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Automatic determination of anticoagulation status with NDF-RT

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ABSTRACT

Objectives: To determine the anti-coagulation status of patients, based on the list of medications they have been prescribed, using the publicly available resource NDF-RT (National Drug File Reference Terminology). **Methods**: We explored the legacy VA classes and we refined the definition of external pharmacologic classes (EXT) in NDF-RT in order to enable inferences by a description logic classifier. **Results**: Of the 9 patients with a positive anticoagulation status, the VA class approach identified only 6, while the EXT approach identified 8. **Conclusions**: This preliminary experiment illustrates the benefits of using a refined definition of external pharmacologic classes in NDF-RT. Further investigation is needed. **Supplementary figure**: Representation of the drug *clopidogrel* in NDF-RT, available at: http://mor.nlm.nih.gov/pubs/supp/2010-bioonto-ob/index.html.

1 INTRODUCTION

Patients suffering from heart failure are increasingly treated with implantable cardioverter defibrillators (ICD) and benefit from home monitoring. In this context of telecardiology, ICDs send remote alerts about arrhythmic episodes to physicians, who have to determine their emergency level. The objective of the French AKENATON project is to integrate the data transmitted by the ICDs with their clinical context, in order to improve alert management (AKENATON, 2010; Burgun, et al., 2010). For example, in case of atrial fibrillation, the thromboembolic risk depends on the medications taken by the patient. The formation of a clot in the heart is a complex process that involves platelets and multiple substances called clotting factors.

Medications that prevent blood clots from occurring include platelet aggregation inhibitors and anticoagulants (Weimar, et al., 2009). Platelet aggregation inhibitors, such as clopidogrel, work by decreasing the ability of platelets to aggregate. Aspirin also makes platelets less likely to form blood clots. Oral anticoagulants, such as warfarin, decrease the body's ability to form blood clots by blocking the formation of vitamin K-dependent clotting factors. Another anticoagulant, heparin, is less likely to be prescribed to patients at home, as it requires parenteral administration (intravenous or subcutaneous route).

From the perspective of clinical pharmacology, *clopidogrel* and *warfarin* are active moieties, while *platelet aggregation inhibitors* and *anticoagulants* are pharmacologic classes. Classes are typically established in reference to some of the properties of the active moiety, with respect to chemistry, physiology, metabolism and therapeutic intent (Carter, et al., 2006). For example, the classes *platelet aggregation inhibitors* and *anticoagulants* refer to the physiologic effect of drugs decreasing platelet aggregation and coagulation, respectively. In contrast, the class *cardiac glycoside* refers to the chemical structure of drugs such as *digoxin*, while the class *antianginal* refers to the therapeutic properties of some drugs on angina pectoris. Some classes are also defined in reference to several properties, e.g., *nitrate vasodilator*, referring to both the chemical structure of nitrates and their relaxing action on the musculature of blood vessels (physiologic effect).

The main objective of this study is to determine the anticoagulation status of patients from the AKENATON project, based on the list of medications they have been prescribed. A secondary objective is to evaluate the extent to which the publicly available resource NDF-RT (National Drug File Reference Terminology) provides appropriate classes and drug-class membership relations to support such a use case.

2 BACKGROUND

The National Drug File Reference Terminology (NDF-RT) is a resource developed by the Department of Veterans Affairs (VA) Veterans Health Administration, as an extension of the VA National Drug File (Lincoln, et al., 2004). Like other modern biomedical terminologies, NDF-RT was developed using description logics and is available in several formats, including XML and OWL. The version used in this study is the latest OWL version available, dated September 1, 2009, downloaded from the NCI website[1]. This version covers 1751 active moieties (level = ingredient) and 4695 clinical drugs (level = VA product). Two independent kinds of drug classes are represented in NDF-RT: legacy VA

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[1] ftp://ftp1.nci.nih.gov/pub/cacore/EVS/NDF-RT/

classes and "external pharmacologic classes" defined in reference to some of the properties of the active moiety.

Legacy VA classes are simply listed as parents of clinical drugs ("VA Products"). For example, the drug *CLOPIDOGREL BISULFATE 75MG TAB* is a subclass of *PLATELET AGGREGATION INHIBITORS*. There are 485 such VA classes, organized in a shallow hierarchy. The set of VA classes forms a classification system, i.e., accommodates virtually any drug through residual classes (e.g., *BLOOD PRODUCTS, OTHER*). In most cases, a clinical drug is associated with one and only one class. No relations are stated between these classes and drug properties.

External pharmacologic classes are defined in reference to the properties of active moieties. A given class can reflect one property (e.g., *Platelet Aggregation Inhibitor*[2], in reference to the physiologic effect *Decreased Platelet Aggregation*) or multiple properties (e.g., *Antiarrhythmic*, in reference to the therapeutic intent – both preventative and curative – expressed as *may_prevent Arrhythmia* and *may_treat Arrhythmia*). There are 408 such external pharmacologic classes, with no hierarchical organization. Although active moieties are also described in terms of similar properties (e.g., *CLOPIDOGREL*, in reference to the physiologic effect *Decreased Platelet Aggregation*), no relations are found between active moieties (ingredients) and external pharmacologic classes. Moreover, from the perspective of description logics (DL), because all concepts in NDF-RT are primitive concepts (i.e., no necessary and sufficient conditions are provided for external pharmacologic classes), no inferred relations can be computed automatically by a DL classifier between active moieties and external pharmacologic classes. In practice, *CLOPIDOGREL* and *Platelet Aggregation Inhibitor* are not related – directly or through inference – in the current OWL version of NDF-RT.

Several groups have investigated various aspects of NDF-RT, including coverage (Brown, et al., 2004), representation of specific drug properties (Rosenbloom, et al., 2003), and fitness for purpose in applications, such as linkage to indications (Burton, et al., 2008) and detection of drug intolerance (Schadow, 2009). Our present investigation of NDF-RT is also performed in the context of an application. The specific contribution of our study is to leverage (and improve) the description logic representation of pharmacologic classes in NDF-RT.

3 MATERIALS AND METHODS

3.1 Establishing medication lists

A list of twelve records was obtained from the AKENATON project, corresponding to patients with implantable cardioverter defibrillators. The list of medications for each patient was extracted manually from the text of the records, yielding a total of 46 medications (3.6 per patient on average). Medication names were mapped manually to generic ingredient names. This step was necessary, because of localized brand names (e.g., *Lasilix* in France vs. *Lasix* in the U.S. for *furosemide*). A total of 23 unique ingredient names were identified. Ingredients were mapped to NDF-RT identifiers automatically through the RxNav API (Peters and Bodenreider, 2008). In four cases, no NDF-RT correspondence was found for the ingredient. In 3 of these cases, the corresponding ingredient was simply discarded, as it was not central to our investigation (*betahistine*, an antivertigo drug; *trimetazidine*, an anti-anginal agent; and *zopiclone*, a hypnotic agent). The remaining ingredient with no mapping to NDF-RT was the anticoagulant *fluindione* – prescribed in Europe, but not in the U.S. – to which we substituted a similar drug, *anisindione*. Finally, in one case, the medication was expressed not as a clinical drug, but directly as a class (*Vitamin K Antagonist*).

3.2 Establishing relations between ingredients and external pharmacologic classes

Unlike for legacy VA classes, no relations are present in the OWL version of NDF-RT between drugs and external pharmacologic classes. Moreover, because the external pharmacologic classes are all primitive concepts, no such relations can be inferred by a DL classifier. In order to support such inference, we modified the OWL version of NDF-RT in the following ways.

Step 1. We transformed the primitive concepts for external pharmacologic classes into defined classes by specifying a set of necessary and sufficient conditions for the class (adding an `owl:equivalentClass` (≡) axiom). The restrictions based on *has_TC* are specific to external pharmacologic classes (providing links to high-level therapeutic class concepts) and not used in the ingredients. For this reason, they were left out of the necessary and sufficient conditions.

Step 2. Because the therapeutic intent properties *may_treat* and *may_prevent* are not always used consistently in the ingredients compared to the external pharmacologic classes, we replaced these two properties by a newly created property *may_treat_or_prevent* (in the definition of the external pharmacologic classes), of which *may_treat* and *may_prevent* were made a sub-property (`rdfs:subPropertyOf`). For example, the class *Antimalarial* is defined as *may_treat* some *Malaria* AND *may_ prevent* some *Malaria*. In contrast, the drug *HALOFANTRINE*, is only defined in reference to the treatment of malaria (e.g., *may_treat* some *Malaria, Falciparum*). Such description of *HALOFANTRINE* is indeed appropriate as *HALOFANTRINE* is not to be used as chemoprophylaxis. However, it would prevent *HALOFANTRINE* from being classified as

[2] The VA classes (e.g., *PLATELET AGGREGATION INHIBITORS*) and the external pharmacologic classes (e.g., *Platelet Aggregation Inhibitor*) are distinct and unrelated in NDF-RT.

Antimalarial (because it lacks the required preventative aspect), which is why we modified the definition of external pharmacologic classes with *may_treat_or_prevent*.

Step 3. Finally, there is a difference in how ingredients and external pharmacologic classes are related to chemical entities. For example, the class *Low Molecular Weight Heparin* is (directly) related to the chemical entity *Heparin, Low-Molecular-Weight* through the property *has_Chemical_Structure*, whereas the drug *ENOXAPARIN* is (indirectly) related to the same chemical entity through a different property, *has_Ingredient*. The absence of any relation between the two properties prevents the classifier from inferring a relation between *ENOXAPARIN* and *Low Molecular Weight Heparin*. Although semantically different, the two properties are "functionally equivalent" for the purpose of relating drugs to classes. We enabled this inference by making *has_Ingredient* a sub-property of *has_Chemical_Structure*.

The modifications described above were implemented into the OWL file using an XSL (eXtensible Stylesheet Language) transformation. The resulting OWL file was classified with HermiT (University of Oxford - Information Systems Group, 2010). Protégé 4.1 was used for visualization purposes (Stanford Center for Biomedical Informatics Research, 2010). The OWL file containing the inferences computed by the classifier was loaded in the open source triple store Virtuoso (OpenLink Software, 2010), along with the transitive closure of `rdfs:subclassOf` relations. The query language SPARQL was used for testing whether a given drug was an anticoagulant or a platelet aggregation inhibitor.

3.3 Determining anticoagulation status

As mentioned earlier two major classes of interest with respect to anticoagulation status in the AKENATON project are *anticoagulants* and *platelet aggregation inhibitors*. We use NDF-RT as a source of relations between ingredients (mapped from the original medication lists) and drug classes. The anticoagulation status for a given patient is "positive" if at least one ingredient from at least one drug prescribed to this patient is linked to any of the two classes of interest; the status is "negative" otherwise. The two types of classes in NDF-RT, legacy VA classes and external pharmacologic classes, are investigated separately.

Using legacy VA classes. The two classes of interest are *[BL110] ANTICOAGULANTS* and *[BL117] PLATELET AGGREGATION INHIBITORS*. A SPARQL query is used to list all VA classes of which a given drug is a subclass (directly or indirectly, through the transitive closure).

Using external pharmacologic classes. The two classes of interest are *Anti-coagulant* and *Platelet Aggregation Inhibitor*. A SPARQL query is used to list all external pharmacologic classes of which a given drug is a subclass (after reclassification of the modified OWL file with HermiT).

3.4 Evaluation

The reference membership of the medications to any of the classes of interest was established manually by one of the authors (OB). The classification obtained using legacy VA classes and external pharmacologic classes was compared to the reference.

4 RESULTS

4.1 Individual drugs

Of the 23 unique ingredients investigated, three were determined to be platelet aggregation inhibitors and anticoagulants: *anisindione*, *aspirin* and *clopidogrel*. The drug-class membership for these three ingredients and the two classes of interest is shown in Table 1.

Anisindione is correctly identified as an *anticoagulant* through both legacy VA classes (VA) and external pharmacologic classes (EXT). Analogously, *clopidogrel* is correctly identified as a *platelet aggregation inhibitor* through both types of classes. In addition, *clopidogrel* is also identified as an *anticoagulant* through EXT. The primary class-membership is to the class *Platelet aggregation inhibitor*, but, since *Platelet aggregation inhibitor* is a subclass of *Anticoagulant* (inferred), *clopidogrel* is also inferred to be an anticoagulant. (In contrast, in the VA class hierarchy, *PLATELET AGGREGATION INHIBITORS* is not a subclass of *ANTICOAGULANTS*). Finally, *aspirin* is correctly identified as a *platelet aggregation inhibitor* only through EXT. Through the various clinical drugs of which it is an ingredient, *aspirin* is linked to several VA classes including *ANALGESICS, NON-OPIOID ANALGESICS, ANTI-RHEUMATICS* and *SALICYLATES, ANTIRHEUMATIC*. None of these classes is related to platelet aggregation inhibition and VA classes fail to identify aspirin as *PLATELET AGGREGATION INHIBITORS*.

Table 1. Drug-class membership for the two classes of interest, determined using legacy VA classes (VA), external pharmacologic classes (EXT), and compared to the reference (Ref)

	Anticoagulant			Platelet aggregation inhibitor		
Ingredient	VA	EXT	Ref	VA	EXT	Ref
anisindione	Yes	Yes	Yes	No	No	No
aspirin	No	*(Yes)*	No	**No**	Yes	Yes
clopidogrel	No	*(Yes)*	No	Yes	Yes	Yes

4.2 Anticoagulation status of AKENATON patients

From the medication lists extracted from AKENATON for the 12 patients under investigation, the reference anticoagulation status was determined to be positive for 9 patients and

negative for 3. Of the 9 patients with positive status, 6 are treated with anticoagulants and 3 with platelet aggregation inhibitors. Both approaches failed to identify as positive one patient whose medication was stated not as a clinical drug, but as a class: *Vitamin K Antagonist*. This class is not part of the list of legacy VA classes and, although it is found among the external pharmacologic classes, it is not listed as a subclass of *Anticoagulant*. Except for this omission, the anticoagulation status determined through external pharmacologic classes was identical to the reference status. Using legacy VA classes, only 6 of the 9 patients with positive status were identified. (In addition to the *Vitamin K Antagonist* case, two patients treated by *aspirin* failed to be identified as treated with *platelet aggregation inhibitors*.)

5 DISCUSSION

5.1 Consequences for AKENATON

The practical objective of AKENATON is to help telecardiology specialists classify the remote alerts sent by ICDs according to their severity and emergency level. This use case illustrates the central role played by a drug ontology in the determination of the anticoagulant status of a given patient, i.e., its role in clinical decision support for telecardiology. The refined version of NDF-RT we created successfully identified the anticoagulation status of 8 of 9 patients and appears to be a useful resource for the AKENATON project with respect to this particular use case.

5.2 Issues

Despite of the small scale of this study, our investigation revealed some issues in using NDF-RT for clinical decision support, related to both the formalism and the content.

Formalism. As indicated by the length of section 3.2, quite a bit of work was required for us to be able to infer drug-class membership for the external pharmacologic classes from the information available in the OWL version of NDF-RT. The name of the file "NDF-RT_OWL_-Inferred" is somewhat misleading, as what is inferred is not drug-class membership, but, more trivially, the properties of ingredients at the clinical drug level.

Content. In addition to the discrepancies between membership to VA and external pharmacologic classes noted above, our exploration revealed missing drug-class membership information. While this was expected for VA classes, for which single membership is customary, missing relations attributable to incomplete and inconsistent class descriptions was also observed in the external pharmacologic classes (e.g., *Vitamin K Antagonist*).

5.3 Limitations and future work

The major limitation of this study is its limited scale, which makes any generalization unreliable. This study is in fact pilot work before performing a systematic investigation of the drug-class membership and its impact on clinical decision support. One minor limitation is the need for extracting medication information from text, leading to imprecise descriptions (e.g., "the patient takes vitamin K antagonists"), and for adapting European branded drug names to ingredients in a US information source. Medication lists coded to standard drug vocabularies should become available in the near future with the deployment of health information technologies (e.g., Computerized physician order entry (CPOE) systems) compliant with "meaningful use" criteria.

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