level of granularity, but do not describe each type of DDI consequence in detail. The **DINTO** specifies different types of DDI effects based on their clinical relevance and potentially beneficial or adverse outcomes. And finally, the **DIKB** differentiates between PK or PD consequences of a DDI.

The mechanism or process that leads to a DDI is represented in only four models **(Mille et al.**, **DIKB**, **DEI** and **DINTO). Mille et al.** provide a very general representation of the concepts, while the **DIKB** and **DEI** represent only enzyme-related PK DDI mechanisms. The **DINTO** includes PK and PD mechanisms further sub-classified according to the proteins involved, leading to a total of 11 classes representing mechanisms at the lowest level.
PK processes and PK parameters can be altered in a PK DDI mechanism. Processes are described in the **DIO**, **DIDEO** and **DIKB.** The latter two include the PK parameter 'Area Under the Concentration Curve', while the **PKO** includes several parameters. The **DINTO** includes both the PK processes and parameters and reuses the PK parameters from the **PKO**. The CM from **Moitra et al.** represents only PK process metabolism. The **DIKB** establishes that a PK DDI results from alteration of a PK process. Likewise, the PD processes and pharmacological effects that are altered by a PD DDI mechanism are represented in the **M-PDAS**, **PDO** and **DINTO** models.

4.5. Representation of Management Options and Adverse Drug Reactions

There are different ways to avoid or reduce the likelihood of a DDI [52]. The **DIDEO** and the CMs of **Mille et al.** and **Rubrichi et al.** refer generally to management options, while the **DINTO** provides a more detailed representation as data properties instead of classes.

Factors that can aggravate a DDI are represented in seven of the described models. The CMs of **Mille et al.** and **Khan et al.** include patient-related factors, while the **DIKB** and **DIDEO** represent drug-related factors; only the **DINTO** and the CM of **Rubrichi et al.** consider both. The overall significance of a DDI is represented only in the **DINTO** and **NDF-RT** models.

Finally, representation of the ADRs in the DDI domain is important because an adverse DDI can reduce expected therapeutic effects or exacerbate toxic or other adverse effects of either drug. However, the ADR concept is represented in only four models: **Rubrichi et al.**, **M-PADS**, **DIDEO** and **DINTO**.

5. DESCRIPTION LANGUAGES AND APPLICATIONS

The scope and content of the different CMs were compared above, and we now describe their final formal representations and applications. Most of the CMs discussed here are implemented as OWL ontologies (**PPO**, **Rubrichi et al.**, **DIO**, **DEI**, **PKO**, **DIDEO** and **DINTO)**. **Moitra et al.** build their CM using SADL [35] and translated it into OWL. **Khan et al.** use RDF, while the **DIKB** represents the CM as a set of rules in FOL and the evidence taxonomy as an OWL-DL ontology. The CM of **Mille et al.** is used to build an XML schema, while **M-PADS** is the only CM using GRAIL. The publicly released version of **NDF-RT** is available in several formats such as XML and OWL.[11] Finally, the **OI** and **PDO** have either not yet been implemented, or their implementation is not described. With the exception of these two models, all the resources discussed here are available either online or by request to

[11] NDF-RT: http://www.cancer.gov/cancertopics/cancerlibrary/terminologyresources/fmt

the authors. The **DINTO** and **DIDEO** are included in the OBO Foundry repository,[12] and the **DINTO** and **DIKB** can also be accessed online at BioPortal.[13]

These CMs have been used for two main applications: NLP (the CMs of **Mille et al.** and **Rubrichi et al.**, **PKO** and **DINTO**) and DDI inference (**DIO**, **DIKB**, the CM of **Moitra et al.**, **DEI**, **M-PADS**, **PDO**, **DIDEO** and **DINTO**).

The CM of **Mille et al.** has proven useful for encoding a total of 1006 monographs on DDIs and creating a knowledge base from the extracted information, while the ontology of **Rubrichi et al.** has been used to annotate a set of Summary of Product Characteristics (SPC) texts for the training and testing of an information extraction (IE) system [24]. The extracted information then automatically populates the ontology [25]. The **PKO** was also created for NLP tasks, and has been used to annotate documents describing PK DDI experiments. Finally, the **DINTO** has been used for different NLP tasks including named-entity recognition (NER) for drugs and relation extraction (RE) for DDIs from different types of documents in the DDI corpus [47].

The other main application of DDI-related CMs is the prediction of DDIs based on their mechanisms. Ten different CMs have demonstrated that the formal representation of DDI knowledge can be used successfully to predict interactions between specific pairs of drugs, although the assessments of these models differ considerably. Some works illustrate the inference capabilities of their approaches with only two or three drugs for PK (**DIDEO**, **DIO** and **Moitra et al.**) or PD mechanisms (**M-PADS**), while other works demonstrate their models with a larger set of drugs. The **DIKB** predicts PK DDIs that occur through inhibition

[12] OBO Foundry repository: http://www.obofoundry.org/
[13] BioPortal repository: http://bioportal.bioontology.org/

of enzymatic metabolism for over 60 drugs using FOL rules, and the **DEI** infers PK DDIs between 104 drugs using property chains. The **PDO** has been used to identify different types of PD DDI mechanisms between 89 drugs. Finally, the largest prediction experiment has been conducted using **DINTO**, which is combined with a set of SWRL rules representing different PK and PD mechanisms to predict DDIs between 426 drugs and also their mechanisms. In addition to protein-related DDIs, the **DINTO** also uses ADR information to predict PD DDIs.

6. DISCUSSION AND FUTURE TRENDS

We have identified, analyzed and compared 15 conceptualization efforts in the DDI domain. To the best of our knowledge, such a comprehensive study of former conceptualizations has not yet been performed or published, although it is an essential step for reusing previous efforts, avoiding duplicated models, and gaining scientific agreement, as recommended by the OBO Foundry. As we have not conducted a systematic review, some related works might have not been included here. However, we have provided a summary of the most relevant representation efforts in the domain. Their representation in a common framework and the analyses described here provide an overview of the conceptualizations conducted for different purposes by various research groups. Therefore, this review should be a useful starting point for researchers initiating conceptualization projects in the pharmacological domain, or as a common framework for those continuing work in the DDI domain.

Readers should keep in mind that not all the models reviewed here were intended to be represented as UML diagrams and that this language is less expressive than others languages such as OWL. Hence, more complex models that include more concepts and relationships, such as DIKB, DIDEO or DINTO, might seem underrepresented here compared to simpler ones. However, the objective of this common representation framework is not to provide an

exhaustive depiction of entire models, but to illustrate the main differences and similarities among them. Through this detailed description and analysis of existing conceptualizations, we have shown that the scope and contents of these models differ considerably, from those that focus on metabolism-related PK DDIs, to those that attempt global representation of the domain. Some models, such as the DIDEO, follow a modularization strategy, in which a resource (e.g., an ontology) exists as a whole or could be seen as a set of parts (modules) [53] and be combined with other resources, such as OAE.

Recent projects, such as the DIDEO or DINTO, provide broad coverage of general aspects of the DDI domain. But although other models, such as the DIO or PDO, provide more detailed descriptions of the underlying physiological processes responsible for DDIs at the molecular level, none have yet attained a comprehensive representation, a complex task due to the large number of physiological processes related to drug activity [42]. Also, detailed representations of pharmacological processes are difficult to populate at the individual level, which limits their further applications. There are, however, well-known examples of knowledge representation of very complex molecular processes such as the highly cited and reused GO [54]. Translating such a large effort to the DDI domain will require great investment of economic and human resources.

As reflected in the numerous efforts described here, DDI knowledge representation is still an active research area. A shared effort is currently being led by the Department of Biomedical Informatics (University of Pittsburgh) for the development of a *"Minimum information model for representing potential DDI knowledge and evidence"*,[14] which involves ~50 experts on DDIs or knowledge representation and aims to translate core information on DDIs and their

[14] http://dbmi-icode-01.dbmi.pitt.edu/dikb-evidence/w3c-ddi/index.html

management [55] into a new DDI minimum information model standard for representing and sharing DDI knowledge and evidence as information artifacts.

Although there is interest in using ontologies in NLP, especially for information retrieval [56] and NER [57,58], their use for RE has been hardly explored [47,59]. Today, there is more interest in applying human language technologies to develop automated pharmacovigilance systems and improve patient safety [60] through the extraction of ADRs from FDA drug labels [61], clinical notes [62], scientific literature [63] and, more recently, social media [64,65]. These approaches rely on medical vocabularies, but more comprehensive conceptualizations such as the DINTO or DIDEO could accelerate advances in this field.

The prediction of DDIs through knowledge-based systems and semantic rules has been a very attractive research area, and its continuing challenges include validating and prioritizing very large numbers of predictions. We envision, however, that these challenges will be addressed in the near future by combining knowledge-based systems with machine learning methods to identify clinically relevant DDIs [66].

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