

RECONCILIATION OF CONCURRENTLY APPLIED CLINICAL PRACTICE GUIDELINES USING CONSTRAINT LOGIC PROGRAMMING

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ABSTRACT

This paper describes a novel methodological approach to reconciling *points of contention* (inconsistencies related to adverse and contradicting actions) when concurrently using multiple *clinical practice guidelines* (CPGs). The need to address these inconsistencies arises when a patient with *comorbidity* (the presence of one or more diseases in addition to a primary one) has to be managed according to different treatment regimens. We explain how to construct a formal guideline model using *Constraint Logic Programming* (CLP) and illustrate it with an example. We also present a procedure for mitigating points of contention that may arise when solving a constructed model given available patient information. The proposed procedure is conducted automatically and it employs mitigation operators that encapsulate clinical knowledge and define possible modifications to the model. The use of the mitigation procedure is demonstrated in a clinical scenario.

1 INTRODUCTION

It is generally agreed upon that managing a patient according to established clinical standards based on sound evidence has a positive impact on the patient's outcomes and improves the quality of care [1]. One of the most common methods for implementing these standards are clinical practice guidelines (CPGs) [2]. A CPG is a disease-specific tool created on the basis of experts' consensus and medical evidence extracted from document repositories [3] such as The Cochrane Library [4]. It reflects best practices in collecting relevant patient data, drawing conclusions from this data with regards to possible diagnoses and prescribing the most effective action plan. While most physicians believe that their actions, while managing a patient, agree with relevant guideline standards and that there is no need to consult a corresponding CPG, the opposite is true [5].

It is believed that presenting CPGs to physicians in forms other than text-based will improve their adherence to

standards of practice, and there is a significant body of literature concerned with evidence of the positive impact of computer-based CPGs on the quality of care provided [6]. These computer-based CPGs become an active support tool helping and guiding physicians throughout the patient management process. Despite all the available evidence, CPG use in clinical practice and at the point of care is still relatively limited [7].

One possible explanation for the CPG's limited uptake in practice is the increasing number of patients with concurrent diseases that need to be managed in a systemic manner. This is especially evident for elderly patients – several studies [3,8,9] show that about 50% of people 65 years old or older have a comorbid condition and improving quality of care provided to this patient population is very important [10]. However, concurrent application of disease-specific guidelines for a patient with a comorbid condition not only might have undesired effects on the patient's care but also may result in an unnecessarily increased financial burden placed on the patient as well as society [11].

Despite the pressing needs to support management of a patient with comorbidity, there is little research (apart from clinical research on different issues associated with comorbidity and treatment of chronic diseases) on (semi-) automatic reconciliation of multiple, simultaneously used CPGs so they can become active support tools assisting physicians at the point of care. Most of the current research is focused on semantic or functional interoperability of concurrently used guidelines and resulting alignment of actions [12,13]. Guidelines are usually represented as ontological models and different alignment strategies are proposed to produce a cohesive recommendation.

The methodology presented in this paper is different in that it moves away from a single disease focus prevalent in CPGs. Instead, using an automatic approach we build a multi-disease guideline model that includes CPGs associated with a comorbid condition, identify inconsistencies - adverse and contradicting actions, and provide ways to address them (or, when it is not possible, we warn the physician about the dangers to a patient associated with the concurrent use of the guidelines). At the core of the proposed multi-disease CPG is a guideline computer model that follows the constraint logic programming (CLP) mathematical paradigm.

The paper is organized as follows. We start with an illustrative clinical scenario that outlines our approach to modeling CPGs according to the CLP paradigm and demonstrate problems associated with concurrent applications of multiple CPGs. Then we introduce the notion of mitigation operators and describe a procedure that employs these operators to mitigate encountered inconsistencies. The proposed procedure is also applied to the clinical scenario introduced previously. We finish with conclusions and a discussion on our future research plans.

2 MOTIVATING CLINICAL EXAMPLE

In this section we present a clinical scenario to illustrate problems associated with the concurrent application of

CPGs for a patient who is treated for a duodenal ulcer and experiences a transient ischemic attack (TIA). CPGs used in this example are based on guidelines published by the National Institute for Health and Clinical Excellence, UK (NICE) [14] and they have been simplified for the sake of clarity.

Our approach to representing, combining and applying concurrent CPGs is outlined below and described throughout this section:

- Phase 1: represent each CPG as a decision graph and enumerate all paths in the graph,
- Phase 2: construct *expanded path tables* (EPTs) to represent the enumerated paths,
- Phase 3: construct individual constraint logic programming models (single CLP-CPG models) from each disease's EPT and merge these models into a combined CLP-CPG model,
- Phase 4: solve the combined model given available patient data and if a solution exists, present it to the physician, otherwise present a partial solution with identified inconsistencies; presented solution (full or partial) is limited to the actions, as they are of primary interest to the physician.

We assume that during the application of our approach we have access to a knowledge base (KB) associated with each CPG that is disease-specific and contains knowledge that is not explicitly represented in a CPG (e.g., possible adverse interactions of treatments).

2.1 Phase 1: Constructing Decision Graphs and Enumerating Paths

A decision graph provides a concise representation of a CPG. It is a directed graph with two types of nodes: action nodes corresponding to action steps and decision nodes corresponding to decision steps in the guideline. These two types of steps appear in the majority of formal representations for CPGs, e.g., GLIF, EON or PROforma (see [15] for a review). To support further analysis we uniquely associate each node with a Boolean variable – these variables are categorized as decision and action ones depending on the type of underlying nodes. Moreover, to complete the representation and to account for transitions between the steps, arcs starting at a decision node are labeled either with *true* or *false* logical values, while arcs starting at action nodes are not labeled (i.e., their traversal is unconditional).

Transforming a CPG from one of the formal representations into a decision graph is relatively straightforward – we proposed an algorithm in [16]. Figure 2 and 1 present decision graphs constructed from CPGs for TIA and duodenal ulcer guidelines respectively. In both figures decision nodes are indicated with diamonds, and action nodes with rectangles. The figures also indicate variables associated with specific steps and provide their descriptions.

Table 2. EPT for ulcer

Decisions		Actions				
<i>HPP</i>	<i>HE</i>	<i>SA</i>	<i>ET</i>	<i>PPI</i>	<i>SC</i>	<i>RS</i>
true	true	true	true	false	true	false
true	false	true	true	false	false	true
false	true	true	false	true	true	false
false	false	true	false	true	false	true

corresponding to all columns in the EPT for a disease and a set CL contains a single constraint being a disjunction of conjunctions representing expanded paths from the EPT. Such constraint translates to a requirement that at least one expanded path is evaluated as *true*.

In order to account for the possible interactions among concurrent CPGs, it is necessary to merge single CLP-CPG models into a combined CLP-CPG model. The sets V and CL in the combined model are unions of the appropriate sets from single models. To complete the combined CLP-CPG model we need to include knowledge about adverse actions related to treatment-treatment and treatment-disease interactions and contradictory actions (e.g., give a specific medication and stop using this medication). Knowledge about adverse and contradictory actions is represented as relationships between variables corresponding to these actions and stored in KBs associated with specific diseases. Thus, the set of constraints in the combined model is augmented with constraints derived from the KBs.

The combined CLP-CPG model for TIA and ulcer is given in Figure 3. It contains 17 variables and 3 constraints. The first two constraints come from the single CLP-CPG models and the last one ($\neg(A \wedge SA)$) comes from KBs associated with these diseases and represents knowledge about a contradictory action – specifically that a physician cannot both prescribe aspirin (A) and ask to stop using aspirin (SA). There are no constraints corresponding to adverse actions, as they have not been associated with TIA and ulcer in any KB.

2.4 Phase 4: Solving a Combined CLP-CPG Model

Generally, solving the CLP-CPG model (either single or

combined) entails assigning a value to each variable such that no constraints are violated. Variables related to available information (known patient information) are instantiated prior to solving the model and cannot be revised by the solving procedure. As such, the solution task can be approached in three different ways: (1) model checking (to determine whether the problem has a solution), (2) search to find a single solution, or (3) search to find all solutions. In this research, we solve the CLP-CPG model by searching to find a single solution.

We use an open source constraint programming system ECLiPSe [18]. It contains several constraint solver libraries, a high-level modeling and control language, interfaces to third-party solvers, an integrated development environment and interfaces for embedding into host environments. We chose it because it enabled us to experiment with various constraint propagation strategies and different methods such as conflict sets and backmarking [17] for identification of possible inconsistencies. Additionally, it provides interfaces we can use to tie our approach into the MET3 point of care system [19] we developed.

In simple cases where there are no shared variables between single CLP-CPG models nor constraints involving variables from different single models, solving the combined model is equivalent to solving each single model independently. In more complex cases dependencies between the single models further constraint a solution. If given patient's information, a single model includes a constraint that explicitly identifies actions that are inconsistent (adverse or contradictory) in combination with some actions defined by another single model, then the combined CLP-CPG model has no solution. These inconsistent actions constitute a *point of contention* (POC). More formally, we define a POC as a set of variables, whose domains are annihilated (reduced to the empty set) during search, resulting in no found solution.

If the combined CLP-CPG model has no solution, we attempt to resolve the POC using the process described in Section 3. For instances where we are unable to resolve POC, we identify a partial solution that includes assignments of values to variables not included in the POC. We

$$\begin{aligned}
V &= \{H, F, NSR, ERS, EC, A, TS, NC, AD, PCS, HPP, HE, SA, \\
&\quad ET, PPI, SC, RS\} \\
CL &= \{ \\
&\quad (H \wedge EC \wedge \neg A \wedge \neg TS \wedge \neg NC \wedge \neg AD \wedge \neg PCS) \vee \\
&\quad (\neg H \wedge F \wedge \neg NSR \wedge \neg EC \wedge \neg A \wedge TS \wedge NC \wedge \neg AD \wedge \neg PCS) \vee \\
&\quad (\neg H \wedge F \wedge NSR \wedge ERS \wedge \neg EC \wedge A \wedge \neg TS \wedge NC \wedge AD \wedge \neg PCS) \vee \\
&\quad (\neg H \wedge F \wedge NSR \wedge \neg ERS \wedge \neg EC \wedge A \wedge \neg TS \wedge \neg NC \wedge \neg AD \wedge PCS) \vee \\
&\quad (\neg H \wedge \neg F \wedge \neg EC \wedge \neg A \wedge \neg TS \wedge \neg NC \wedge \neg AD \wedge PCS), \\
&\quad (HPP \wedge HE \wedge SA \wedge ET \wedge \neg PPI \wedge SC \wedge \neg RS) \vee \\
&\quad (HPP \wedge \neg HE \wedge SA \wedge ET \wedge \neg PPI \wedge \neg SC \wedge RS) \vee \\
&\quad (\neg HPP \wedge HE \wedge SA \wedge \neg ET \wedge PPI \wedge SC \wedge \neg RS) \vee \\
&\quad (\neg HPP \wedge \neg HE \wedge SA \wedge \neg ET \wedge PPI \wedge \neg SC \wedge RS), \\
&\quad \neg(A \wedge SA) \\
&\quad \}
\end{aligned}$$

Figure 3. Combined CLP-CPG model for TIA and ulcer

use backmarking, available as part of the ECLiPSe system, as the method to generate a partial solution. The POC and the partial solution are presented to the physician who decides how to amend the patient's treatment plan while consulting the presented information.

Solving the combined CLP-CPG model shown in Figure 3 with instantiated variables $H = false$, $F = true$ and $NSR = true$ (no signs of hypoglycaemia, positive FAST and resolved stroke symptoms) fails. We find the partial solution $\{EC = false, TS = false, NC = false, AD = false, PCS = true\}$ and variables A and SA are identified as causing the POC. In this case CPGs associated with TIA and ulcer need to be modified in order to mitigate the encountered POC. This can be done either manually by the physician or by an automatic mitigation procedure that is described in the next section.

3 MITIGATING POC

In this section we describe a procedure that allows for mitigating POCs encountered when solving combined CLP-CPG models. While this procedure is automatic, it relies on *mitigation operators* (MOs) that are defined by the expert and that allow modifying CPGs associated with specific diseases (more precisely, they modify corresponding EPTs and these changes are further propagated in single and combined CPG-CLP models). A formal definition of an MO is given further in this section and we also expand the scope of KBs associated with specific diseases that allows for storing defined MOs.

The procedure for mitigating POCs expands the approach presented in Section 2. The procedure is triggered when a POC has been encountered and the combined CLP-CPG model cannot be solved (see Section 2.4). Currently we assume the POC results from interactions between two CPGs, as this represents a typical clinical use case. However, as part our future research we plan to expand the procedure to handle more than two CPGs.

Our mitigation procedure is outlined below and individual phases are described in details further in the text:

- Phase 1: identify MOs associated with considered diseases that are applicable to the encountered POC,
- Phase 2: iteratively apply identified MOs to construct and solve a modified CPG-CLP model; if a solution exists, it is presented to the physician together with the applied MO and the mitigation process is terminated.

3.1 Mitigation Operators

Each MO is formally defined as 6-tuple: $\langle bd, td, poc, lhs, rhs, ma \rangle$, where:

- bd and td are *base* and *target* diseases accordingly for which associated EPTs are modified by the operator. As explained below most major changes are introduced in

the EPT for bd , and changes in the EPT for td are minor;

- poc is a label pointing to the POC mitigated by the operator;
- lhs and rhs describe modifications introduced to the EPT for bd . They are represented as conjunctions of action variable – value pairs. lhs is a pattern that is searched for in individual rows of the EPT, and once the row containing lhs is located, it is modified according to rhs ;
- ma is a set of action variables associates with the columns in the EPT for td that need to be removed. In other words, ma indicates mitigated and discarded actions in the CPG for td . This set can be empty, if no actions have to be discarded.

The operation of modifying the row the EPT containing lhs according to rhs is governed by the following principles:

- if a variable V_{ni} appears in lhs only (i.e., it has been eliminated from rhs), then a value in the located row and column corresponding to V_{ni} should be set to *false*;
- if a variable V_{ni} appears in both lhs and rhs or it appears only in rhs and a corresponding column to V_{ni} exists in the EPT, then the value of V_{ni} indicated in rhs is stored in the located row and column corresponding to V_{ni} ;
- if a variable V_{ni} is presented in rhs only and column corresponding to V does not exist in the EPT, the EPT is expanded with a new action column filled with *false* values by default. Then the value for V_{ni} in the located row is set to the value indicated in rhs .

Figure 4 shows two MOs for TIA and ulcer guidelines ($bd = TIA$, $td = ulcer$) that mitigate the POC demonstrated in Section 2.4 ($\{A, SA\}$). Both MOs imply removing SA from the EPT for ulcer. Operator $m1$ modifies the EPT for TIA by replacing aspirin with clopidogrel ($rhs = \neg A \wedge CL$) if aspirin is not combined with antiplatelets ($lhs = A \wedge \neg AD$). Operator $m2$ implies augmenting administration of aspirin and antiplatelets ($lhs = A \wedge AD$) with PPI ($rhs = A \wedge AD \wedge PPI$).

$m1: \langle TIA, ulcer, \{A, SA\}, A \wedge \neg AD, \neg A \wedge CL, \{SA\} \rangle$
 $m2: \langle TIA, ulcer, \{A, SA\}, A \wedge AD, A \wedge AD \wedge PPI, \{SA\} \rangle$

Figure 4. MOs for TIA and ulcer

The EPT for TIA revised according to $m2$ is given in Table 3. In comparison to the original EPT in Table 1, a new action column has been added (PPI) and row 4 has been modified (changed values are marked with bold font). The modified EPT for ulcer no longer includes the column for SA ; however, the remaining content is not changed, therefore we do not present it in the paper.

Table 3. Modified EPT for TIA (application of operator m_2)

Decisions				Actions						
H	F	NSR	ERS	EC	A	TS	NC	AD	PCS	PPI
true				true	false	false	false	false	false	false
false	true	false		false	false	true	true	false	false	false
false	true	true	true	false	true	false	true	true	false	true
false	true	true	false	false	true	false	false	false	true	false
false	false			false	false	false	false	false	true	false

3.2 Phase 1: Identifying Applicable MOs

As we mentioned in Section 3.1, MOs are defined in KBs associated with their respective diseases. We focus on these MOs for which both diseases are indicated as bd and td (base and target diseases) and that address the encountered POC. Identified applicable MOs are ordered to make phase 2 of the mitigation process more efficient. Such criterion can be either domain-specific, e.g., cost or difficulty of modifications implied by the MO, or domain-independent, e.g., the number of modified variables in the target disease.

For example, considering the MOs for TIA and ulcer presented in Figure 4 (both addressing the POC involving A and SA) and a domain-independent criterion that favors simpler modifications (smaller number of modified variables), m_2 is ordered first. This operator introduces a single additional action while m_1 both introduces one action and discards another one and it is ordered second.

3.3 Phase 2: Applying Identified MOs and Solving Modified Combined CLP-CPG Models

We iteratively apply each of the ordered MOs identified in the previous phase and check if the introduced modification leads to a solution of the combined CLP-CPG model. During the iterative process, the current MO is applied to the EPTs associated with both diseases (as per the description in Section 3.1) – this results in modified EPTs that are further used to modify single and combined CLP-CPG models. We follow the process described in Section 2.3 to create these CLP-CPG models.

Since applying the MO results in removing and introducing action variables, the modified combined model is likely to include different constraints corresponding to adverse and contradictory actions when compared to the original combined model. If the modified combined model has a solution, it is presented to the physician together with the applied MO and the mitigation process terminates. Otherwise, the next MO in the ordered list is applied. If after applying all mitigation operators no solution is found, the physician is presented with a partial solution for the last modified combined CLP-CPG model along with the identified POC.

Figure 5 shows the modified combined CLP-CPG model revised according to the operator m_2 (the first considered for TIA and ulcer). In comparison to the original combined model in Figure 3 it has less variables and does not include the constraint with contradicting actions A and SA , because SA has been removed as part of the m_2 mitigation operator. Additionally, because the interaction between the two single models no longer exists (as a result of removing the variable SA), the combined model can be easily solved given the available patient information ($H = false, F = true, NSR = true$). The variables H, F , and NSR in the modified combined CLP-CPG model are instantiated accordingly and ECLiPSe is able to find a valid solution – $\{EC = false, A = true, TS = false, NC = true, AD = true, PCS = false, ET = true, PPI = true, SC = false, RS = true\}$. Thus, the other m_1 does not have to be applied and we are able to provide the physician with a complete solution.

$$\begin{aligned}
 V &= \{H, F, NSR, ERS, EC, A, TS, NC, AD, PCS, HPP, HE, ET, PPI, SC, RS\} \\
 CL &= \{ \\
 & (H \wedge EC \wedge \neg A \wedge \neg TS \wedge \neg NC \wedge \neg AD \wedge \neg PCS \wedge \neg PPI) \vee \\
 & (\neg H \wedge F \wedge \neg NSR \wedge \neg EC \wedge \neg A \wedge TS \wedge NC \wedge \neg AD \wedge \neg PCS \wedge \neg PPI) \vee \\
 & (\neg H \wedge F \wedge NSR \wedge ERS \wedge \neg EC \wedge A \wedge \neg TS \wedge NC \wedge AD \wedge \neg PCS \wedge PPI) \vee \\
 & (\neg H \wedge F \wedge NSR \wedge \neg ERS \wedge \neg EC \wedge A \wedge \neg TS \wedge \neg NC \wedge \neg AD \wedge PCS \wedge \neg PPI) \vee \\
 & (\neg H \wedge \neg F \wedge \neg EC \wedge \neg A \wedge \neg TS \wedge \neg NC \wedge \neg AD \wedge PCS \wedge \neg PPI), \\
 & (HPP \wedge HE \wedge ET \wedge \neg PPI \wedge SC \wedge \neg RS) \vee \\
 & (HPP \wedge \neg HE \wedge ET \wedge \neg PPI \wedge \neg SC \wedge RS) \vee \\
 & (\neg HPP \wedge HE \wedge \neg ET \wedge PPI \wedge SC \wedge \neg RS) \vee \\
 & (\neg HPP \wedge \neg HE \wedge \neg ET \wedge PPI \wedge \neg SC \wedge RS) \\
 & \}
 \end{aligned}$$

Figure 5. Modified combined CLP-CPG model for TIA and ulcer (application of operator m_2)

4 CONCLUSIONS

In this paper, we presented an approach to reconciling multiple clinical practice guidelines for patients with comorbidity. We introduced extended path tables (EPTs) as a means to represent possible paths in a decision graph representing a CPG. Subsequently we transform each EPT, incorporating information about adverse and contradictory actions contained in external knowledge bases, into a computer solvable model (a single CLP-CPG model) using the constraint logic programming paradigm. To customize treatment for a comorbid patient, we combine single CLP-CPG models to create a combined CLP-CPG model that constraints possible actions based on interactions that exist between concurrently occurring diseases.

To reconcile multiple guidelines that introduce inconsistent actions (constituting a POC) into the treatment regimen for a patient, we introduce *mitigation operators*. These operators encapsulate expert knowledge not captured in a guideline and provide modifications that mitigate the inconsistent actions in the model. We proposed a mitigation process that orders these operators according to the scope of revisions required for the target disease EPT as a way to facilitate the modification process. If a solution to a modified CLP-CPG model exists, we return it to a physician from which they create a complete management plan for the patient. In instances where no complete solution is found at the end of the mitigation process, we return a partial solution along with the identified POC to the physician. This information is valuable in that it provides a physician with partial information they can use to help them decide how best to proceed with treatment such that no inconsistent actions are taken.

To the best of our knowledge, the methods we present here are the first attempt at both automatically combining and reconciling multiple clinical practice guidelines to be used as support tools at the point of care. With the increased frequency of comorbid patients, we see our research as playing an important role in providing clinical support to physicians faced with ever more complex treatment scenarios. Our future research in this area focuses on supporting the concurrent application of more than two guidelines. Additionally we are exploring ways of extending the mitigation operators to include complex interactions between diseases, such as complex drug-disease interactions that are not easily represented using logical conjunctions. Finally we are looking at ways to reformulating constraints in the CLP-CPG model to make it easier to identify POC.

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