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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.

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. 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,

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[1] http://bioportal.bioontology.org/.
[2] http://www.obofoundry.org/.

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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

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

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.

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).

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] 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.

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