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FIDEO: Food Interactions with Drugs Evidence Ontology

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Abstract. In this paper we propose the Food Interactions with Drugs Evidence Ontology (FIDEO), an ontology used for annotation and retrieval of scientific articles about food-drug interactions. Currently available ontologies address mainly drug-drug interactions, but much less attention has been given to clinically significant food-drug interactions. This work proposes an extension of a drug interaction ontology following the METHONTOLOGY methodology with the goal of representing potential drug interactions with foods, food components and food categories. To evaluate the proposed formal ontological model, we discuss the results of populating the ontology with information from manually annotated abstracts and from a compendium.

Keywords. Biomedical Ontology, Food-Drug Interactions, Text Mining, Adverse Drug Effects

1. INTRODUCTION

In clinical practice convenience, safety and reduced costs are some of the reasons that make the oral route a preferred method for drug administration. But a main limitation of this route of administration is related to the way drugs move through the digestive tract because of their likely association with other drugs and foods, which may affect how much and how fast a drug is absorbed. To prevent undesired interactions, clinical trials are required prior to drug marketing to systematically analyse the absorption of a drug with respect to standard meals. Additionally, chemical substances and compounds contained in specific foods may occasionally interact with drugs, dramatically increasing or reducing the effect of a drug. Grapefruit for example contains bioactive furocoumarins and flavonoids that activate or deactivate many drugs in ways that can be life-threatening [8]. With a rapid increase in the number of biomedical publications that report food-drug interactions [4], there is a growing need for systems that automatically process scientific literature and for formal models to represent this information. The Food Interactions with Drugs Evidence Ontology, namely FIDEO[2], is created in the frame of the French ANR MIAM (Maladies, Interactions Alimentation-Médicaments, 2017-2020)

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[2] FIDEO Git: `https://gitub.u-bordeaux.fr/erias/fideo.git`

project[3] aiming to automatically extract interactions between foods and drugs and to represent them in an ontology. More precisely, the objectives of this research project are: (i) to automatically identify mentions of food-drug interactions in scientific articles using text analysis, (ii) to represent these interactions in a formal way, and (iii) to make them accessible to healthcare professionals within the Thériaque® database[4], which contains exhaustive information related to drugs marketed in France [19]. This widely used national database, curated by pharmacists, is independent from pharmaceutical companies and the national healthcare insurance fund, gathering information from official sources and from reference books. In this work, we address the second objective of the project and we describe the resulting ontology and the methodology followed to design it.

This paper is organised as follows: we first give an overview of the related work in section 2, than we describe the FIDEO requirements in section 3. We discuss the materials used to engineer the ontology in section 4 and we present the followed methodology in section 5. We conclude this work with a discussion in section 6 and conclusions in section 7.

2. RELATED WORK

The FIDEO ontology builds on one side on large scale efforts modelling the foods domain, namely the FoodOn ontology [9], and on another side on recent work in building evidence-driven ontologies for potential drug-drug interactions, that is the DIDEO ontology [7]. Both ontologies are based on the Basic Formal Ontology, BFO [12] and are compliant with the OBO Foundry [25] principles[5]. FoodOn has been adopted by health researchers and is extended by the Ontology for Nutritional Epidemiology (ONE) with nutritional epidemiology concepts, to assesses the relations between diet, nutrients and health, and disease outcomes [26]. An annotated corpus of online recipes is available [23] that uses FoodIE, an approach for named entity recognition which identifies food items in text [22]. Although FoodOn is a large and growing resource about foods, the types of foods described are far from complete and lag behind information contained in Wikipedia. Recent work proposes a dataset for extracting domain-specific information about foods from a knowledge graph [3]. DIDEO takes an evidence-driven approach to representing drug-drug interactions, acknowledging the need to provide users with supporting evidence to allow them to assess the clinical importance of an interaction and to make management decisions [6]. The type of study that describes an interaction is also represented in the ontology, including for example *in vitro* experiments, population pharmacokinetic analyses, randomised controlled clinical trials, and observational epidemiologic studies. In [7], DIDEO developers point out that the main drawbacks of the Drug Interaction Ontology (DIO) [27] are the following: (i) it contains inconsistencies, and (ii) it does not specify how main entities differ (*i.e.*, drugs, chemicals and molecules). Compared to DIDEO, the Drug-Drug Interactions Ontology (DINTO) [17] received higher traction from the ontology learning community mainly because of a shared task on drug-drug interaction extraction [24] and the associated annotated corpus [18]. But a main limitation of this ontology is that it is not designed from the start based on the BFO ontology, although a concept alignment to BFO is proposed. DINTO does not allow us to

[3]MIAM project: `https://miam.limsi.fr/`

[4]Thériaque database: `http://www.theriaque.org/`

[5]OBO Foundry principles: `http://obofoundry.org/principles/fp-000-summary.html`

describe potential drug interactions, although this is the main type of interactions that are generally described in the literature. Additionally, DIDEO is extended to cover interactions between drugs and natural products including vitamin, mineral, or herbal supplements [20].

3. REQUIREMENTS

Ontology requirements are commonly expressed through competency questions [13], which are natural language questions that illustrate typical knowledge required from the ontology. The following competency questions guide the design of FIDEO:

1. What foods potentially interact with simvastatin?
2. Which drugs potentially interact with grapefruit juice?
3. Which cardiovascular drugs may interact with grapefruit juice?
4. What type of interaction mechanisms underlie the interaction between grapefruit juice and simvastatin?
5. What type of studies describe the interaction between grapefruit juice and simvastatin?
6. What is the level of clinical importance of the grapefruit - simvastatin interaction?
7. Which citrus fruits can be safely consumed by patients taking simvastatin?
8. What alternative drugs can be taken to avoid the interactions between simvastatin and grapefruit?

4. MATERIALS

Three main sources of information are consulted to identify knowledge to be represented in FIDEO: a drug interaction compendium, existing corpora of scientific publications about food-drug interactions, and the contents of the Thériaque database. First, we consult a corpus of relevant scientific publications retrieved from the MEDLINE database. Previously, the POMELO corpus [15] related to food-drug interactions has been constructed using a query in the MEDLINE database with the following terms ([MH] indicates that the keyword had to appear among the MeSH terms chosen to index the articles):

```
(‘‘FOOD DRUG INTERACTIONS’’[MH] OR ‘‘FOOD DRUG INTERACTIONS*’’) AND
(‘‘adverse effects*’’)
```

However, a bibliographic analysis of references cited in a compendium on drug interaction information (*i.e.*, the 8th edition of the Stockley's Drug Interactions[6]) shows that the POMELO corpus only covers 3% of scientific articles related to food-drug interactions that are cited in the Stockley [5]. As this reference is widely used by pharmacovigilance professionals from France, we additionally make use of a larger corpus that contains 1610 abstracts including articles cited in the Stockley compendium. Finally, we consider the types of interaction mechanisms used in Thériaque. Although this list is not meant to be exhaustive, it has the added advantage that it is focused on the most well understood interaction mechanisms.

[6]Stockley: `https://about.medicinescomplete.com/publication/stockleys-drug-interactions/`

5. METHODOLOGY

We present the conception of FIDEO according to the METHONTOLOGY [10] methodology. The first version of the FIDEO ontology follows a waterfall-like process but this knowledge domain can only be accurately represented by an ever-evolving ontology, therefore a more iterative way of maintaining the ontology will be considered for future versions of the ontology [1].

Specification The FIDEO ontology represents knowledge that is necessary to describe interactions between foods and drugs. This ontology makes it possible to structure information related to these interactions, facilitating its exploitation within Thériaque. In addition, for interactions that involve a drug class or a food class, it is useful to infer that potential interactions may occur if other drugs or foods from the same class are ingested concomitantly. Finally, FIDEO can be used to identify food-drug interactions in future scientific articles for feeding the Thériaque database when new knowledge about this type of interactions arises. Users of FIDEO have different profiles: (i) curators of Thériaque interested in integrating FIDEO in the search process of their search engine, (ii) end users of Thériaque's search engine, including health professionals and patients, may browse FIDEO, and (iii) researchers in Natural Language Processing (NLP) may use it as background knowledge to advance research in information extraction methods from medical text. Relevant research areas include food- and drug-related entity extraction, extraction of adverse drug effects, and relation extraction.

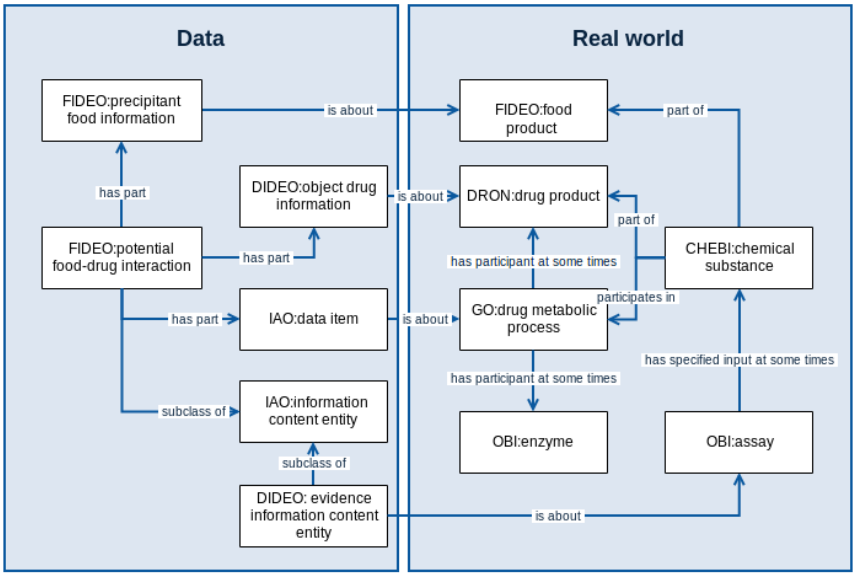

Figure 1. Representation of potential food-drug interactions in FIDEO. Prefixes show concept provenance.

Knowledge acquisition Existing ontologies are investigated using BioPortal[7], a repository that contains the highest number of biomedical ontologies. Starting from the main entity types of interest within FIDEO, we identify relevant ontologies, ontology design

[7]BioPortal: `https://bioportal.bioontology.org`

patterns and external entities to be reused. We first search for ontologies describing drug interactions because pharmacology experts we consulted report they are very similar to food-drug interactions. The main ontologies describing drug interactions are DIO (Drug Interaction Ontology) [27], DINTO (Drug-Drug Interactions Ontology) [17] and DIDEO (Drug-drug Interaction and Drug-drug Interaction Evidence Ontology) [7], all three aligned with the upper ontology BFO [11]. Next, we study existing ontologies related to foods. When analyzing the interactions mentioned in our corpus, we find that in addition to the foods themselves and their categories (*e.g.*, cruciferous vegetables, foods containing tyramine), it is also necessary to represent their cooking preparation and/or preservation methods since these methods may be involved in food-drug interactions (*e.g.*, grilled meat, infused tea, frozen grapefruit juice).

When searching for these terms in BioPortal, we find that a `Food` concept exists in ChEBI (Chemical Entities of Biological Interest) [16], which is particularly interesting since this ontology is used in DIDEO to represent chemical substances. However, this concept is defined as a role according to BFO (`role` being a descendant of `specifically dependent continuant`) while chemical substances (which are used to describe drugs) are material entities (`material entity` being a descendant of `independent continuant`). As we aim to represent these two entities in the same way, the `Food` concept of ChEBI is not appropriate on its own. We finally opt for FoodOn (Food Ontology) [9] because it meets our requirements, with a representation of foods as material entities as well as the presence of the `Food transformation process` concept and its two child concepts `Food cooking process` and `Food preservation process`. Finally, the pharmacology experts involved in the process of designing FIDEO pointed out that DIDEO does not describe types of interactions but this type of information should be represented in the ontology. On the other hand, DINTO contains a `DDI mechanism` (Drug-Drug Interaction mechanism) concept and relevant sub-concepts, but the coverage of interaction types is incomplete. We are currently working on this part in order to enrich the representation of DINTO interactions, notably according to the Interaction Network Ontology (INO) [21] and the interaction types described in the Thériaque database. INO represents general and species-neutral types of interactions and interaction networks, and their related elements and relations.

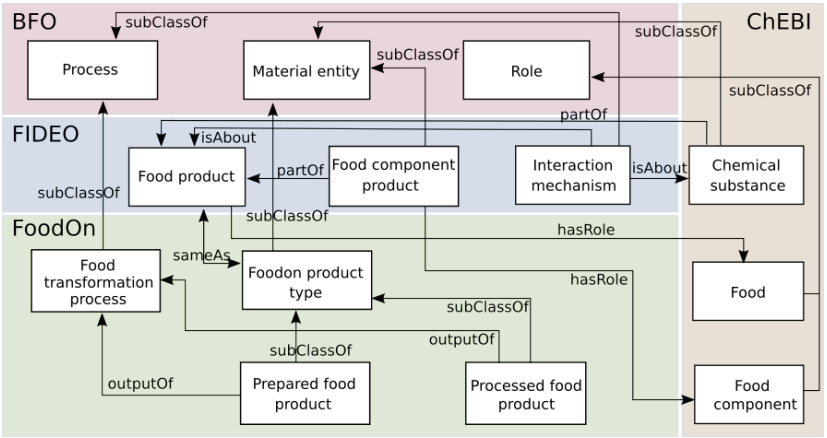

Figure 2. Organisation of top-level concepts in FIDEO according to the ontology they come from.

Conceptualisation Following previous work on formally representing drug interactions, FIDEO makes the distinction between potential interactions as described in biomedical literature and actual interactions that are typically defined in relation with a specific patient. Figure 1 shows on the left side information derived from scientific articles (Data) and on the right side information about biological processes (Real world). FIDEO defines two core concepts, the concept `Potential food-drug interaction` that is linked through a *hasPart* relationship to the `Precipitant food information` entity, identifying the food item that causes the relation. We reuse the `Object drug information` concept from DIDEO to represent the drug that is impacted by the interaction. Concepts from the Information Artifact Ontology (IAO)[8] are used to denote the link to a scientific publication, that is `Data item` and `Information content entity`, with FIDEO interactions being defined as a subclass of the latter one. On the side of biological processes, there are the FIDEO-defined `Food product` concept and the `Drug product` concept from the Drug Ontology (DRON)[9]. Other concepts represented here include those related to the mechanism of interaction described in the Gene Ontology (GO)[10] and the assays described in the scientific publication using the Ontology of Biomedical Investigations (OBI)[11].

Integration Figure 2 illustrates the way top-level concepts are interrelated within FIDEO and how they are associated with BFO concepts. At the top of the figure, we find the main concepts referred from BFO, while the bottom of the figure represents concepts defined in FoodOn. The right hand side of the figure presents the concepts reused from ChEBI. The center of the image describes the main entities defined by FIDEO creators. The integration step is performed manually in order to better structure the concepts coming from the reused ontologies and the new concepts introduced in FIDEO. Thus, drugs are modelled in Figure 2 through the `Chemical substance` concept from ChEBI, which is linked to the `Drug product` concept of DIDEO according to a *partOf* relationship. Drugs and foods are thus represented as material entities (being *subClassOf* `Material entity` in BFO).

For simplicity, we introduce a `Food product` concept being equivalent to the `Foodon product type` concept. This concept has been linked to the ChEBI `Food` concept via an *hasRole* relationship for reflecting that a food as a material entity can only interact with a drug if it is actually used in its nutritional role (*i.e.*, consumed). Food components, designated as `Food component product`, are linked to `Food product` through a *partOf* relationship. The concept `Chemical substance` is also linked to `Food product` by a *partOf* relationship because some foods may contain chemical substances. This link may be useful in inferring a potential interaction with a food containing a chemical substance that is described as interacting with another chemical substance in the frame of a drug-drug interaction. The `Food transformation process` concept is used to describe the transformation processes that foods can undergo (via an *outputOf* relationship). Finally, the `Interaction mechanism` concept, initially defined as a DINTO concept, is renamed since its hierarchy will be enriched and modified to represent the interactions between a food and a drug. This concept is defined as a BFO

[8]IAO: `https://github.com/information-artifact-ontology/IAO/`
[9]DRON: `https://bitbucket.org/uamsdbmi/dron/src/master/`
[10]GO: `http://geneontology.org/`
[11]OBI: `http://obi-ontology.org/`

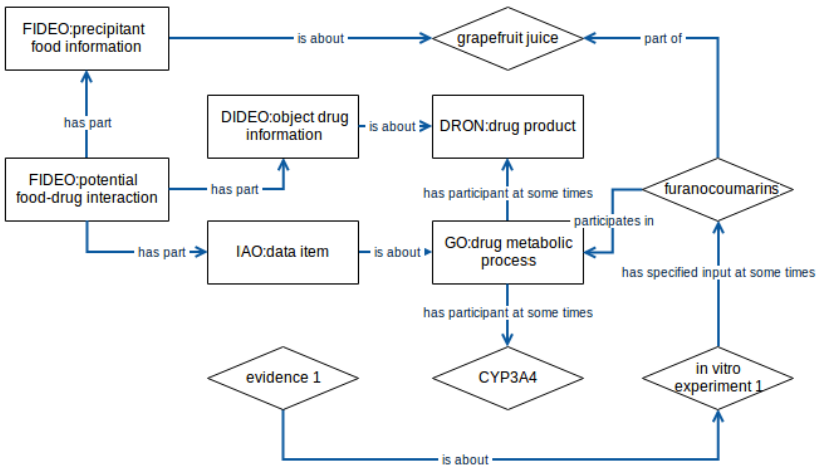

Figure 3. Example of instantiation of a food-drug interactions in FIDEO.

process in FIDEO, similar to other interactions represented in INO. The `Food product` and `Chemical substance` concepts are linked to the `Interaction mechanism` by an *isAbout* relationship.

Implementation FIDEO is implemented in OWL[12] and the definition of FIDEO top-level concepts is done manually using Protégé[13]. Importing concepts from different ontologies using separate modules is also done manually because we include only drugs and foods involved in at least one interaction mentioned in our corpus. This choice is motivated by the fact that ontologies such as ChEBI and FoodOn contain many concepts that are not relevant for the purpose of FIDEO and are impractical when loaded in full in Protégé. Figure 3 provides an instantiation example that represents information given in the following statement from an article about drug interactions of grapefruit juice [14]:

In vitro *experiments confirmed that* ***furanocoumarins*** *from* ***grapefruit juice*** *are both competitive and mechanism-based inhibitors of* ***CYP3A4***.

Based on this statement, a new record is added in FIDEO as shown in the figure, representing evidence from an *in vitro* experiment about active chemical substances contained in grapefruit juice. These chemical substances modify the usual metabolic process of the drug through enzyme inhibition. For the first version of the ontology, we use 20 abstracts annotated by drug safety professionals that curate Thériaque and the Bordeaux pharmacovigilance center within the MIAM project. To map terms used in scientific articles to concepts in FIDEO, terms are first normalised in a basic way (*e.g.*, removal of plurals and special characters, conversion to lower case) and synonyms coming from the UMLS [2] are recovered. In addition, we consider concatenating terms with several frequently used phrases including *food product*, *ratio*, and *of material*. To find potential matches for annotated entities in the reused ontologies, a knowledge graph platform called Stardog[14] is used. This tool allows, among other things, to store large ontologies,

[12] OWL: https://www.w3.org/OWL/
[13] Protégé: `https://protege.stanford.edu`
[14] Stardog: `https://www.stardog.com/`

Drugs	Drug classes	Foods	Food categories	Interactions	Interaction mechanisms
134	4	76	2	569	18

Table 1. Statistics about food-drug interactions described in the current version of FIDEO

to perform SPARQL queries and path queries. Each annotated entity is then searched in the ontologies loaded in Stardog. If a match is found, the concept is imported in FIDEO and if no match is found, the concept is integrated in FIDEO by hand. Additionally, we populate FIDEO with all the foods, drugs, food categories and drug classes that are identified as potentially interacting in the index of the Stockley compendium. The FoodOn taxonomy is used to link food items to corresponding food categories and the ChEBI taxonomy is similarly used to add drugs in the appropriate drug class.

Evaluation As FIDEO has not yet been finalised, the evaluation results are still preliminary. Following the implementation of FIDEO with the 20 abstracts annotated by the experts, the following coverage was obtained for the main entities:

- 82% of drugs and 90% of drug classes are found in ChEBI,
- 62% of foods and 76% of food components are found in FoodOn.

A manual evaluation showed that annotated drugs could not be found in FIDEO because the abstracts mention branded names not generic names (e.g., *Bonefos* instead of *Sodium clodronate*), acronyms (e.g., *Tcy* instead of *tetracycline*) and composed phrases that are not represented as such in FIDEO (e.g., *diclofenac softgel*). There are also incomplete annotations (e.g., *hydroxide gels* instead of *aluminium hydroxide gels*) and a much larger number of foods is not yet represented in FoodOn including food items from Japanese cuisine (e.g., *natto*), generic foods (e.g., *milk*, *juice* and *coffee*), and scientific names (e.g., *Amblygaster*, *Sardinella*). These encouraging results indicate that external ontologies imported by FIDEO cover the knowledge about drugs involved in food-drug interactions in an acceptable manner and about foods to a lesser degree. With respect to the compentency questions used to define the FIDEO requirements in section 3, the current version of the ontology is currently able to answer the questions 1 to 5, while questions 6 to 8 will be part of future work. This is because at the moment our efforts are focused on representing evidence about food-drug interactions. Providing options for the management of food-drug interactions in a clinical setting is an equally important task that will be addressed in the future.

Documentation The present article is the first publicly available document describing the creation of FIDEO.

6. DISCUSSION

An important aspect regarding the types of interactions remains unsolved, that is adjusting the granularity of information which is represented in the ontology. An illustration of this complexity is the change in pharmacokinetic parameters of drugs due to interactions (*e.g.*, increase in plasma concentration, decrease in bioavailability). While this type of information is often discussed in scientific articles, it is typically considered too detailed to be efficiently used in clinical practice and it is beyond the scope of the current version of FIDEO. To assess the clinical importance of food-drug interactions, medical professionals typically take into consideration the level of evidence provided in the literature, but the FIDEO ontology will be populated in the future by a partially automated process

based on information extraction from text, including entity recognition, entity linking and relation extraction. This process will add a level of uncertainty, as automated text analysis introduces errors as well. Ongoing work investigates a metric of confidence that provides an indication of the quality of available evidence about an interaction in combination with information extraction accuracy. A limitation of existing ontologies on representing drug interactions that are extended by FIDEO is that they are not aligned with broader efforts of modelling interactions as biological processes. Current implementations introduce ambiguities, for example *antagonism* has a different meaning when used to describe a *physiological effect antagonism* in the context of a pharmacodynamic drug interaction and when used to describe a type of biochemical binding, where a substance binds to the same site an agonist would bind to without causing activation of the receptor.

7. CONCLUSIONS

In this work, we proposed an ontology that describes potential food-drug interactions along with supporting evidence from scientific articles. We extend existing work on representing foods, drugs and drug-drug interactions to represent food-drug interactions. The METHONTOLOGY methodology was followed to represent foods, food components and food categories as well as specific interaction mechanisms with drugs. The resulting ontology was manually populated using several abstracts annotated by pharmacology experts in addition to information described in a compendium of drug interactions. Evaluation results show higher coverage of drugs and drug classes than of foods, food components and food categories in the ontologies extended by FIDEO. Future work will include an integration of automated processes of information extraction from scientific publications, along with a confidence score that provides a combined indication of text analysis accuracy and evidence level. We will also propose a closer alignment of drug interaction ontologies with existing work on representing interaction networks.

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