Categorizing the suitability of an alternative for a subject

An application to antibiotics prescription recommendation

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***Abstract*—Nowadays there is a real need to operate and link existing knowledge expressed by experts, in domains in which highly reliable recommendation systems are needed. This is especially true in the medical domain where knowledge sources are heterogeneous, since they are separately formed in different contexts. A major difficulty is to relate these sources together in a way that respects the specic medical recommendation requirements. Using MCDM (Multi-Criteria Decision Making) models can help in this aim. The general problem we address is to assess the suitability of an alternative (or a solution) for a given subject in a specific context. For instance, which antibiotic (alternative) should be prescribed to a patient (subject) who suffers from bacterial infection, taking into account characteristics of the patient such as allergies, renal problems, etc. We use a MCDM sorting method (MR-Sort with Veto, a variant of ELECTRE TRI), to categorize the pairs alternative-solution (e.g. antibiotic-patient) according to their degree of suitability. The contextual knowledge (e.g. side-effects of antibiotics, characteristics of patient), structured in several ontologies, is linked to the assessment model through a semantic model. The approach is applied to the recommendation of antibiotic prescription, in collaboration with the EpiCura Hospital Center.**

I. Introduction

Knowledge sources in the medical domain are spread and heterogeneous since they are created separately in different contexts. Thus it is often uneasy to link them together in a way that can support decision making and recommendations. The main challenge here is to combine these sources in a way that can provide broader understanding, as well as improved and consistent knowledge relating to the recommendation task.

Using MCDA (Multi - Criteria Decision Aiding) in a knowledge-driven DSS (Decision Support System) can help alleviate this problem. A knowledge-driven DSS provides expertise to specialized problems storing facts, rules, procedures or similar structures [1]. Knowledge in a DSS can be expressed in different ways such as databases, thesauri or ontologies. In several cases a DSS needs to be based on a relatively wide domain of knowledge. The "expertise" in these human-computer systems consists of (a) knowledge of a particular domain (b) understanding of problems within that domain, and finally (c) in "skills" at solving some of these domain problems. Our objective in this work is to conceive a system architecture that allows to assess the suitability of an alternative (or a solution) for a given subject in a specific context. For instance, in a medical context, which antibiotic (alternative) should be prescribed to a patient (subject) who suffers from bacterial infection, taking into account characteristics of the patient such as allergies, renal problems, etc. As an instantiation of this system architecture, we shall build a model for a medical DSS that links knowledge structures for prescription recommendation. Our proposed method of combining ontologies with MCDM aims to allow physicians to have a sorted list of antibiotics assessed according to their adequacy to a given patient with a disease. We use ontologically structured knowledge about the pharmacological characteristics of antibiotics and an ontology describing the critical clinical criteria of patients. These ontologies are then linked through a set of rules structured in our adaptation of the ELECTRE TRI model [2], the Majority Rule Sorting model (MR-Sort) with Veto [3], that sorts alternatives into ordered categories. This process results in antibiotic prescription recommendations categorized by the risk of their side effect toxicity. We model the relations between concepts by broad rules with a small number parameters, to guarantee generality and maintainability of the knowledge model.

The main contributions of this paper are :

- The proposal of a general system architecture for assessing the suitability of pairs alternative-subject in a specified context;
- A new model for medical Decision Support Systems combining MCDM with ontologies;

- An adapted version of ELECTRE TRI, the Majority Rule Sorting model (MR-Sort) with Veto that is tailored to prescription recommendation;
- An experimental validation of the above model for categorization of antibiotics through side-effect toxicity for a given patient.

The rest of this work is organized as follows: Section 2 presents our problem statement and related work as well as additional background information. Section 3 describes how we have adapted the MR-Sort model to combine knowledge about antibiotics side effects and the patient's profile, encoded in ontologies, to produce recommendations. Section 4 details our validation for categorizing antibiotics w.r.t. side-effect toxicity for each patient. Finally in section 5, we conclude the paper and present future perspectives.

II. The problem and related work

Adverse drug events are one of the most important causes of mortality in the healthcare context. They cause each year between 700000 and 1.5 million casualties in the United States [4]. From these, antibiotics are the second most common cause of drug related adverse events [5] [6] [7] and one of the most common class of drugs associated with medical malpractice claims [8]. In this context, many hospitals use guidelines to guide antibiotic prescriptions by linking infection diagnosis to its relevant antibiotic therapies.

As an example our collaborators in the EpiCura hospital center have been using a one hundred pages guideline [9] since 2011. The existence of these guidelines does not seem to have had a significant impact w.r.t. the malpractice issue. This is due to the fact that in their current textual form these guidelines are static, making them hard to use and adapt to either specific needs of the patient or changing contexts in the environment (usage in the emergency rooms, etc). We thus believe that an automated or semi-automated knowledge based information system will be very beneficial to physicians in this particular context.

One of the main ways to represent knowledge is through ontologies, which were introduced in Computer Science by Gruber [10]. Gruber defines an ontology as "an explicit specification of a conceptualization" and described the main ontological elements, such as classes, relations, functions, and other objects [10] [11].

Although much research has been conducted recently on generating medical ontologies based on the semantic web, most of them have been focused on differential diagnosis of either specific or general diseases. From the perspective of antibiotics, a recent study [12], developed a formal ontology to structure the empiric antibiotic therapy guidelines of the New-York Presbyterian Hospital (NYP). The guidelines have been explicitly entered in Protégé [13]. This system was able to generate three kinds of prescribing alerts when the guidelines were not respected. Despite its advantages, this approach has serious limitations. Its main drawback is that both the basic data and the relationships between them should be explicitly entered in the system (i.e. the system cannot generalize to new data), making maintainability difficult, if not impossible.

Other works tried to handle this problem by combining machine learning algorithms with semantic web technologies. In this case, the work presented in [14] has proposed a case-based reasoning methodology for querying a diagnostic knowledge base. Their proposal uses ontologies on diagnosis of the tuberculosis disease and tries to recommend relevant treatments. Nevertheless, one of the main problems with this approach is that it cannot be easily extended. The ontology in this case is only applicable for the treatment of a specific disease (tuberculosis). Furthermore, recommendations based on previous treatments (i.e. through learning) alone cannot safely satisfy all cases in the area of medical knowledge.

Moreover funded projects around semantic technologies for medical procedures such as the REMINE project [15] and PSIP [16] use data mining to reduce drug adverse effects by taking into account the patient's medical records. Despite these efforts there is currently no widely accepted standardized framework that will help physicians in their day to day prescriptions needs, although some researchers have tried to move towards this direction [17], [18]. The broader approach taken by [19] aims to cover drug to drug interactions and drug to diseases interaction but with no apparent consideration of patient sensibilities to drug side effects.

In other application domains (such as the touristic sector), it has been proposed to recommend actions using ontological knowledge representations with MCDM. The two most prominent examples [20] [21] are recommendation systems of touristic activities. On the one hand [20] is a Web-based system which combines ontologies to provide personalized recommendations of activities. While [21] uses linguistic tags to describe user preferences in an ontological structure. From that an outranking, knowledge based relation is constructed.

The general type of problems we aim to address in this work can be described as categorizing the suitability of alternatives (e.g. drugs, trips) by taking into account the characteristics of the subject (e.g. patient, client). This is basically the aim of recommender systems, except that, in our case, we cannot learn the "preferences" of the subjects from categorized examples. Instead, we need to build an explicit model of preference (or suitability) that assesses the quality of matching between the characteristics of each alternatives and the related characteristics of the subject. In this work, this assessment will be performed by assigning each pair (alternative, subject) to a category selected in a predefined ordered set of categories. In such a problem, it is essential to know which characteristics of the alternatives and the subject are relevant for the suitability assessment and which ones are related to the others. Ontologies provide good means for structuring the knowledge describing respectively the alternatives and the subject. A MCDM model can be used to link the appropriate features of alternatives and subjects and assess the suitability of pairs (alternative, subject) for a given purpose.

In this paper we tailor such an approach to the recommendation of antibiotic prescription for a given patient with a particular disease, personal features and medical history. It serves the three main goals of antibiotic prescription (described in [22]), namely: (a) Maximizing the likelihood and rate of cure (b) Minimizing toxic and deleterious side effects and (c) Reducing the risk of bacterial resistance to the antibiotic. This paper focuses on the second goal of *minimizing toxic and deleterious side effects* through the combination of MCDM with semantic technologies. The combination of these technologies has the potential to be transferred to other domains (see e.g. [20]).

III. The model

A. Adapting MR-Sort to the categorization of suitability

MR Sort with Veto ([3] [23] [24] [25] and [26]) is a simplification of ELECTRE TRI [27] [28], which belongs to the family of the ELECTRE model [28] [29] [30] , itself included in a larger family known as the Outranking methods [2] [29] . The goal of MR Sort and ELECTRE TRI [27] is to sort alternatives in ordered categories based on their performance in several criteria. More specifically, each category $C_i, i = 1, \ldots, p$, is associated a lower profile $t^-(C_i)$, which is a vector of levels on each criterion representing the minimal requirements to belong to category C_i. The upper profile $t^+(C_i)$ of the category C_i is the lower profile of the category C_{i+1}, implying that this category contains better alternatives. Figure 1 shows the relationship between these thresholds and the categories.

The principle implemented in ELECTRE TRI and MR-Sort with Veto to assign alternatives into categories is the following. An alternative is assigned to category C_i or better (i.e. C_{i+1} up to C_p) if the performances of the alternative are at least as good as these of the profile $t^-(C_i)$ on *a majority* of criteria and none of these performances is unacceptably bad. Unacceptably bad performances are determined by *veto thresholds* on each criterion.

In this work, we use MR-Sort with Veto to model and assess the quality of the matching between an alternative and a subject.

We consider cases in which each alternative may have, or not, some disadvantages or drawbacks and the subject may be sensitive, or not, to each disadvantage. Let A_i, $i = 1, \ldots, n$, denote the alternatives that are considered as potentially suitable. Their actual suitability for a given subject has to be assessed. The set of all possible disadvantages is $\{D_j,\ j = 1, \ldots, m\}$. For a given subject and a given alternative A_i, we have to determine whether the alternative has the disadvantage D_j and whether the subject is sensitive to D_j. This information will be extracted from the knowledge bases using appropriate ontologies (see The Semantic Model section below). For a fixed subject, the degree of seriousness of disadvantage D_j for the alternative A_i is encoded as the variable DAS_{ij}. For the needs of the application to antibiotics prescription, we set DAS_{ij} as follows :

DAS_{ij}, $i \in 1, \ldots, n$, $j \in 1, \ldots, m$ is a variable taking its values from $\{0, 1, 2, 3\}$.

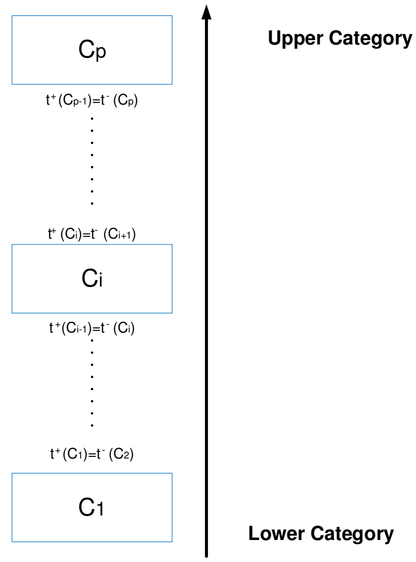

Fig. 1. Categories and their Separating Thresholds

- $DAS_{ij} = 0$ indicates that the subject is not sensitive to disadvantage D_j or alternative A_i does not have this disadvantage.
- $DAS_{ij} = 1$, 2 or 3 indicates that A_i has disadvantage D_j and the subject is sensitive to this disadvantage. $DAS_{ij} = 1$ (resp. 2, 3) if the consequences for the subject of disadvantage D_j are moderate (resp. major, extreme).

Note that this is only an example of a scale for DAS_{ij}. More general scales can be considered.

In the application, the alternatives are sorted in three categories $(p = 3)$: R ("recommended"), P ("possible") and TBA ("to be avoided"). The MR-Sort with Veto assigns alternatives as follows. An alternative is assigned to category R for a given subject if it has only a small number of disadvantages that the subject is sensitive to and if there is no unacceptable disadvantages for the same subject (no veto for R). A similar rule applies for an alternative being assigned to category P. The number of disadvantages tolerated can be higher than those for category R and the list of unacceptable disadvantages can possibly be smaller. If none of these conditions are fulfilled, the alternative is assigned to category TBA.

These assignment principles are implemented using the following mathematical representation. Let DAS_i be a number associated to alternative A_i and counting for a given subject, the number of disadvantages D_j such that $DAS_{ij} \neq 0$.

For a given subject, the assignment of a suitable alternative A_i to the class R, P or TBA is summarized in Table I. If the number DAS_i of disadvantages of alternative A_i for the subject is smaller than λ_R and if no major disadvantage $(DAS_{ij} = 2)$ belongs to the set Veto[R] of unacceptable

$DAS_i < \lambda_R$ and no veto [R]	Recommended
$DAS_i < \lambda_P$, no veto [P] and not Recommended	Possible
$DAS_i > \lambda_P$ or veto [P]	To be avoided

TABLE I

MR-SORT WITH VETO SORTING RULE

disadvantages for R, then A_i is assigned to category R. Otherwise, A_i is assigned to category P provided the number of disadvantages DAS_i is less than λ_P and no extreme disadvantage ($DAS_{ij} = 3$) belongs to Veto[P]. If these conditions are not fulfilled, A_i is assigned to TBA. Using such a rule, this requires to set the following parameters:

- Two tolerance levels λ_R, λ_P with $\lambda_R < \lambda_P$ determine the maximal number of disadvantages that are compatible with an assignment in categories R and P, respectively.
- A major disadvantage $DAS_{ij} = 2$ (resp. $DAS_{ij} = 3$) can preclude assignment of A_i to category R or P. The list of unacceptable disadvantages for an assignment to category R (resp. P) is a subset Veto[R] (resp. Veto[P]) of the set of all disadvantages.

Again, this example can be generalized to the assignment to an arbitrary number p of categories $C_1, \ldots, C_p$ (numbered in increasing order of suitability). This would require the definition of thresholds $\lambda_p \leq \lambda_{p-1} \leq \ldots \leq \lambda_2$ and of veto sets Veto$[C_p]$ $\supseteq$Veto$[C_{p-1}]$ $\supseteq \ldots \supseteq$Veto$[C_2]$. Note also that a weight w_j can be associated to each disadvantage, in which case DAS_i should be computed as the sum of the weights of the disadvantages of alternative A_i to which the subject is sensitive.

B. The Semantic Model

The semantic model is specific to each application. It aims at assigning values to DAS_{ij} for any given subject by extracting information from databases. This can be performed by using ontologies which structure the knowledge about alternatives and subjects that is relevant in the application context. In this section, we outline how this was done in our application case. The subject is a patient who hosts pathogens which cause a bacterial infection. A list of antibiotics covering these germs has been determined. They constitute the alternatives that are potentially suitable. At this stage, we have to take into account the patient's characteristics in order to assign each antibiotic to a class of suitability among $\{R, P, TBA\}$.

For this purpose we use an ontology O_P that corresponds to the patient characteristics. It contains his/her gender, age, comorbidities, allergies, and all the necessary patient information in order to assess the efficiency and the risks of an antibiotic. All these characteristics influence the antibiotic choice in a way that is specified in reasoning rules. Indeed, a given antibiotic could suit a pregnant woman but not an old diabetic man, and vice versa. In this setting, the disadvantages D_j, $j = 1, \ldots, m$ are *side effects* of the antibiotics and they are denoted by S_j, $j = 1, \ldots, m$.

The variable $SP_j \rightarrow \{0, 1, 2\}$ which is described in Figure 2 (a), represents the sensitivity indication of patient to the side

(a)

Side effects	Patient
S_1	SP_1
....	....
S_j	SP_j
S_m	....

(b)

Side effects / antibiotics	A_1	A_2	....	A_i	.....	.....	A_n
S_1	....	....	....	....	....	....	....
....	....	....	....	....	....	....	....
S_j	....	....	....	SA_{ij}	....	....	....
S_m	....	....	....	....	....	....	....

(c)

Side effects	Antibiotic per patient
S_1	
....	....
S_j	**$DAS_{ij} \longrightarrow \{0,1,2,3\}$**
....	....
S_m	

Fig. 2. (a) Patient criteria to side effects relation (b) Relationship between Antibiotics and Side effects (c) Connection between Patient criteria and antibiotics

effect S_j. A value of 0 here means "no sensitivity", a value of 1 "minor sensitivity", while 2 represents "major sensitivity".

Our second ontology O_A provides us with all side effects S_j of a given antibiotic A_i.

The variable $SA_{ij} \rightarrow \{0, 1, 2\}$ described in Figure 2 (b), represents the relation between an antibiotic A_i and a side effect S_j with indication of seriousness. A value of 0 here indicates that the antibiotic A_i does not have the side effect S_j, a value of 1 that the antibiotic A_i has the side effect S_j but with a mild seriousness indication and a value of 2 that the antibiotic A_i has the specific side effect S_j and it's very serious.

Finally the term $DAS_i = \sum_j min\{DAS_{ij}, 1\}$ described in Figure 2 (c), represents for every antibiotic A_i the number of side effects that the patient is sensitive too with DAS_{ij}. We then define: :

$$DAS_{ij} = \begin{cases} 0 & if\ SA_{ij} = 0\ or\ SP_j = 0 \\ 1 & if\ SA_{ij} = 1\ and\ SP_j = 1 \\ 2 & if\ SA_{ij} = 1\ and\ SP_j = 2 \\ & or\ SA_{ij} = 2\ and\ SP_j = 1 \\ 3 & if\ SA_{ij} = 2\ and\ SP_j = 2 \end{cases}$$

In the application to antibiotic prescription recommendation, the total number of side effects considered is 45 for 60 antibiotics and 18 patient characteristics. These characteristics determine the patient's sensitivity to the side effects.

C. Using MR-Sort with the Semantic Model

Finally in the next step (illustrated in Figure 3), the combined MR-Sort with Veto/Semantic model assesses one by one each antibiotic A_i. It counts the number of side effects the patient is sensitive to. This number is represented by the term DAS_i in our model.

At the same time, two additional thresholds are implemented in the model. The first, λ_1, is the maximum number of side effects the antibiotic could have to be in the R (recommended) category. The second, λ_2, is the maximum number of side effects the antibiotic could have to be in the P (possible) category. Of course here we have $\lambda_1 < \lambda_2$.

Furthermore, some side effects can have a severe impact on a patient, that is why two vetoes are added to the model. A first veto, Veto[P], is put when the antibiotic has an unbearable side effect for the patient. This antibiotic could not be prescribed, even though it only has this side effect. For example, this veto would be raised if the antibiotic contains penicillin and if the patient has a major allergy to penicillin. With a Veto[P], the considered antibiotic is put in the TBA category. Similarly, a second veto, Veto[R], is put when the antibiotic has a severe impact on the patient's health, which, however, is not unbearable. For instance, an antibiotic which contains penicillin would get this Veto[R] if the patient has a minor allergy to penicillin. With the Veto[R], the considered antibiotic A_i is put either in the P (possible) or in the TBA (to be avoided) category, depending on the value of DAS_i.

IV. Validation

For validating our approach we have built multiple scenarios in close cooperation with practitioners of the EpiCura hospital center [9] (infectiologist, microbiologist). Through several sessions we were able to fine-tune the sensitivities and the profiles of our model. In order to illustrate this work, let us consider the following case :

Dolly is a pregnant woman, she is 35, she is in good health without medical incidents history. Her laboratory tests reveal that she does not have allergies and her creatinine level is 90ml/min which is in the normal interval for a pregnant woman

Our goal here is to apply our model to sort a list of antibiotics for this profile in order to assist practitioners in their work. For this we begin with a general unsorted list of antibiotics for pregnant women. Our system takes this unsorted list as input (as shown in Figure 4) and combines this information with the patient's profile in order to provide the sorted recommendation to the physician. For example, for this particular case, the output of our system will be the following:

R: *Rifampicin*
R: *Penicillin_G (Penicillins)*
R: *Amoxicillin (Penicillins)*
P: *Clarithromycin*
P: *Cotrimoxazole*
TBA: *Tetracycline (Tetracyclines)*
TBA: *Moxifloxacin (Quinolones)*

Then the validity of this output can be checked by referring to the categorization provided in the EpiCura guidelines [9] (shown in Table II). Subsequently using these results, we are able to validate more complex scenarios, by diversifying over 60 antibiotics. Our model is able to make the exact desired classification considering the following equivalences: R ("recommended") ≈ Probably safe, P ("possible") ≈ Only compelling indications and TBA ("to be avoided") ≈ Contraindicated.

Probably safe	Only compelling indications	Contraindicated
Penicillins	Cotrimoxazole	Tetracyclines
Amoxicillin_ Acid clav	Clarithromycin	Quinolones
Piperacilline_ Tazobactam	Vancomycine	Trimethoprim
Aztreonam	Colistine	Aminoglycosides
Rifampicine	Fluconazole	Amantadine
Clindamycin	Itraconazole	
Cephalosporins	Pyrazinamide	
...	...	

TABLE II
EpiCura guidelines p. 19: Table of antibiotics indication classification for pregnant woman

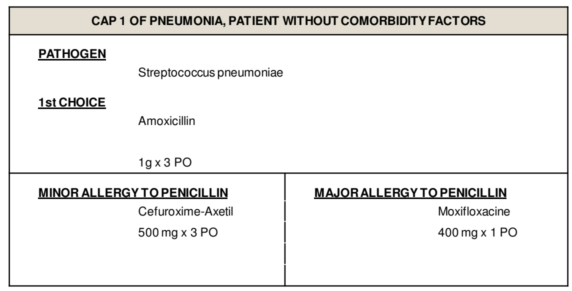

Fig. 5. Guidelines Pneumonia cap1

To further illustrate our results we can now consider that *Dolly the pregnant woman, is suffering of CAP1 of Pneumonia*.

The guidelines (Figure 5) inform us about the pathogens which cause the infection. In our example, the pathogen in question is *streptococcus pneumoniae*, as indicated in the second line of Figure 5. To suggest an appropriate antibiotic, the guidelines distinguish three situations with respect to penicillin: (a) a patient who is not allergic to penicillin, (b) a patient with a minor allergy and (c) a patient with a major allergy. For these last two cases it suggests two different antibiotics.

The following list gives us, the set of antibiotics which are effective against or cover the germs causing the infection of *Dolly*:

- *Penicillin_G (Penicillins)*
- *Ampicillin (Penicillins)*
- *Amoxicillin (Penicillins)*
- *Amoxicillin_Calvulanic (Penicillins)*
- *Clindamycin*
- *Cefuroxim_axetil (Cephalosporins)*
- *Vancomycin*
- *Moxifloxacin (Quinolones)*
- *Piperacillin_Tazoboctam (Penicillins)*

We sort this list by suitability to *Dolly*.The output of our system for this case is the following:

R: *Penicillin_G (Penicillins)*

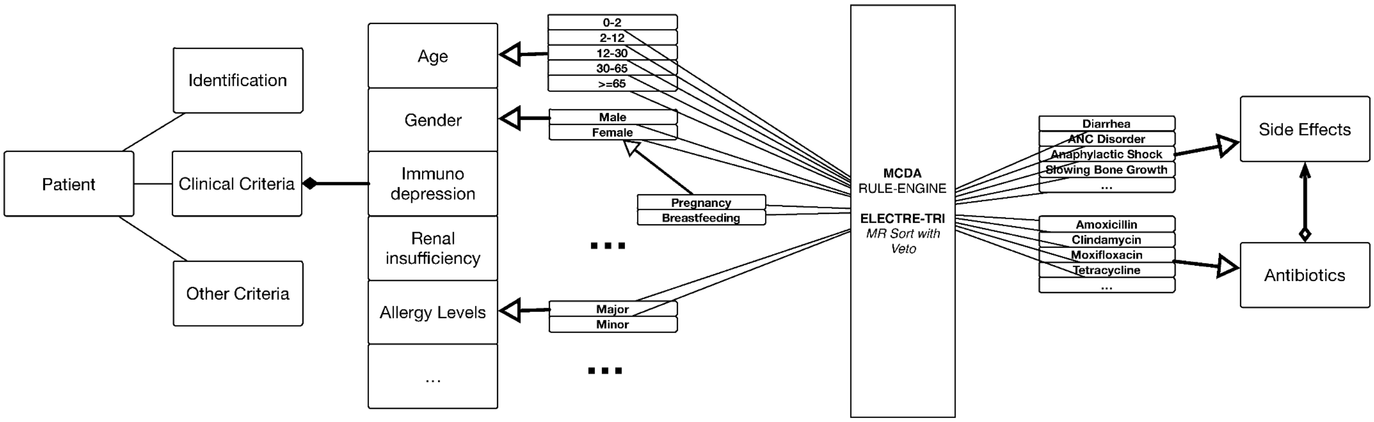

Fig. 3. Combining our Semantic Model with an adapted MR Sort method with Veto to link a patient to a model for antibiotics recommendation

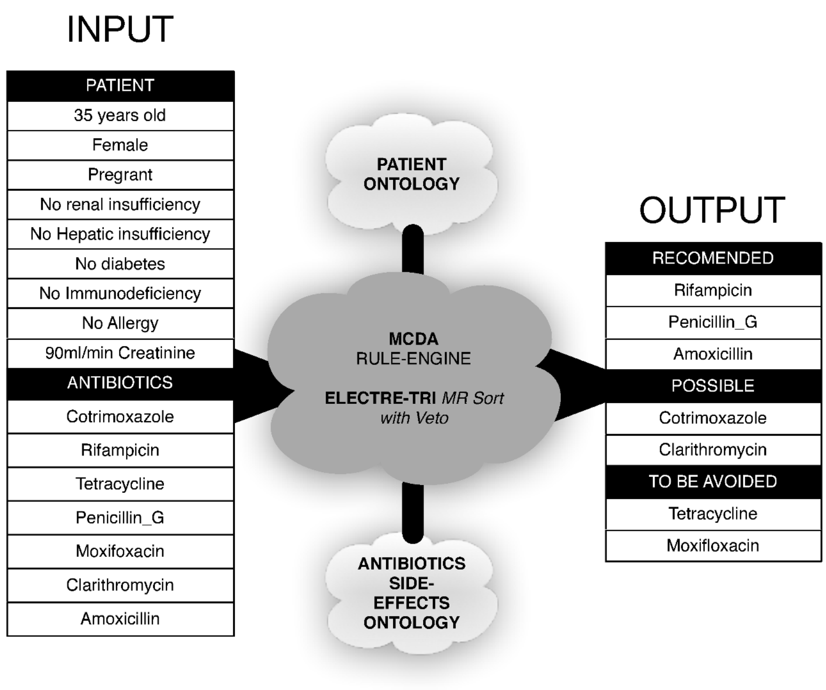

Fig. 4. Antibiotics classification according to the toxicity of side effects for the Patient (Dolly)

R: *Ampicillin (Penicillins)*
R: *Amoxicillin (Penicillins)*
R: *Amoxicillin_Calvulanic*
R: *Clindamycin*
R: *Cefuroxim_axetil (Cephalosporins)*
R: *Piperacillin_Tazoboctam*
P: *Vancomycin*
TBA: *Moxifloxacin (Quinolones)*

We note here that currently, in order to get these results (without using our system), the physician has to manually cross-check and combine several different sections of the guidelines.

As a second variation, let us consider that *Dolly has a major allergy to penicillin*. Then the disadvantage D_j becomes

$$major\ allergyand$$

$\mathrm{SP}_j = 2$. In this case the output of our system will be:

R: *Clindamycin* $SA_{ij} = 0$, $DAS_{ij} = 0$
P: *Cefuroxim_axetil (Cephalosporins)* SA_{ij}=1, $DAS_{ij} = 2$
P: *Vancomycin* $SA_{ij} = 0$, $DAS_{ij} = 0$
TBA: *Penicillin_G (Penicillins)* $SA_{ij} = 2$, $DAS_{ij} = 3$
TBA: *Ampicillin (Penicillins)* $SA_{ij} = 2$, $DAS_{ij} = 3$
TBA: *Amoxicillin (Penicillins)* $SA_{ij} = 2$, $DAS_{ij} = 3$
TBA: *Amoxicillin_Calvulanic* $SA_{ij} = 2$, $DAS_{ij} = 3$
TBA: *Piperacillin_Tazoboctam* $SA_{ij} = 2$, $DAS_{ij} = 3$

TBA: *Moxifloxacin (Quinolones)* $SA_{ij} = 0$, $DAS_{ij} = 0$

More precisely, when the patient has a major allergy to Penicillin ($SP_j = 2$) both of the vetoes [R] and [P] are activated (since antibiotics of the Penicillin family have $SA_{ij} = 2$). These antibiotics are classified in the TBA category. Furthermore, Cefuroxim_axetil gets $DAS_{ij} = 2$ which activates a veto [R]. As a consequence, Cefuroxim_axetil is classified in the P category. For the quinolones family (which has $DAS_{ij} = 0$), no veto is raised for the side effect j *major allergy*, but since *Dolly* is a pregnant woman, Moxifloxacin is classified in the TBA category. This reduces the suitable antibiotics from 8 to 3 which further aids the physician with his decision.

Given these results, our knowledge-based system proves to be more flexible and dynamic than the static guidelines currently in use. When the physician uses the static text, he has to manually cross-check and combine several different sections of the guidelines. On the contrary, with our solution, not only the decision process becomes more straightforward, but it is possible to dynamically update the subject's profile with additional characteristics (such as the allergy to penicillin that we saw above). This addition reduces the list of suitable antibiotics, thus further aiding the decision process. On the contrary, the guidelines cannot explicitly list the recommendation for every specific type of patient, or accommodate context changes (such as new antibiotics, side effects, development of resistant germs, etc.).

V. Conclusion

We have developed an innovative model to assess the suitability of pairs (*alternative, subject*) in a given context. This approach contrasts with recommender systems in that it is not based on implicit learning of the subject preferences regarding the alternatives but on explicit models and knowledge. It consists of the coupling of a general MCDM sorting model with a semantic model, the latter being specific to each application context. This architecture proves appropriate for supporting antibiotics prescription. The conception of this system allowed us to link heterogeneous ontologies, elaborated by experts in different fields, by using a MCDM model (MR-Sort with Veto) in a way that respects the specic medical recommendation requirements.

Our method sorts antibiotics in three categories: R ("recommended"), P ("possible") and TBA ("to be avoided") based on a small number of general rules. It is able to take into account a patient's specic clinical criteria as well as generalize to new cases when for example a new antibiotic is added to the knowledge base. Using input from practitioners in the EpiCura hospital center [9] we tuned the sensitivities and thresholds of our model and we were able to validate our approach through examples that categorize prescription recommendations according to the risk of side effect toxicity.

Further developments are planned in two directions. First, in a theoretical and methodological perspective, the elaboration and study of assessment models for the suitability of pairs (*alternative, subject*) in contexts that can be described by knowledge structures such as ontologies is a promising field of investigation.

Second, from an applicative point of view, the medical domain offers good perspectives. Reliable and evolutive models & knowledge based recommendation systems supporting doctors in making appropriate drug prescriptions would clearly be useful. In the particular case of antibiotics prescription, we plan to expand our model to take into account other dimensions of the adequate prescription problem including costs, drug-drug interaction and drug-disease interaction among others. We want to use a more standardized representation (such as ATC[1], ICD-10 [2] or UNII[3]) to expand our model to other dimensions of the prescription problem .

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References

[1] D. J. Power. Web-Based and Model-Driven Decision Support Systems: Concepts and Issues. Proceedings of the 2000 Americas Conference on Information Systems Long Beach, California, August 10-13, 2000.

[2] B. Roy, D. Bouyssou, Aide Multicritère à la décision : Méhodes et Cas. Economica, 1993.

[3] A. Leroy, V. Mousseau, M. Pirlot, Learning the parameters of a multiple criteria sorting method, in: R. Brafman, F. Roberts, A. Tsoukis (Eds.), Algorithmic Decision Theory, vol. 6992, Lecture Notes in Artificial Intelligence, Springer Berlin, Heidelberg, pp. 219233, 2011.

[4] L. Landro. Incentives Push More Doctors to E-Prescribe. The Wall Street Journal, (B7-8), January 2009.

[5] T. Gandhi, S. Weingart, J. Borus, A. Seger, J. Peterson, E. Burdick, et al. Adverse Drug Events in Ambulatory Care. New England Journal of Medicine, 348(16), 2003.

[6] J. Gurwitz, T. Field, L. Harrold, J. Rothschild, K. Debellis, A. Seger, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA, 289(9). 2003.

[7] A. Forster, H. Murff, J. Peterson, T. Gandhi, D. Bates. Adverse Drug Events Occurring Following Hospital Discharge. Journal of General Internal Medicine. March, 2005.

[8] J. Rothschild, F. Federico, T. Gandhi, R. Kaushal, D. Williams, D. Bates. Analysis of medication-related malpractice claims: causes, preventability, and costs. Arch Intern Med. 2002.

[9] S. Place, M. Delphine. Recommandations pour l'usage des antibiotiques: traitement empirique des problèmes infectieux courants. Guidelines. Baudour-Belgium: Centre hospitalier EpiCura, Réseau hospitalier de médecine. 2011.

[10] T. Gruber. A translation approach to portable ontologies. Knowledge Acquisition. 5(2), 199–220, 1993.

[11] T. Gruber. Toward Principles for the Design of Ontologies Used for Knowledge Sharing. International Journal Human-Computer Studies 43, 907–928, 1993.

[12] T. Bright, E. Furuya, G. Kuperman, J. Cimino, S. Bakken. Development and evaluation of an ontology for guiding appropriate antibiotic prescribing. Journal of Biomedical Informatics. 2012.

[1] Anatomical Therapeutic Chemical classification: http://www.whocc.no/atc/structure_and_principles/

[2] International Classification of Diseases: http://www.who.int/classifications/icd/en/

[3] Unique Ingredient Identifier: http://www.fda.gov/ForIndustry/DataStandardsSubstanceRegistrationSystemUniqueIngredientIdentifierUNII/default.htm

[13] J. Gennari, M. Musen, R. Fergerson, W. Grosso, M. Crubzy, H. Eriksson, et al. The evolution of Protégé: an environment for knowledge-based systems development. International Journal of Human-Computer Studies. January, 2003.
[14] S. Mya, T.M, K. Moon, N.S. Case-based Medical Diagnostic Knowledge Structure Using Ontology. 2nd International Conference on Computer and Automation Engineering. Singapore, pp. 729-733, 2010.
[15] W. Ceusters, M. Capolupo, G. De Moor, J. Devlies. Introducing realist ontology for the representation of adverse events. In Proceedings of the 2008 conference on Formal Ontology in Information Systems, pages 237-250, Amsterdam, The Netherlands, 2008.
[16] R. Beuscart, P. McNair, J. Brender, and PSIP consortium. Patient safety through intelligent procedures in medication: the PSIP project. Studies in Health Technology and Informatics, 148, 6-13, 2009.
[17] S. Stephens, A. Morales, M. Quinlan. Applying semantic web technologies to drug safety determination. Intelligent Systems, IEEE, 21(1), 82-88, 2006.
[18] M. Adnan, J. Warren, M. Orr. Ontology based semantic recommendations for discharge summary medication information for patients. In Computer-Based Medical Systems (CBMS), 2010 IEEE 23rd International Symposium on, pages 456- 461, 2010.
[19] C. Doulaverakis, G. Nikolaidis, A. Kleontas, I. Kompatsiaris. GalenOWL:Ontology based drug recommendations discovery. J Biomed Semantics, 3(14), 2012.
[20] A. Moreno, A. Valls, D. Isern, L. Marin, J. Borrs, SigTur/E-destination: ontology-based personalized recommendation of tourism and leisure activities, Engineering Applications of Artificial Intelligence, 26 (2013) 633-651.
[21] M. Martnez-Garca , A. Valls, A. Moreno, Construction of an Outranking Relation Based on Semantic Criteria with ELECTRE III. Information Processing and Management of Uncertainty in Knowledge-Based Systems, 611, pp 238-249, 2016.
[22] B. Levin, P. Ankomah. Exploring the Collaboration between Antibiotics and the Immune Response in the Treatment of Acute, Self-Limiting Infections. Proceedings of the National Academy of Sciences of the United States of America. June, 2014.
[23] D. Bouyssou. An axiomatic approach to noncompensatory sorting methods in MCDM I : The case of two categories. European Journal of Operational Research. 178(1), 217-245, 2007.
[24] D. Bouyssou, T. Marchant. An axiomatic approach to noncompensatory sorting methods in MCDM II : More than two categories. European Journal of Operational Research. 178(1), 246-276, 2007.
[25] O. Sobrie, V. Mousseau, M. Pirlot, Learning a majority rule model from large sets of assignment examples, in: P. Perny, M. Pirlot, A. Tsoukiàs (Eds.), Algorithmic Decision Theory, Lecture Notes in Artificial Intelligence, Springer, pp. 336350, 2013.
[26] O. Sobrie, M. Lazouni, S. Mahmoudi, V. Mousseau, M. Pirlot, A new decision support model for preanesthetic evaluation. Computer Methods and Programs in BioMedicine 133:183-193, 2016.
[27] V. Mousseau, R. Słowiński et P. Zielniewicz : A user-oriented implementation of the ELECTRE TRI method integrating preference elicitation support. Computers & Operations Research, 27(7-8), 757-777, 2000.
[28] J. Figueira, V. Mousseau et B. Roy : ELECTRE methods. In J. Figueira, S. Greco et M. Ehrgott, éds : Multiple Criteria Decision Analysis: State of the Art Surveys. Springer Verlag, Boston, Dordrecht, London, pages 133-162, 2005.
[29] B. Roy: Méthodologie multicritère d'aide la décision. Economica, 1985.
[30] V. Belton, T. Stewart. Multiple Criteria Decision Analysis: An Integrated Approach. Kluwer Academic, Dordrecht, 2002.