

First-Order Logic Theory for Manipulating Clinical Practice Guidelines Applied to Comorbid Patients: A Case Study

Martin Michalowski, PhD¹, Szymon Wilk, PhD², Xing Tan, PhD³, Wojtek Michalowski, PhD³

¹Adventium Labs, Minneapolis, MN; ²Poznan University of Technology, Poznan, Poland; ³University of Ottawa, Ottawa, Canada

Abstract

Clinical practice guidelines (CPGs) implement evidence-based medicine designed to help generate a therapy for a patient suffering from a single disease. When applied to a comorbid patient, the concurrent combination of treatment steps from multiple CPGs is susceptible to adverse interactions in the resulting combined therapy (i.e., a therapy established according to all considered CPGs). This inability to concurrently apply CPGs has been shown to be one of the key shortcomings of CPG uptake in a clinical setting¹. Several research efforts are underway to address this issue such as the K4CARE² and GuideLine INteraction Detection Assistant (GLINDA)³ projects and our previous research on applying constraint logic programming to developing a consistent combined therapy for a comorbid patient⁴. However, there is no generalized framework for mitigation that effectively captures general characteristics of the problem while handling nuances such as time and ordering requirements imposed by specific CPGs. In this paper we propose a first-order logic-based (FOL) approach for developing a generalized framework of mitigation. This approach uses a meta-algorithm and entailment properties to mitigate (i.e., identify and address) adverse interactions introduced by concurrently applied CPGs. We use an illustrative case study of a patient suffering from type 2 diabetes being treated for an onset of severe rheumatoid arthritis to show the expressiveness and robustness of our proposed FOL-based approach, and we discuss its appropriateness as the basis for the generalized theory.

Introduction

Clinical practice guidelines (CPGs), as knowledge-based tools for disease-specific patient management⁵, encapsulate evidence-based practices for devising the most appropriate treatment for patients with regard to relevant patient information and possible diagnoses. CPGs are normally created by a panel of experts and in a number of instances are computerized. However, CPGs are not designed for use on patients with comorbid diseases and who require a combined therapy (i.e., a therapy established according to all simultaneously applied CPGs). This problem was identified as one of the major shortcoming of CPG uptake in practice and as such there exists a need for research to address it¹. Given a comorbid patient's available medical information, it is likely that the application of multiple disease-specific CPGs results in direct adverse interactions between individual medical actions that manifest as contradictory recommendations (e.g., "administer NSAID" in one CPG and "do not administer NSAID" in the other). The concurrent application of disease-specific CPGs for such patients can also result in undesired consequences due to drug-drug or drug-disease interactions, a term we refer to as indirect adverse interactions⁴. More broadly, the synthesis of two or more guidelines for treating patients with comorbidities is a challenging problem involving sophisticated design of processes for the identification and elimination of potential redundancies, contradictions, and discordances⁶. Therefore, combining CPGs in order to cross-check CPG-based medical recommendations requires the introduction of new combinatorial, logical, or semantic approaches⁷.

Our recent research^{4,8,9} responds to this need by introducing and formally defining a logical model of CPGs and developing a mitigation algorithm that operates on these models in order to identify and address adverse interactions. In the mitigation algorithm, clinical knowledge is encoded as interaction and revision operators within the constraint logic programming (CLP) paradigm. The operators characterize adverse interactions and describe revisions to logical models required to address encountered interactions. CLP allows one to efficiently solve these models where a solution represents a consistent combined therapy free of any adverse interactions.

More specifically, we apply our CLP-based approach to a situation when at least two CPGs are applied to a comorbid patient in order to obtain a combined therapy – a combination of at least two individual therapies derived from disease-specific CPGs. With available patient information, a combined therapy might not be consistent if there are adverse (in)direct interactions between the diseases, between medications that are applied to the patient as suggested by the disease-specific CPGs, or between diseases and prescribed medications. In these cases, CPGs and

associated therapies need to be revised using secondary clinical knowledge. This knowledge is not encoded in the guidelines themselves but comes from domain experts, textbooks, or repositories of clinical evidence.

While the CPG mitigation paradigm proposed in our earlier research is powerful enough to handle a number of different clinical scenarios associated with the management of comorbid conditions, it also has several limitations. The critical limitation is the lack of support for using temporal and associated precedence relationships between CPG actions. It is well documented that medical actions (tests or administration of medication) often follow time-dependent sequences that need to be preserved, even when new or modified actions are introduced. Our desire to capture the time dependencies commonly found in CPGs motivates the research presented in this paper that extends the CLP-based approach.

Our current research focuses on extending the CLP-based approach to handle the temporal relationships and more broadly it aims at developing a general framework for the concurrent application of CPGs. Towards this end, we present our work on representing CPGs as first-order logic (FOL) theories. FOL allows us to define CPGs as logical theories, take patient information and mitigation strategies that incorporate time and precedence relations into account, and include the modeling capabilities developed in our earlier CLP-based work. As a matter of fact, precedence relationships are only FOL definable. Further, using FOL to represent and manipulate the CPGs allows us to introduce semantics to guide the interpretation of the concepts and relieve the user of “manual” interpretations of the mitigation results – an additional limitation of our CLP-based work.

Our current methodological foundation is adopted largely from our previous work^{4,8,9} and expanded as required. The conceptual framework describing this extension, using a case study based on the concurrent management of type 2 diabetes and rheumatoid arthritis, is the focus of this paper. We start by providing a brief overview of FOL and theorem proving – the methods used in our research. We then describe the methodological foundation of our proposal to model the mitigation problem as a FOL theory. Next we present a case study to ground the theory in a clinical example, and we conclude with a discussion of our contributions and potential areas for future work.

Methodology

In order to better illustrate the proposed FOL-based mitigation of guidelines, we start with brief introductions of the basic concepts and notation of FOL and theorem proving. We then present the methodological foundations of our approach.

First-Order Logic and Theorem Proving

First-order logic (FOL) is a formal system in which formulas of a formal language may be interpreted to represent propositions (particular sentences, such as “administer NSAID”). FOL distinguishes itself from propositional logic by providing additional expressive power through the use of quantified variables (for example $x > 1$ meaning all values of x must be greater than 1). With FOL, properties of objects in the domain and relationships between objects can be specified by introducing predicates and a set of inferences rules and axioms allow the derivation of theories from this language. In FOL, a theory is a collection of sentences describing some domain (i.e. CPGs). We further assume that it is possible to reason over a theory, and the result of this reasoning is referred to as a model. Thus, given a theory D and a sentence φ in the language of D , we say that φ is consistent with D if there exists a model of the theory that satisfies φ . The sentence φ can be deduced (or implied) from D if the sentence is satisfied by all models for D . Formally, we write

$$D \models \varphi$$

Therefore, the notion of theorem proving is a procedure to check whether a theory is satisfiable (meaning if it is possible to derive models from this theory). One way to check for satisfiability is by formulating an entailment problem (understood as a logical consequence of the sentences where one follows from the other) over D . Moving from our previous work^{4,8,9} to a FOL-based approach substantially increases our ability to represent and reason over clinical knowledge by representing CPGs, patient information, and basic properties of mitigation as FOL-based theories. As part of this reasoning, we generate an entailment problem over the generated theory to check for the satisfiability of the theory. A so-called grounded instance of a satisfiable theory represents a consistent therapy.

FOL Theory for CPG Mitigation

Before introducing the main concepts and components of FOL theories employed to mitigate adverse interactions between CPGs, we briefly recall the notion of an *actionable graph* (AG)⁴ which we use as a representation of an individual CPG. An AG expresses a single CPG in form of a directed graph composed of three types of nodes –

context, *action*, and *decision*, and arcs that correspond to transitions between nodes. A *context* node defines an entry point and indicates the disease associated with the CPG, an *action* node indicates a medical action that needs to be executed, and finally a *decision* node indicates a selection from several alternative choices and it allows for conditional branching. An AG may contain loops however, in this paper we assume an AG contains no loops, and is thus an acyclic graph. The formal definition of an AG, based on the SDA* notation, and several examples are provided in our previously published work⁴.

The three key components of using FOL for CPG mitigation are: (1) a vocabulary used to construct the theory, (2) a set of “sub-theories” to describe various components of the mitigation problem, and (3) a set of operators that define the secondary knowledge needed to identify and mitigate adverse interactions in the theory. We describe each in turn below.

The vocabulary is made up of constants (denoted with lower case letters, e.g., x , a), variables (denoted with upper case letters, e.g. X , Z) and predicates. Table 1 lists core predicates that are central to the case study described later (the vocabulary includes other predicates as well, but we have omitted them for the sake of simplicity). We note there is no predicate corresponding to a context node, as information embedded in this node is provided by the predicate $disease(d)$.

Table 1. Defined predicates

Predicate	Explanation
$node(x)$	x is a node in AG
$disease(d)$	CPG is associated with disease d
$action(x)$	x is an action node in AG
$diagnosed(d)$	disease d is diagnosed for the given patient
$decision(x)$	x is a decision node in AG
$executed(x)$	task node x is or has been executed
$value(x, v)$	value v is associated with decision node x
$dosage(x, n)$	task node x is characterized by dosage n
$directPrec(x, y)$	node x directly precedes node y (in AG there is an arc from x to y)
$prec(x, y)$	node x precedes node y (in AG there is a path from x to y)

A FOL theory is a collection of logical sentences constructed using the defined vocabulary. In our research we create the following theories that represent relevant components of the mitigation problem:

- D_{common} – a common theory that axiomatizes the universal characteristics of CPGs as part of a FOL-based representation for mitigation. It introduces axioms that ensure important properties of precedence and relations between various types of nodes and their characteristics. More specifically, introduced axioms ensure anti-symmetry and transitivity of precedence, uniqueness of node types (a node cannot be both an action and decision node, only an action node may be associated with medication dosage, etc.) and similar properties,
- D_{cpg}^d – the theory that represents an actionable graph AG (and thus the underlying CPG) for disease d . It encapsulates treatments for this disease, enlists all paths in the AG in the form of disjunctions of conjunctions (where each conjunction corresponds to a path), gives information about direct precedence between nodes, and finally provides information on dosages associated with selected action nodes,
- D_{pi} – the theory that represents available patient information, where each data item is given as a separate logical sentence,
- D_{mit} – the theory (initially empty) that stores new sentences introduced during the mitigation process.

These theories are used as building blocks to construct a combined theory that describes a particular mitigation instance personalized to a patient encounter. Formally, the combined theory D_{comb} is defined as the union of the theories described above:

$$D_{comb} = D_{common} \cup D_{cpg}^{d_1} \cup D_{cpg}^{d_2} \cup \dots \cup D_{cpg}^{d_m} \cup D_{pi} \cup D_{mit},$$

where d_1, d_2, \dots, d_m are the diseases a comorbid patient suffers from and for which the patient is concurrently managed according to the associated CPGs. To further simplify the presentation in this paper yet without the loss of generality we limit the number of concurrently applied CPGs to two, thus we define the combined theory as follows:

$$D_{comb} = D_{common} \cup D_{cpg}^{d_1} \cup D_{cpg}^{d_2} \cup D_{pi} \cup D_{mit}$$

FOL-based Mitigation of Adverse Interactions

The process of mitigating (identifying and addressing) adverse interactions consists of two main phases. The first phase aims at mitigating direct adverse interactions that manifest as inconsistencies in the combined theory D_{comb} . Their identification is relatively easy as it involves checking the satisfiability of D_{comb} . If the theory is satisfiable, then there are no direct interactions. Otherwise the theory needs to be revised by applying revision operators. These *revision operators* capture expert knowledge that is not encoded in CPGs and they are formally defined later in the text.

The second phase of the mitigation process aims at identifying and addressing indirect adverse interactions. Checking the satisfiability of D_{comb} is not sufficient for identifying indirect interactions and additional expert knowledge is required. This knowledge is encoded in form of *interaction operators*. An interaction operator IO^k is formally defined as

$$IO^k = \langle \alpha^k \rangle,$$

where α^k is a logical sentence that describes a particular interaction. Checking whether a particular IO^k is applicable to D_{comb} is formulated as the entailment problem $D_{comb} \models \alpha^k$.

Encountered interactions (both direct and indirect) need to be addressed by applying relevant revision operators to D_{comb} . A revision operator RO^k is formally defined as

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

where β^k is a logical sentence that defines the applicability of the operator (the relevance of a revision operator for a particular theory given specific patient information), and Op^k describes the revisions introduced by RO^k . In particular, Op^k is a list of n pairs of logical expressions $\langle \varphi_i^k, \phi_i^k \rangle$ ($i = 1 \dots n$) that define individual operations carried out as part of applying the revision operator. To ensure that patient information is not modified and general practices of mitigation are not violated as part of the revision process, the operations Op^k are only applicable to a subset of the theories that comprise D_{comb} – namely $D_{cpg}^{d_1}$, $D_{cpg}^{d_2}$ and D_{mit} . Furthermore there are three possible types of operations in Op^k – *removal*, *addition*, and *substitution*. These types are defined as follows, where \otimes represents an empty expression:

- $\langle \varphi_i^k, \otimes \rangle - \varphi_i^k$ is removed from any sentence that appears in $D_{cpg}^{d_1}$, $D_{cpg}^{d_2}$ or D_{mit} ,
- $\langle \otimes, \phi_i^k \rangle - \phi_i^k$ is added as a new sentence to D_{mit} ,
- $\langle \varphi_i^k, \phi_i^k \rangle - \varphi_i^k$ is replaced by ϕ_i^k in any sentence that appears in $D_{cpg}^{d_1}$, $D_{cpg}^{d_2}$ or D_{mit} .

Checking the applicability of RO^k is analogous to checking the applicability to IO^k and translates to formulating and solving the entailment problem $D_{comb} \models \beta^k$.

In the context of FOL, a consistent combined therapy is a model of D_{comb} that represents an assignment of values to predicates.

Case Study: Management of a Patient with Type 2 Diabetes and an Onset of Severe Rheumatoid Arthritis

To ground the theoretical concepts presented above, we use the following case study. Let's consider a 70 year old male with type 2 diabetes (DB2), who suffers from symptomatic hyperglycemia and has consistently measured over 8.5 on the A1C test. As such, his sugar level is being controlled by a daily insulin dosage of 40 international units.

The patient also suffers from relatively mild rheumatoid arthritis (RA) (comorbid condition) that is being managed using a maintenance dosage of plaquenil. In the two clinical scenarios described below, we will show how the patient's therapy can be revised through the mitigation of adverse interactions using the formalism described above. For the sake of simplicity we only present the relevant interaction and revision operators and omit the details of the FOL-based theories D_{cpg}^{db2} and D_{cpg}^{ra} representing CPGs for type 2 diabetes and a rheumatoid arthritis.

Clinical Scenario 1: Managing the Administration of Glucocorticoids

In the first scenario we assume there is a sudden relapse of RA accompanied by the onset of severe pain and significantly reduced mobility. Typically in such cases, the patient is initiated on glucocorticoid treatment to control the onset of pain. However, considering that the patient is diabetic, the increased sugar level associated with the administration of glucocorticoids needs to be mitigated with an increased maintenance dosage of insulin. In this clinical scenario, the daily dosage is increased to 48 international units and maintained until sugar level stabilizes or the patient no longer requires glucocorticoid therapy.

Supporting this scenario requires the codification of secondary knowledge describing the use of and interactions with glucocorticoids. As stated in medical literature, glucocorticoids increase the blood sugar level and require the dosage of insulin in DB2 patients (if administered) to be increased by 20%. The interaction operator IO^1 represents the drug-drug interaction when a DB2 patient, also being treated for RA, is prescribed with glucocorticoids while taking insulin.

$$IO^1 = \langle \alpha^1 \rangle,$$

where $\alpha^1 = \text{diagnosed}(db2) \wedge \text{diagnosed}(ra) \wedge \text{executed}(gluco) \wedge \text{executed}(insulin)$.

The revision operator RO^1 modifies the theory representing this DB2 and RA patient by increasing the dosage of insulin by 20%.

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

where $\beta^1 = \alpha^1$ and $Op^1 = \langle \text{dosage}(insulin, X), \text{dosage}(insulin, X * 1.2) \rangle$. We note the definition of the operation in Op^1 employs variable X . Variables act as "wildcards" that can be bound to different constants to increase the flexibility of operations, thus in this case it is possible to define a substitution operation that increases the dosage of a medication by a certain ratio.

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

$$D_{pi} = \text{diagnosed}(db2). \text{diagnosed}(ra). \text{executed}(gluco). \text{executed}(insulin).$$

The following sentence is part of the theory for DB2 prescribing 40 international units of insulin to the patient.

$$D_{cpg}^{db2} \ni \text{dosage}(insulin, 40)$$

To check for the existence of an indirect interaction we formulate the entailment problem $D_{comb} \models \alpha^1$. Because α^1 is consistent with D_{comb} , we know an indirect interaction exists. We then formulate the entailment problem $D_{int} \models \beta^1$ -- since $\beta^1 = \alpha^1$ we immediately know RO^1 is applicable to D_{comb} and we consequently apply Op^1 to substitute the dosage of insulin with a dosage that is 20% higher. This is done by removing $\text{dosage}(insulin, 40)$ from D_{cpg}^{db2} and adding $\text{dosage}(insulin, 40 * 1.2)$ to D_{mit} , which resolves to the dosage of insulin being adjusted to 48 international units (X is bound to 40). Note the use of variables to support different values for the same expression, rather than creating an expression for each possible value.

Clinical Scenario 2: Managing Immunosuppressive Medication

In this clinical scenario we consider the same patient that was initiated on glucocorticoid therapy supplemented with a calcium antagonist (in place of a NSAID that is not recommended for diabetic conditions). The daily insulin dosage was increased (as explained in Scenario 1) to manage the elevated sugar level, however the prescribed therapy did not work as expected. In order to better control the relapse of rheumatoid arthritis, the next therapeutic option is to put the patient on DMARD combination therapy that normally includes cyclosporine. While all immunosuppressive medications are diabetogenic (with hyperglycemia being a common adverse event), some like azathioprine proved in clinical trials to be better tolerated by type 2 diabetics. Therefore, the revised DMARD combination therapy is prescribed for this patient, and it uses azathioprine as a replacement for cyclosporine.

The interaction operator IO^2 represents the drug-disease interaction that occurs when a DB2 patient, being treated for RA, is prescribed cyclosporine as part of DMARD combination therapy.

$$IO^2 = \langle \alpha^2 \rangle,$$

where $\alpha^2 = \text{diagnosed}(db2) \wedge \text{diagnosed}(ra) \wedge \text{executed}(\text{cyclosporine})$.

The revision operator RO^2 modifies the theory D_{comb} for the DB2 and RA patient by replacing cyclosporine with azathioprine. As we show below, this revision also maintains the precedence of executed tasks when performing the replacement.

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

where $\beta^2 = \alpha^2$ and Op^2 is the following list of logical expressions.

$\langle \text{node}(\text{cyclosporine}), \text{node}(\text{azathioprine}) \rangle. \langle \text{action}(\text{cyclosporine}), \text{action}(\text{azathioprine}) \rangle.$

$\langle \text{directPrec}(\text{methotrexate}, \text{cyclosporine}), \text{directPrec}(\text{methotrexate}, \text{azathioprine}) \rangle.$

$\langle \text{directPrec}(\text{cyclosporine}, \text{observ_ra}), \text{directPrec}(\text{azathioprine}, \text{observ_ra}) \rangle.$

To check for the existence of an indirect interaction we formulate the entailment problem $D_{comb} \models \alpha^2$ and subsequently $D_{comb} \models \beta^2$ to find the relevant revision operator. Using patient information represented in D_{pi} above, we infer that RO^2 is in fact applicable to this patient encounter and we apply the corresponding logical expressions to the theory.

We note here that we are revising the theory for the patient to replace cyclosporine with azathioprine **and** maintain the order in which tasks are to be executed according to the CPG for RA (not shown here due to space limitations). Specifically, we are ensuring that the task of administering *methotrexate* (to treat RA) is done before the administration of *azathioprine* (as was the case for cyclosporine), and that the patient's onset of RA is observed (*observ_ra*) after administering azathioprine. Similarly to the first clinical scenario, the removal of sentences is done from D_{cpg}^{ra} and sentences are added to D_{mit} .

Discussion and Conclusions

In this paper we described our preliminary research on developing a general theory of mitigation expressed in FOL for concurrently applied CPGs. This research builds upon our foundational work in using the CLP paradigm to handle mitigation and extends it by using a paradigm with greater expressive power (FOL) to handle temporal relationships such as task precedence. We used a case study of a patient suffering from type 2 diabetes while being treated for an onset of severe rheumatoid arthritis to illustrate the added benefit of our new approach. Through two simple scenarios we demonstrated the power of our FOL-based approach by applying an adjustment of medication dosage and through the substitution of tasks while maintaining the task execution order as defined by one of the CPGs.

Our proposed FOL-based approach provides an expressive and robust language in order to represent and apply temporal relationships represented in CPGs while also easily capturing common knowledge applicable to all mitigation scenarios. Furthermore, by separating the overall theory (D_{comb}) into "sub-theories" we are able to provide finer grained control over how to apply revisions to a proposed theory. Specifically, we limit the addition, deletion, and substitution of logical sentences to the theories representing CPGs (D_{cpg}^{di}) and to the theory representing added mitigation actions (D_{mit}). As such, we ensure that a patient's state is consistent since information describing a patient (D_{pi}) cannot be inadvertently changed. Additionally, the common characteristics of mitigation, applicable to all mitigation instances, are maintained in a single theory (D_{common}) and cannot be altered by any mitigation operations.

As future research, we are exploring ways to make the proposed approach more general and robust. As stated at the beginning, our ultimate goal is to develop a general framework of mitigation and towards this end we are studying various clinical situations involving comorbid patients to extract the full set of properties that hold across all mitigation scenarios. Furthermore, we are working on inductive reasoning techniques to automatically infer precedence relationships as logical operations are applied to the theories representing CPGs. The addition, deletion, and substitution of logical sentences impacts the underlying structure represented by these theories and automating

the maintenance of correct precedence relationships goes a long way to realizing our goal of using FOL-based methods to drive a point-of-care clinical decision support system.

References

1. Peleg M. Computer-interpretable clinical guidelines: a methodological review. *J Biomed Inform* 2013;46(4):744-63.
2. Isern D, Moreno A, Sánchez D, Hajnal Á, Pedone G, Varga LZ. Agent-based execution of personalised home care treatments. *Appl Intell* 2011;34(2):155-180.
3. Stanford University. GLINDA: GuideLine INteraction Detection Architecture [Internet]. [cited March 10, 2014]. Available from: <http://glinda-project.stanford.edu/>.
4. Wilk S, Michalowski W, Michalowski M, Farion K, Hing MM, Mohapatra S. Mitigation of adverse interactions in pairs of clinical practice guidelines using constraint logic programming. *J Biomed Inform* 2013;46(2):341-53.
5. Rosenfeld RM, Shiffman RN. Clinical practice guideline development manual: a quality-driven approach for translating evidence into action. *Otolaryngol Head Neck Surg* 2009;140(6 Suppl 1):S1-4.
6. Sittig DF, Wright A, Osheroff JA, Middleton B, Teich JM, Ash JS, et al. Grand challenges in clinical decision support. *J Biomed Inform* 2008;41(2):387-92.
7. Fox J, Glasspool D, Patkar V, Austin M, Black L, South M, et al. Delivering clinical decision support services: there is nothing as practical as a good theory. *J Biomed Inform* 2010;43(5):831-43.
8. Michalowski M, Wilk S, Lin D, Michalowski W, Tan X, Mohapatra S. Procedural approach to mitigating concurrently applied clinical practice guidelines. In: Workshop on Expanding the Boundaries of Health Informatics Using Artificial Intelligence (HIAI'13) at the Twenty-Seventh AAAI Conference on Artificial Intelligence; 2013.
9. Michalowski M, Wilk S, Michalowski W, Lin D, Farion K, Mohapatra S. Using constraint logic programming to implement iterative actions and numerical measures during mitigation of concurrently applied clinical practice guidelines. In: Peek N, Morales RM, Peleg M, editors. *Artificial Intelligence in Medicine, 14th Conference on Artificial Intelligence in Medicine, AIME 2013, Murcia, Spain, May/June 2013, Proceedings*. Springer; 2013. p. 17-22.