Expanding a First-Order Logic Mitigation Framework to Handle Multimorbid Patient Preferences

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Abstract

The increasing prevalence of multimorbidity is a challenge for physicians who have to manage a constantly growing number of patients with simultaneous diseases. Adding to this challenge is the need to incorporate patient preferences as key components of the care process, thanks in part to the emergence of personalized and participatory medicine. In our previous work we proposed a framework employing first order logic to represent clinical practice guidelines (CPGs) and to mitigate possible adverse interactions when concurrently applying multiple CPGs to a multimorbid patient. In this paper, we describe extensions to our methodological framework that (1) broaden our definition of revision operators to support required and desired types of revisions defined in secondary knowledge sources, and (2) expand the mitigation algorithm to apply revisions based on their type. We illustrate the capabilities of the expanded framework using a clinical case study of a multimorbid patient with stable cardiac artery disease who suffers a sudden onset of deep vein thrombosis.

Introduction

Mitigating clinical practice guidelines (CPGs) for a multimorbid patient is identified as a crucial step in the adoption of CPGs at the point of care[1,2]. The key problem lies in identifying and mitigating adverse interactions between guidelines given a specific multimorbid patient encounter. In addition to the CPGs, secondary knowledge applicable to both the multimorbidities and the patient state, and patient preferences must be used to propose a consistent therapy for the particular patient encounter. In previous work we proposed a logic-based approach to the mitigation problem that uses first-order logic (FOL) as the formalism for representing CPGs, patient information, and secondary medical knowledge in the form of revision operators[3,4]. With the emergence of personalized and participatory medicine[5], patient preferences have become important components of the care process[6,7].

Representations for CPGs, secondary medical knowledge, and patient information have been studied and formalized[8,9], including in our own previous research[3,4,10,11]. Yet up to this point preferences were applied to decisions made together by the physician and patient (shared decision making) or by the patient (informed decision making). Furthermore these preference were represented at a very high level and not considered alongside revisions made to CPGs, making it difficult to identify and mitigate adverse interactions introduced by these preferences. Therefore, a multimorbid patient's preferences must be represented formally so they can be part of the reasoning needed to mitigate concurrently applied CPGs.

In this paper we show how our FOL-based mitigation framework is flexible enough to support patient preferences and we describe how these preferences are represented in a format that is compatible with our FOL-based CPG formalism. Specifically, we broaden our previous definition of an operator and define revisions described in secondary medical knowledge and in preferences as two classes of operators. We also introduce a slight modification to our mitigation algorithm to apply as many preferences as possible while maintaining the consistency of the proposed therapy. Finally, we use a clinical scenario with a multimorbid patient who suffers from deep vein thrombosis (DVT) and a pulmonary embolism (PE) while being treated for stable cardiac artery disease (SCAD) and who has stated preferences for novel oral anticoagulants versus low molecular weight heparin and warfarin.

Supporting Preferences in a First-Order Logic Mitigation Framework

In this section, we describe the extensions to our first-order logic-based mitigation framework to support patient preferences. Our most recent published work covered our mitigation framework's transition to FOL[3], including a case study of a patient managed for type 2 diabetes and an onset of severe rheumatoid arthritis[4], and our extension of the framework to support a broader set of CPGs (such as those that include parallel paths) and more complex secondary medical knowledge[12]. The extensions presented in this work serve two purposes: (1) to represent patient preferences and (2) to apply preferences during the mitigation process rather than as a post-processing step. These extensions demonstrate the flexibility of our mitigation framework in supporting an additional form of secondary knowledge (patient preferences). To ground the extensions described below, we briefly reintroduce those framework components that are affected by or extended to support patient preferences. These include the combined mitigation theory $\mathcal{D}_{comb}$, revision operators, and the mitigation algorithm.

FOL is a widely used formal system for representing and reasoning about knowledge[13]. This knowledge is represented as a logical theory $\mathcal{D}$, which is a collection of sentences in a first-order language L defined over vocabulary *V*. *L* consists of logical symbols (quantifiers, connectives, variables, and logical constants) and a finite number of non-logical symbols (predicates and functions) from *V*. The former have a fixed meaning in any FOL language, the latter are domain-dependent. The meaning of the non-logical symbols in *L* is given by an interpretation $\mathcal{I}$. If $\mathcal{I}$ satisfies all sentences in $\mathcal{D}$, then it is called a *model* for $\mathcal{D}$. Theory $\mathcal{D}$ is *consistent*, iff there exists at least one model of this theory, and consistency is checked using *theorem proving* techniques. If $\mathcal{D}$ is consistent, it is possible to find models for this theory using *model finding* techniques, and to check for implications (logical consequences) of this theory through *entailment*[3].

In our work we assume a specific patient encounter is represented as the combined theory $\mathcal{D}_{comb}$. $\mathcal{D}_{comb}$ uses our defined vocabulary (see[3] for its description) and is defined formally as the triple:

$$\mathcal{D}_{comb} = \langle \mathcal{D}_{common}, \mathcal{D}_{cpg}, \mathcal{D}_{pi} \rangle,$$

where $\mathcal{D}_{common}$ is a theory that axiomatizes the universal characteristics of CPGs as part of a FOL representation. It is the common (shared and reusable) component of all mitigation theories. $\mathcal{D}_{cpg}$ is a union of theories, each theory representing a single CPG that is being applied to a multimorbid patient. And $\mathcal{D}_{pi}$ is the theory that describes available patient information. It contains FOL sentences representing patient data, including results of tests and examinations, or indicates already prescribed therapies and procedures.

In our mitigation framework, all secondary knowledge is captured in *revision operators*. In our recent work[12] we expanded the definition of a revision operator to allow for a more detailed description of the context and type of modifications they perform. This flexibility allows us to use these operators to represent patient preferences without any changes to their definition.

Formally, a revision operator RO^k is defined as:

$$RO^k = \langle \alpha^k, Op^k \rangle$$

where α^k is a logical sentence that describes the interaction applicability of the operator to the theory $\mathcal{D}_{cpg}$, and Op^k describes the revisions introduced by RO^k. In particular, Op^k is a set of *n* pairs of formulas $\langle \varphi_i^k, \phi_i^k \rangle$ $(i = 1 \dots n)$ that define a single operation within the operator. These operations are applied only to $\mathcal{D}_{cpg}$, so other components of $\mathcal{D}_{comb}$ are protected from unwanted revisions. For example, $\mathcal{D}_{pi}$ is never modified thus patient information is never inadvertently changed. The formulas are interpreted as follows (where $\emptyset$ indicates an empty formula):

- $\langle \varphi_i^k, \emptyset \rangle$ means that φ_i^k is removed from any sentence in $\mathcal{D}_{cpg}$ where it appears,
- $\langle \emptyset, \phi_i^k \rangle$ means that ϕ_i^k is added as a new sentence to $\mathcal{D}_{cpg}$,
- $\langle \varphi_i^k, \phi_i^k \rangle$ means that φ_i^k is replaced by ϕ_i^k in any sentence in $\mathcal{D}_{cpg}$ where it appears.

Checking the applicability of RO^k to $\mathcal{D}_{comb}$ translates into the entailment problem $D_{comb} \vDash \alpha^k$. We demonstrate in the *Applying Preferences* section how we leverage this property in our mitigation algorithm.

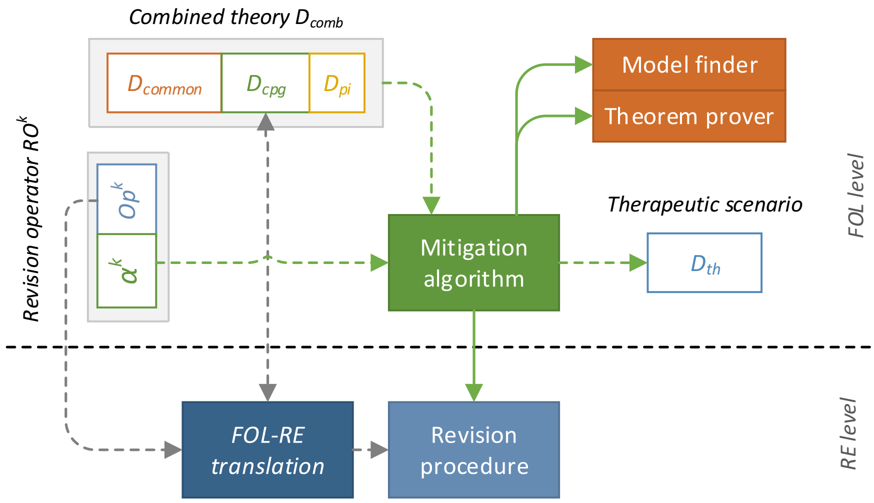

Figure 1. Overview of FOL-based mitigation framework.

Figure 1 shows the general architecture of our mitigation framework. It involves two levels of operation -- FOL and regular expressions (RE), i.e. string patterns, often used in *find and replace*-type operations on text in document retrieval, data analytics and database queries. The core component is the mitigation algorithm, presented later in detail, that operates at the FOL level. The algorithm takes as input a combined theory $\mathcal{D}_{comb}$, uses revision operators RO^k to mitigate (identify and address) adverse interactions, and finally constructs a therapeutic scenario $\mathcal{D}_{th}$ -- a theory that represents a "safe" (free of adverse interactions) course of action. $\mathcal{D}_{th}$ highlights the clinical actions to be taken (along with the order in which they should be carried out), and includes assumptions made about the patient's state.

Previous work on Applying Patient Preferences

Patient preferences and values are considered the third important component of evidence-based medicine[14], the other two being research evidence and clinical experience. Incorporation of patient preferences is especially relevant when dealing with "gray zone" decisions associated with a high level of uncertainty[15]. This uncertainty is associated with insufficient evidence[7], evidence indicating the same attractiveness of multiple options or significant differences in preferences across target population. As such these decisions are often referred to as "preference-sensitive"[15]. Patient preferences are also relevant when deciding on long-term treatments (for example in case of diabetes, hypertension or osteoporosis)[14]. Given the importance of patient preferences, it is now advocated that patients should not only be involved in making decisions when a CPG is being followed, but they should also participate in the development of CPGs[16].

There has been significant research on decision aids that help patients express their preferences (see the next section for more details)[15]. Depending on the applied approach to treatment decision making (shared or informed), preferences are considered by the physician and patient or by the patient alone when manually making a specific treatment decision[17]. A trial of decision aid tools (implemented as paper charts) for patients considering total knee arthroplasty was described in [18]. According to the results of the trial, patients exposed to decision aids demonstrated significantly higher quality decisions (informed choice -- surgery vs. non-surgery -- that matched their values for outcomes of options) than patients that did not use decision aids.

There is also ongoing work on embedding patient preferences in clinical decision support systems. This line of work is exemplified by the MobiGuide system[19,20]. MobiGuide supports remote and CPG-based patient management. The system first learns patient preferences (given in the form of utilities) and applies them when making preference-sensitive decisions in order to establish support for specific options. The system currently contains CPGs for atrial fibrillation[19] and gestational diabetes[20].

Eliciting Preferences

Patient preferences represent "the desirability of a health-related outcome, process or treatment choice[6]." Patients might prefer less invasive tests or procedures over those that cause discomfort, tests that are carried out by nurse practitioners versus those performed by physicians, or specific drugs over others within the same drug class. Such preferences are often represented using "health utilities"[6] that are elicited using various decision aids integrated with

CPGs[15]. These aids typically take the form of charts where patients assign weights or utilities to available options[16]. However, there is no consensus whether this is the best approach that should be adopted in practice[16].

In our research we use a different approach to elicit patient preferences -- instead of asking patients for direct specification of utilities associated with individual options, we ask them to compare pairs of selected options (for example those for which they have pronounced preferences). These comparisons are then used to derive a preference model in the form of an additive value function that is a sum of marginal value functions associated with specific features of considered options (e.g. their cost, complexity, or side effects). For this purpose we employ the Generalized Regression with Intensities of Preference (GRIP) method[21] that not only constructs value functions, but also allows for detailed analysis of pairwise comparisons and for indicating conflicting or inconsistent answers. This makes GRIP very well suited for interactive use and an example of using GRIP to elicit patient preferences related to pain management therapies is presented in [22].

Value functions constructed by GRIP can be used to evaluate options, also these not included in pairwise comparisons. In our framework we use these evaluations to define *desired* revisions to CPGs. Specifically, we consider pairs of options for a given action, i.e. a default option and its alternative. If an alternative option receives a better evaluation than the default one, we introduce a revision that replaces the default option with the alternative (see *Representing Preferences* section below for more information).

Representing Preferences

Up to this point, our mitigation framework only used revision operators to represent secondary medical knowledge (such as drug-drug or drug-disease adverse interactions) that, when relevant to the patient encounter, *must* be applied to the combined theory used to construct the therapeutic scenario for the patient. Support for preferences introduces the notion of modifications to the combined theory that are *desired* but not required. Therefore, the mitigation framework must distinguish between these two classes of revisions and apply **all** applicable interaction-related revisions, while it can skip any of the triggered preference-related revisions that medically invalidate the combined theory.

In this work, we describe revisions as one of two types: those related to preferences and those related to adverse interactions. As such we broaden the definition of an operator to cover all secondary knowledge to be considered when mitigating concurrently applied CPGs. Using this broader definition of a revision operator, we introduce two classes of operators: *preference-related revision operators* and *interaction-related revision operators*. The class distinctions are used to define what secondary knowledge must be contained in the combined theory and what secondary knowledge is desired by not required in the combined theory. We note however that the framework uses the same formalism to represent both classes. Therefore, preference-related as well as interaction-related operators can replace, remove, or add clinical actions.

Specific examples of both classes of revision operator are given in the *Case Study* section. While the preference-related revision operator example and its representation is quite simple, our mitigation framework supports more complex revisions. Preferences for drugs can include dosage adjustment, ordering changes (taking some drug before/after another) and other supported revisions as further described in [3].

Applying Preferences

Providing a formal representation for preferences enables our mitigation framework to apply them *while* constructing a therapeutic scenario. As integral components, preferences must be vetted medically to ensure no adverse interactions are introduced as a result of their application. Furthermore, formally representing preferences means they can be expressed across a broad range of therapy characteristics. Not only can they refer to higher level concepts such as drugs or medical tests, but preferences can be defined for the type of drug administration (oral, injection, etc.), the number of times the drug is taken per day, if a drug is covered/not covered by insurance, and other similar characteristics. The power of FOL allows our mitigation framework to expand the vocabulary as needed to increase the richness of preferences. In this section we describe how preferences are applied by an extended mitigation algorithm while maintaining medical validity of the proposed therapy.

Our existing mitigation algorithm is a core component of the mitigation framework and it is described in pseudocode in Figure 2. The algorithm takes as input a combined theory $\mathcal{D}_{comb}$, uses interaction-related revision operators RO^k to mitigate (identify and address) adverse interactions, and finally constructs a therapeutic scenario $\mathcal{D}_{th}$. The algorithm iterates over available interaction-related revision operators (line 3). It checks through entailment whether the current operator RO^k is applicable to $\mathcal{D}_{comb}$ (line 5) using a theorem prover. If RO^k is applicable, then the mitigation algorithm invokes a specialized revision procedure that addresses the encountered interaction (line 8). If the revised theory is inconsistent (again this is checked by a theorem prover), then the algorithm terminates indicating that the therapeutic scenario does not exist (lines 13-14). Finally, when no more interactions have been encountered in $\mathcal{D}_{comb}$, the mitigation algorithm finds a model for $\mathcal{D}_{comb}$ by invoking a model finder (line 19) and constructs the therapeutic scenario $\mathcal{D}_{th}$ (line 20).

```
procedure mitigate(inout $\mathcal{D}_{comb}$, out $\mathcal{D}_{th}$)
begin
1     repeat
2           interaction_encountered := false;
3           foreach interaction-related $RO^k$ do
4           begin
5                 if $\mathcal{D}_{comb} \vDash \alpha^k$ then
6                 begin
7                       interaction_encountered := true;
8                       $\mathcal{D}_{comb}$ := revise $\mathcal{D}_{comb}$ using $Op^k$;
9                       if $\mathcal{D}_{comb}$ is consistent then
10                            break
11                      else
12                      begin
13                            $\mathcal{D}_{th}$ := null;
14                            return;
15                      end
16                end
17          end
18    until not interaction_encountered;
19    $\mathcal{I}$ := find model of $\mathcal{D}_{comb}$;
20    $\mathcal{D}_{th}$ := construct therapeutic scenario from $\mathcal{I}$ and $\mathcal{D}_{pi}$
end
```

Figure 2. Existing mitigation algorithm.

The mitigation algorithm in Figure 2 employs interaction-related revision operators. When applicable, they must be used so that the therapeutic scenario $\mathcal{D}_{th}$ can be constructed. With the introduction of preference-related revision operators, whose application is desired but not strictly required to produce the therapeutic scenario, we extend the mitigation algorithm to treat each type of revision operator differently. The key innovation lies in an extended procedure that acts as a wrapper around the existing *mitigate* procedure.

Our extended algorithm is more formally shown in Figure 3 as procedure *customize_and_mitigate*. As input it takes the combined theory $\mathcal{D}_{comb}$ and outputs the therapeutic scenario $\mathcal{D}_{th}$ that includes changes introduced by all applicable interaction-related revision operators and those preference-related revision operators that do not conflict with the CPGs and with interaction-related revisions. The extended algorithm first orders preference-related revision operators RO^k in decreasing priorities (line 2), as identified by the patient. It then iterates over the ordered operators (line 3), considering more important ones first. For each preference-related RO^k, the algorithm checks its applicability through entailment (line 5). If RO^k is applicable, then the algorithm creates a temporary combined theory $\mathcal{D}_{comb}'$ by revising $\mathcal{D}_{comb}$ (line 7). If $\mathcal{D}_{comb}'$ is consistent (i.e. the preferences represented by RO^k do not conflict with the CPGs), then it is passed to the *mitigate* procedure defined in Figure 2 to apply relevant interaction-related revision operators and to ensure the existence of a therapeutic scenario $\mathcal{D}_{th}$. If $\mathcal{D}_{th}$ exists, the preference-related revisions are preserved (lines 13-14), otherwise they are discarded due to their conflict with interaction-related revisions. The extended algorithm also invokes the *mitigate* procedure if no preference-related revision operators were successfully applied, due to no applicable preference operators or applied operators only resulted in conflicts (line 19-20). This case is equivalent to the operations carried out by our existing *mitigate* algorithm.

Here we note that because the extended mitigation algorithm sequentially applies preference-related revision operators in order of decreasing priority, it is possible that preference-related revisions introduced earlier could "block" preference-related revision operators with lower priorities. Still, the algorithm attempts to consider as many preference-related revision operators as possible given it does not terminate when a specific operator introduces conflicts, but instead skips over this operator. The framework also assumes that it is better to select the therapeutic scenario $\mathcal{D}_{th}$ that contains paths through the CPGs that do not require a preference-related revision to be made. Intuitively, this means the framework elects to return the scenario with as many actions as possible to which the patient has no applicable preference-related revision operators. Our expanded mitigation approach, with respect to preferences, assumes when a patient does not express preference-related revisions for a given clinical action, she fully accepts what is suggested by the CPG.

```
procedure customize_and_mitigate(inout $\mathcal{D}_{comb}$, out $\mathcal{D}_{th}$)
begin
    preferences_applied := false;
    order preference-related RO^k s according to their decreasing priorities;
    foreach preference-related RO^k do
    begin
        if $\mathcal{D}_{comb} \models \alpha^k$ then
        begin
            $\mathcal{D}_{comb}'$ := revise $\mathcal{D}_{comb}$ using $Op^k$;
            if $\mathcal{D}_{comb}'$ is consistent then
            begin
                mitigate($\mathcal{D}_{comb}'$, $\mathcal{D}_{th}$);
                if $\mathcal{D}_{th}$ <> null then
                begin
                    preferences_applied := true;
                    $\mathcal{D}_{comb}$ := $\mathcal{D}_{comb}'$
                end
            end
        end
    end
    if not preferences_applied then
        mitigate($\mathcal{D}_{comb}$, $\mathcal{D}_{th}$);
end
```

Figure 3. Extended mitigation algorithm.

Case Study: Management of a Patient with Stable Cardiac Artery Disease Who Suffers a Sudden Onset of Deep Vein Thrombosis

Stable coronary artery disease (SCAD) encompasses several patient populations at different stages and with different types of coronary disease, excluding acute coronary syndromes. SCAD has a number of manifestations, including some form of chest discomfort (the most common one) that is induced by exercise, emotion, or stress. People with hypertension, hypercholesterolemia, diabetes, obesity, and those who smoke are at a higher risk of developing SCAD[23]. Treatment of a typical SCAD patient begins with short acting nitrates combined with beta blockers or calcium channel blockers as well as lifestyle management to control for cardiovascular risk factors. If SCAD symptoms persist, a second line of treatment is initiated that includes long lasting nitrates combined with potassium channel activators (e.g. nicorandil), statins, and aspirin.

In the clinical scenarios described below we assume a SCAD patient presenting with symptoms of deep vein thrombosis (DVT) related to either DVT itself or a pulmonary embolism (PE) -- we refer to this presentation as DVT/PE. A patient diagnosed with DVT/PE is managed according to the standard CPG[24] and a simplified version of this guideline is presented in Figure 4 as an actionable graph[10] (we omit the figure showing the SCAD CPG due to space limitations but it is available from the authors upon request). The management of DVT/PE involves aggressive in-patient therapy especially for those patients who exhibit haemodynamic instability or are diagnosed with renal failure. Such a therapy is followed by out-patient management. The development of novel oral anticoagulants (NOACs) opened up new treatment options beyond management with low molecular weight heparin (LMWH) and warfarin. It is in the context of NOACs that patient preferences start playing an important role in selecting the most suitable and clinically sound treatment. In the case of DVT/PE out-patient management, a patient can consider one of the following therapeutic options:

- LMWH and warfarin; this is the default treatment (and presented in Figure 4) that requires regular blood work in order to assess the effect of oral anticoagulation with warfarin. This assessment is done using the *international normalized ratio* (INR).
- LMWH for 5 days followed by NOAC (dabigatram) twice daily; some patients may prefer to start with a parenteral agent (e.g., LMWH injection) as it is perceived as a more effective immediate treatment. No blood work is required for this option.
- NOAC alone; possibilities include either rivaroxaban that is taken once a day or apixaban that is taken twice a day and has a slightly lower risk of bleeding than rivaroxaban. Treatment with NOACs does not require blood work.

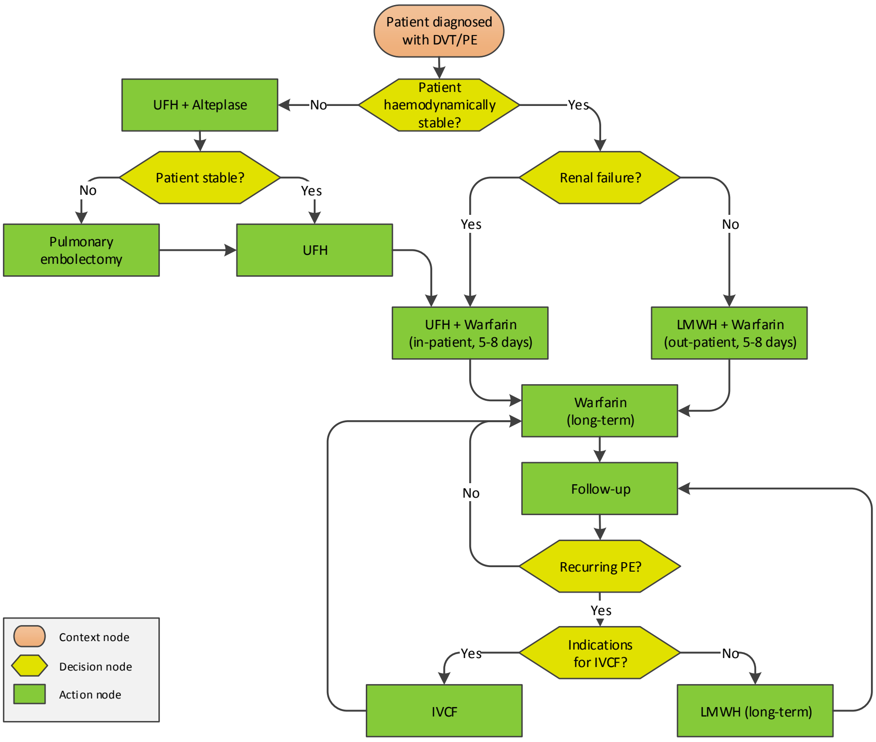

Figure 4. DVT/PE CPG represented as an actionable graph (DVT = deep vein thrombosis, PE = pulmonary embolism, UFH = unfractioned heparin, LMWH = low molecular weight heparin, IVCF = inferior vena cava filter)

Patient preferences governing the selection of a given treatment option may include such factors as perceived effectiveness (injection vs. oral administration), ease of use (injection vs. oral vs. number of daily administrations), convenience (no need to monitor effects of anticoagulation, no need to buy and store syringes), or insurance coverage of medication (government, private, or out of pocket expense). In the subsequent sections we illustrate how patient preferences are modeled as part of our mitigation framework and how they impact the development of a therapeutic scenario. We start with a simple illustration of mitigation that does not include patient preferences and finish with one that does.

Clinical Scenario 1: Mitigating Adverse Interactions

In the first scenario we assume an elderly male patient is treated for recurring SCAD and has not expressed any preferences for their DVT/PE treatment. According to the SCAD CPG, he is placed on long lasting nitrates, potassium channel activators, statins, and aspirin. This patient arrives at the Emergency Department (ED) complaining of swelling and tenderness in his left leg. An ultrasound and D-dimer test confirm DVT. Further investigations rule out haemodynamic instability and renal failure. The patient is immediately started on anticoagulation therapy (unfractioned heparin (UFH) and warfarin).

However, a patient should not be put on two different anticoagulation treatments (in this case aspirin or clopidogrel for SCAD and any type of anticoagulation for DVT/PE). Supporting this scenario requires the codification of secondary knowledge preventing the use of two anticoagulation therapies. As stated in medical literature for patients treated for DVT/PE, the administration of aspirin and clopidogrel must be stopped when the patient is put on another anticoagulation therapy. The interaction-related revision operator RO^1 represents the secondary knowledge that can be used to mitigate this drug-drug interaction. Note we use a simplified representation that does not use variable names but only presents their labels:

$$RO^1 = \langle \alpha^1, Op^1 \rangle,$$

$$\alpha^1 = \mathit{diagnosed(DVT\_PE)} \wedge \mathit{execute(anticoag)} \wedge \mathit{execute(aspirin)},$$

$$Op^1 = \{< \mathit{execute(aspirin)} \wedge \mathit{execute(clopidogrel)}, \emptyset >\}$$

For this scenario we have the following subset of sentences describing the patient's state D_{pi}.

$$D_{pi} = \mathit{diagnosed(DVT\_PE).\ diagnosed(SCAD).\ execute(aspirin).}$$

The following sentences are part of the theories for SCAD and DVT/PE, including a sentence describing the applied anticoagulation therapy that uses warfarin and unfractioned heparin (UFH).

$$D_{cpg}^{SCAD} \ni \mathit{execute(clopidogrel)}$$

$$D_{cpg}^{DVT\_PE} \ni \mathit{execute(anticoag)} \Rightarrow \mathit{execute(warfarin)} \wedge \mathit{execute(UFH)}$$

To check for the applicability of RO^1 we formulate the entailment problem $D_{comb} \vDash \alpha^1$. Because α^1 is entailed by D_{comb}, we immediately establish that RO^1 is applicable to D_{comb} and we consequently apply Op^1 to remove aspirin and clopidogrel from D_{cpg}^{SCAD}. This resolves the drug-drug interaction and the returned therapeutic scenario D_{Th} includes the administration of long lasting nitrates, potassium channel activators, statins, but not aspirin or clopidogrel for the subset of the model for D_{Th} related to treating the patient's SCAD. Had the entailment problem $D_{comb} \vDash \alpha^1$ failed, we would be unable to revise D_{comb} and find a model for it. Similarly, because no preferences were expressed by the patient, only interaction-related revision operators are checked and applied. We omit the full theory describing this patient encounter due to space limitations and refer the reader to previous work for more detailed scenarios[3,4,12].

Clinical Scenario 2: Applying Patient Preferences

Considering the same patient as in the first scenario, now the patient has expressed a preference for a simple treatment of DVT/PE, defined as the fewest drug administrations in a day as possible, oral route preferred over injection, and the administration of drugs covered by insurance (the patient has supplementary private health insurance). Due to the blood work required before administering warfarin, the patient prefers to take rivaroxaban. Taking this drug allows the patient to start with pills only (no parenteral agent), does not require blood work, the pill is taken only once a day, and is covered by the government (e.g., for seniors) and private insurance. This is a common patient preference as indicated by the medical expert (Dr. Carrier) on our team. The preference-related revision operator RO^2 represents, in a structured form, the above expressed patient preference that was elicited prior to prescribing a treatment. Note again we use a simplified representation to improve readability:

$$RO^2 = \langle \alpha^2, Op^2 \rangle,$$

$$\alpha^2 = \mathit{diagnosed(DVT\_PE)} \wedge \mathit{execute(anticoag)},$$

$$Op^2 = \{< \mathit{execute(warfarin)} \wedge \mathit{execute(UFH)}, \mathit{execute(rivaroxaban)} >\}$$

To check for the applicability of the preference-related revision operator RO^2 we first formulate the entailment problem $D_{comb} \vDash \alpha^2$. Because α^2 is entailed by D_{comb}, we immediately establish that RO^2 is applicable to D_{comb} and we consequently apply Op^2 to replace the anticoagulation therapy that uses warfarin and UFH with one that uses rivaroxaban in $D_{cpg}^{DVT\_PE}$. Note that this results in the sentence *execute(anticoag) ⇒ execute(rivaroxaban)* as part of D_{comb}'. Applying the *mitigate* procedure to D_{comb}' results in a revision made according to RO^1 since α^1 is still entailed by D_{comb}'. As such, the returned therapeutic scenario D_{Th} both resolves the drug-drug interaction described in RO^1 and applies the patient's preference for a simpler treatment of his DVT/PE condition as represented by RO^2. We again omit the full theory describing this patient encounter due to space limitations.

Discussion

In this paper we describe extensions to our FOL-based mitigation framework to add support for patient preferences when mitigating multiple concurrently applied CPGs to a multimorbid patient. The flexibility provided by FOL allowed us to easily expand the definition of an operator to include two subclasses that use the same representation formalism as before. We leverage these classes of operators in an extended mitigation algorithm to either apply all revisions represented by the set of interaction-related revision operators or as many as possible from the set of preference-related revision operators. We also describe how preferences are formally elicited, further demonstrating our incorporation of preferences as first-class citizens in the mitigation process.

In supporting preferences, we demonstrate our mitigation framework's ability to represent different types of secondary knowledge. The current version of the framework supports preferences that replace a medical action(s) with one or more different ones. As future work we will support the full range of operations for preference-related revision operators. Additionally we are further working on the mitigation framework's theoretical foundations that will make it possible to expand the notion of mitigation to include preferences, with the goal of developing an interactive clinical decision support system (CDSS) to be used at the point of care.

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