Temporal reasoning techniques for the analysis of interactions in the treatment of comorbid patients

Temporal reasoning techniques for the analysis of interactions in the treatment of comorbid patients

Luca Anselma
Dipartimento di Informatica
Università di Torino
corso Svizzera 185
10149 Torino (Italy)
+39 0116706769
anselma@di.unito.it

Luca Piovesan
Computer Science Institute, DISIT
Università del Piemonte Orientale
viale Teresa Michel 11
15121 Alessandria (Italy)
+39 0116706724
luca.piovesan@uniupo.it

Paolo Terenziani
Computer Science Institute, DISIT
Università del Piemonte Orientale
viale Teresa Michel 11
15121 Alessandria (Italy)
+39 0131360174
paolo.terenziani@uniupo.it

ABSTRACT
Clinical practice guidelines are assuming a major role in the medical area, to provide physicians with evidence-based recommendations for the treatment of single pathologies. The treatment of comorbid patients (i.e., patients affected by multiple diseases) is one of the main challenges for the modern healthcare. It requires the development of new methodologies, supporting physicians in the treatment of interactions between guidelines. Several Artificial Intelligence approaches have started to face such a challenging problem. However, current approaches have a substantial limitation: they do not take into account the temporal dimension. This is a strong limitation. For instance, the effects of two actions taken from different guidelines may potentially conflict, but practical conflicts happen only if effects of such actions overlaps in time. In this paper, we propose an approach to support the temporal detection of interactions. Artificial intelligence temporal reasoning techniques, based on temporal constraint propagation, are widely exploited to such a purpose.

CCS Concepts
• CCS → Information systems → Information systems applications → Decision support systems → Expert systems

• CCS → Applied computing → Life and medical sciences → Health care information systems

• CCS → Computing methodologies → Artificial intelligence → Knowledge representation and reasoning → Temporal reasoning

Keywords
Computer-interpretable clinical guidelines; comorbidity treatment; guideline interaction detection; temporal reasoning; medical knowledge representation.

1. INTRODUCTION
Clinical Practice Guidelines (CPGs) are "*systematically developed statements to assist practitioner and patient decisions about appropriate health care in specific clinical circumstances*" [1]. Thousands of CPGs have been devised in the last years. For instance, the Guideline International Network includes more than 100 organizations representing 48 countries and provides a library of more than 6500 CPGs. The adoption of computerized approaches to acquire, represent, execute and reason with CPGs can further increase the advantages of CPGs. Thus, in the last twenty years, several different approaches to Computer-Interpretable Guidelines (henceforth *CIGs*) have been developed (see, e.g., [2], [3]).

By definition, clinical guidelines address specific clinical circumstances (i.e., specific diseases). Unfortunately, in many cases patients are affected by more than one disease. The treatment of *comorbid patients* (i.e., patients affected by multiple diseases) is one of the main challenges for the modern health care, also due to the aging of population and the consequent increase of chronic diseases.

Though some CPGs covering frequently occurring comorbidities might be devised, the approach of considering all the possible combinations of pathologies does not scale up. Thus, there is a need for *formal methodologies* to support physicians in the detection and resolution of interactions between guidelines, and, ultimately, in the process of merging two or more guidelines. This is an increasingly "hot topic" within the Medical Informatics community, and several approaches have been proposed in the last years (see Section 5). In such approaches, new methodologies, mostly based on Artificial Intelligence techniques, have been proposed. Despite the treatment of time in CIGs has received some attention (see, e.g., [4], [5]), to the best of our knowledge, until now no CIG approach in the literature has taken into consideration the ***temporal dimension in the study of interactions***. This is a crucial limitation. Indeed, a non-temporal analysis can only detect *theoretically possible* interactions between actions in different CIGs, identifying, e.g., a potential conflict between their effects. However, as long as no temporal analysis is performed, such an interaction is only "*potential*": *actual* interactions occur *in time*, i.e., just in case that the considered effects *overlap in time*. The approach in this paper is, to the best of our knowledge, the first one starting to face such a challenging problem. To do so, an extended ***representation formalism*** has to be identified, to model time and temporal interactions, as well as advanced ***temporal reasoning*** techniques, to discover whether the effects of potentially conflicting actions overlap in time. In this paper, we propose an advanced Artificial Intelligence approach facing such issues, developed on top of the GLARE system [6], [7]. Notice, however, that the methodology we propose is largely system-independent.

The paper is organized as follows. Section 2 briefly introduces GLARE and previous work to cope with comorbidities in GLARE. Section 3 describes the extensions to the representation needed to deal with time. Section 4 discusses our solution to the detection of temporal interactions. Finally, Section 5 proposes related works and comparisons.

2. PRELIMINARIES: GLARE
GLARE (Guideline Acquisition, Representation and Execution) [6], [7] has been built starting from 1997 in a long-term

cooperation between the Department of Computer Science of the University of Piemonte Orientale, Alessandria, Italy and the Azienda Ospedaliera San Giovanni Battista in Turin (one of the largest hospitals in Italy). GLARE supports the use of advanced artificial intelligence techniques and decision-support techniques in the treatment of CIGs [7] (a comparison of GLARE with other approaches coping with CIGs can be found in [3]). In GLARE, a CIG can be represented as a hierarchical graph, where nodes are the actions to be executed and arcs are the control relations linking them. GLARE distinguishes between *atomic* and *composite* actions (plans), where atomic actions represent simple steps in a CIG and plans represent actions that can be defined in terms of their components via the *has-part* relation. GLARE adopts different types of atomic actions. In this paper, we just focus on *work* and *pharmacological* actions.

Actions in a CIG are connected through *control* relations, establishing which actions can be executed next and in what order. In particular, the *sequence* relation explicitly establishes what the following action to be executed is; the *alternative* relation describes which alternative paths stem from a decision action and the *repetition* relation states that an action has to be repeated several times. The *constrained* relation is used in order to express more complex temporal constraints between actions (see Section 3).

2.1 Coping with comorbidities in GLARE: previous work

Starting from 2013, GLARE has started to be extended to cope with comorbidities. The long-term goal of such a work is that of providing physicians with a domain-independent and guideline-independent set of tools and methodologies:

1. to detect and analyze the interactions between CIGs,
2. to solve the detected interactions,
3. to merge multiple CIGs in the treatment of a specific comorbid patient at hand.

In this paper, we focus on issue (1) only. In [8], we identified three different knowledge levels at which interactions might occur: (i) level of the goals of the CIG actions, (ii) level of the effects of the actions, and (iii) level of the drugs recommended by pharmacological actions. [8] also proposes a knowledge base (henceforth called ***ontological model***) representing the interactions at the different levels and provided support for interactive physician-driven analysis of the interactions at the different levels (without considering time). Interactions can be (i) automatically detected by a reasoning tool or (ii) manually inserted in the knowledge base. However, querying the knowledge base and simply giving as output all the interactions between all the actions belonging to the two CIGs is not useful for physicians during the analysis. The output would contain too many elements, most of which would be irrelevant. For such a reason, in [9] we proposed a tool to support physicians to navigate CIGs at different levels of abstraction, allowing them to focus on relevant parts of the CIGs and to compare only those actions considered important and potentially interacting.

Example 1 (Description and non-temporal analysis). The running example is a situation in which a patient treated for deep venous thrombosis develops a respiratory tract infection. We also assume that the patient is currently treated with Warfarin (an anticoagulant drug) for the thrombosis. The CIG for the respiratory tract infection suggests, among the others, the treatment with Erythromycin (an antibiotic). The drug interaction between Erythromycin and Warfarin is well known in medical literature (see, e.g., [10]) and, in our model, it is represented by an interaction between the anticoagulant effect of Warfarin and the metabolism reduction caused by Erythromycin. Their concomitant use increases the anticoagulant effect of Warfarin, raising the risk of bleedings.

Using the non-temporal detection of interactions facilities of GLARE, the physician navigates the two CIGs. Then, s/he focuses on the Warfarin treatment (for the first CIG) and on the Erythromycin treatment (for the second CIG). At such a level of detail, the (simplified) CIG for thrombosis contains three Warfarin administrations (W1, W2 and W3), as well as a calculation of the International Normalized Ratio (INR) and its evaluation (INR evaluation). See the upper part of Figure 1. In the lower part of Figure 1 we show the actions of Erythromycin administration (E1 and E2) in the respiratory infection CIG.

In the example, we suppose that the first two Warfarin administrations have been already executed. On the other hand, the Erythromycin treatment contains two Erythromycin administrations, none of which has been executed yet. The physician may now want to know whether the last executed Warfarin administration (W2) can interact with the first Erythromycin administration that has to be executed next (E1). GLARE detects such interaction from the non-temporal point of view. However, a temporal analysis is required to ascertain whether the interaction can occur in time. ■

3. REPRESENTATION OF TEMPORAL INFORMATION

In this section we describe the temporal formalism we adopt for CIGs, the temporal phenomena involved by comorbidities and the extension of the temporal formalism to deal with such phenomena. Our temporal representation satisfies two main requirements:

i. it is expressive enough to represent the temporal phenomena we focus on and
ii. its temporal constraints can be translated into STP [11].

3.1 Representing Temporal Constraints

We admit two basic *temporal entities: Time Intervals* and *Time Points*. We consider both *qualitative* and *quantitative* temporal constraints between temporal entities. Qualitative constraints represent the relative position of two temporal entities. We use a fragment of Vilain's algebra in [12] to represent qualitative

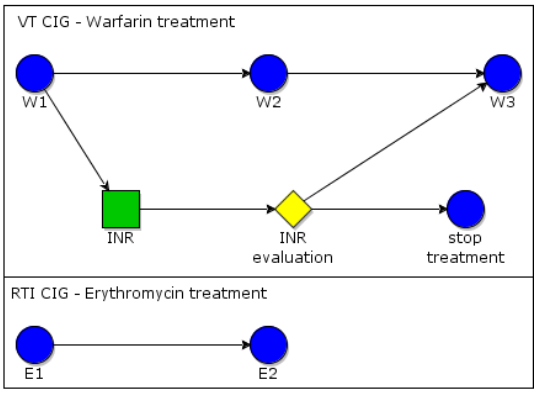

Figure 1. Focused part of the venous thrombosis (upper part of the figure) and respiratory tract infection (lower part) CIGs, in the analysis of interactions.

relations between time points and time intervals. Vilain distinguishes between point-point constraints (●Before●, ●After●, ●Equals●), point-interval constraints (●Before, ●Begins, ●During, ●Ends, …) and interval-interval constraints (Before, After, Ends …) (the latter are usually known as Allen's basic temporal relations [13]). Vilain considers also arbitrary disjunctions of such constraints. In our approach, we restrict our attention to the subset of Vilain's constraints that can be expressed in STP, i.e., on the *continuous pointizable* constraints [14]. On the other hand, quantitative constraints consider *metric* time. In our approach, they are characterized by a *minimum* and a *maximum* value bounding the span of time between two time points and a *time unit* for the bounds. It is worth stressing that such a representation supports ***temporal indeterminacy***, since the maximum and minimum values can be different. We identify three basic types of quantitative constraints: *Date*, *Delay* and *Duration*. Dates model "absolute" metric time. Indeed, a date can be represented by a constraint between a time point and a *reference time*, which is a fixed point on the timeline unique for all the dates. Durations characterize a time interval representing the distance between its ending and starting points. Delays represent the distance between two general time points.

3.2 Temporal Extension of the Knowledge Sources

To analyse CIG interactions, we have to consider different *sources* of temporal information: the two interacting CIGs, the log of the CIG actions already executed on the patient, and the knowledge base (ontological model) describing actions, and their interactions.

CIG temporal knowledge. GLARE allows to annotate the arcs between actions (in particular, the *sequenced* and the *constrained* arcs) with temporal constrains expressed using the formalism in Section 3.1.

For example, the temporal constraints concerning the part of the venous thrombosis CIG in Figure 1 are shown in the upper part of Figure 2. Warfarin is usually administered once a day. Thus, the CIG for thrombosis contains temporal constraints between consecutive warfarin administrations (W1, W2 and W3) binding the delay between them to be greater than or equal to one day and to be less than two days (constraints between non-consecutive administrations can be inferred later by our STP reasoner). In the example, we work at the granularity of days. Notice that both quantitative and qualitative constraints are represented.

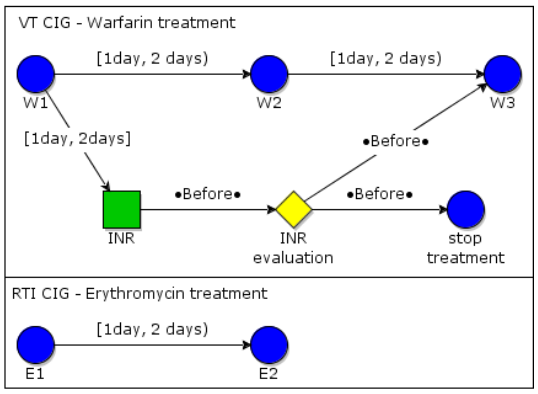

Figure 2. Part of the venous thrombosis CIG and of the respiratory tract infection CIG annotated with temporal constraints.

Log knowledge. In many medical contexts, it is not realistic to assume to know the exact execution time of each action executed on the patient. We thus support imprecise temporal information in the log, represented through the formalism proposed in Section 3.1. For example, the log temporal constraints for the Warfarin administrations may be:

- Warfarin treatment started on 01/04/2015
- W1 executed on 01/04/2015
- W2 executed ●after● W1

Temporal information in the Knowledge base (ontological model). The ontological knowledge contains temporal information about the interacting elements. In particular, the ontological knowledge models the delay between action execution and the manifestation of their effects, and the durations of such effects (expressed through the formalism in Section 3.1).

4. TEMPORAL REASONING

To detect temporal interactions between actions, temporal reasoning on the above pieces of temporal information must be provided.

We defined two main modules to manage the temporal extension of our system (see Figure 3). The first one, the "Visualization" module, provides a high-level interface to communicate with users, hiding the details of the underlying second module, i.e., the "Temporal Reasoner" module. The Temporal Reasoner module is subdivided into five sub-modules. "Extraction" and "Translation" modules collect the temporal constraints from the log, the CIGs and the ontological model and translate them into STP. The remaining three modules are organized in a "multi-layered structure". The innermost module is the standard STP constraint propagation framework developed by Dechter et al. [11]. In STP, temporal constraints are represented as ***bounds on differences*** of the form $c \leq P1\text{-}P2 \leq d$, where *P1* and *P2* are time points, and *c* and *d* represent the minimum and maximum distance between them. Correct and complete temporal reasoning in STP can be performed through an application of *Floyd-Warshall's all-pairs shortest-paths algorithm*, which operates in cubic time, and provides as output a ***minimal network***, i.e., the strictest possible

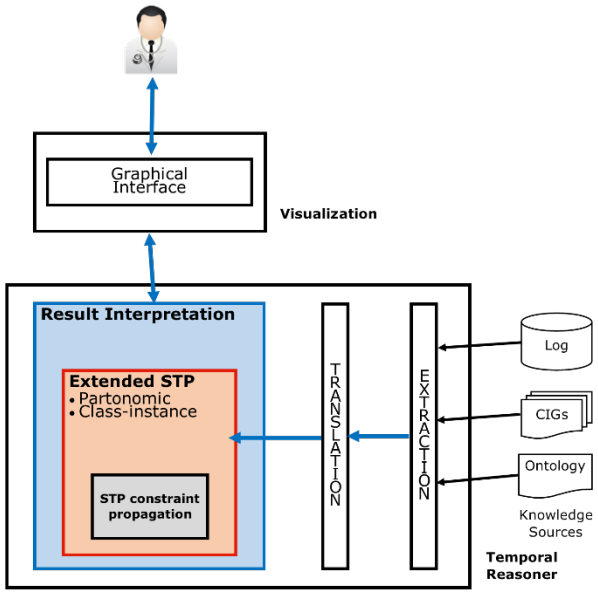

Figure 3. Architecture of our temporal approach.

distances between each pair of time points, or an *inconsistency* [11]. However, such a standard approach must be extended to cope with the phenomena related to interaction detection. We do so in the "Extended reasoning" module, which extends STP to provide more complex reasoning tasks. Then, the outer layer ("Result Interpretation") module interprets results of temporal reasoning. It is worth noting that the overhead of our extensions is negligible since their complexity is dominated by the complexity of STP constraint propagation.

Example 1 (Query). We assume that the physician is interested in the interaction between the Warfarin and the Erythromycin treatments. Specifically, s/he may want to know whether the last executed Warfarin administration W2 can interact with the first (not performed yet) administration of Erythromycin E1.

4.1 Constraint extraction and translation

The temporal constraints from the CIGs, the log and the knowledge base are collected, and then translated into STP (the translation is easy –operating in linear time and space– and it is omitted for the sake of brevity). To collect the temporal constraints, we have devised an algorithm that, starting from the temporal entities involved in an interaction, navigates backward and across the knowledge sources, retrieving all (and only) the temporal constraints that can influence them.

First, we extract from the knowledge base the temporal constraints between the actions (involved in the interactions) and their effects. Then, we extract from the log the temporal constraints concerning the CIG actions that have been already executed on the patient.

Finally, from the CIGs we extract the temporal constraints imposed by *control* arcs between the interacting actions and the other actions belonging to the same CIG, and corresponding to the executed actions in the log. Once extracted the relevant temporal information, we translate it into STP. It is worth noticing that all the constraints expressed through our formalism (see Section 3.1) can be automatically mapped to STP.

Notation. Henceforth, given an action Act, if Act is punctual, Act_P represents the time point in which Act is executed. If Act is durative, Act_S represents its starting point and Act_E its ending point. ■

Example 1 (Extraction and Translation). Considering a granularity of days and reference time RT = 01/04/2015 (corresponding to the time of execution of the first Warfarin administration), the STP constraints derived from the Warfarin administrations (CIG for venous thrombosis) of Example 1 are[1]

(C1) $0 \leq \mathrm{AN2_S} - \mathrm{W2_P} \leq 1$
(C2) $1 \leq \mathrm{AN2_E} - \mathrm{AN2_S} \leq 4$
(C3) $0 \leq \mathrm{W1_P} - \mathrm{RT} \leq 0$
(C4) $0 < \mathrm{W2_P} - \mathrm{W1_P} \leq +\infty$
(C5) $1 \leq \mathrm{W2_P} - \mathrm{W1_P} < 2$

Constraints C1 and C2 are extracted from the ontological knowledge while constraints C3, C4 and C5 are extracted from CIG and log. Similarly, constraints regarding the CIG for respiratory tract infection are collected and translated, obtaining the following:

(C6) $0 \leq \mathrm{RM1_S} - \mathrm{E1_P} \leq 1$

(C7) $2 \leq \mathrm{RM1_E} - \mathrm{RM1_S} \leq 6$

4.2 Extended STP Reasoning

Unfortunately, the "standard" STP approach is not sufficient to cope with our temporal interaction problem. Thus, we provide a module of our temporal reasoner which extends STP to cope with partonomic temporal reasoning and with class/instance reasoning.

Partonomic temporal reasoning

Partonomic relations in the CIGs (i.e., the fact that composite actions can be defined in terms of their components) induce temporal constraints that have to be represented in the STPs. Indeed, this phenomenon can be easily managed on top of STP. In particular, when an action B is part of an action A, we have the STP constraints $0 \leq B_S - A_S \leq +\infty$ and $-\infty \leq B_E - A_E \leq 0$. For instance, in Example 1, the action E1 is part of the high-level action Erythromycin treatment. Then, our system extracts also the partonomic constraints $0 \leq \mathrm{E1_P} - \mathrm{ET_S} \leq +\infty$ and $-\infty \leq \mathrm{E1_P} - \mathrm{ET_E} \leq 0$ (where $\mathrm{ET_S}$ and $\mathrm{ET_E}$ are the starting and ending points representing the action Erythromycin treatment and $\mathrm{E1_P}$ is the time point representing the punctual action E1).

Class-instance reasoning

The temporal constraints in the CIGs can be considered constraints on *classes* of actions, which are instantiated each time a CIG is executed on a specific patient. Thus, the problem of checking whether a specific execution (instance) of a CIG satisfies the temporal constraints of a CIG corresponds to checking whether the temporal constraints of the instances satisfy the temporal constraints of the classes. This problem has been dealt with in [4]. In that work, the authors have considered the problem of "inheriting" the temporal constraints from classes of events to instances of events. They have also singled out two issues that, in general, make the inheritance a difficult problem: *correlation* and *observability*. Given a temporal constraint between two classes of actions, correlation concerns the issue of identifying the corresponding pair of instances of such actions that have to inherit the temporal constraint. Observability concerns the issue of knowing whether and/or to what extent one can assume that the executed actions are indeed observed (and recorded). As stated in [4], in the CIG domain, which is also the context we consider in this paper, it is possible to assume that correlation is exactly known and that there is full observability of the instances. Therefore, it is possible to cope with the class-instance temporal reasoning by merging in a single STP both the constraints between classes and the constraints between instances, and then performing STP temporal reasoning. For each pair of time points, STP can take into account just one minimum and one maximum distance; in case both the CIG and the LOG provide such pieces of information, they have to be "merged" by considering the maximum of the minimum distances, and the minimum of the maximum distances. For instance, given two time points A and B, and two constraints $c_1 \leq B - A \leq d_1$ and $c_2 \leq B - A \leq d_2$, the "merge" (to be inserted in the STP) is $\max(c_1, c_2) \leq B - A \leq \min(d_1, d_2)$. In our example, constraints C4 and C5 are both referred to the difference $W2_p - W1_p$. Then, the resulting constraint is $1 \leq \mathrm{W2_P} - \mathrm{W1_P} < 2$.

4.3 Result Interpretation

We need to check whether the times of the effects of two possibly interacting actions in two CIGs intersect in time. Considering two effects A and B, the answer YES must be provided just in case A and B necessarily intersect in time. Such a test can be directly performed through an inspection in the *minimal network* produced

[1] Legend for the time points: $\mathrm{Wn_P}$ time of execution of the n^{th} warfarin administration; $\mathrm{ANn_S}$ and $\mathrm{ANn_E}$ endpoints of the anticoagulant effect of the n^{th} warfarin administration; RT reference time; $\mathrm{En_P}$ time of execution of the n^{th} erythromycin administration; $\mathrm{RMn_S}$ and $\mathrm{RMn_E}$ endpoints of the reducing metabolism effect of the n^{th} erythromycin administration.

by the application of an *all-pairs shortest paths algorithm* to the temporal constraints. Specifically, to ascertain the intersection we have to check whether the following condition is necessarily true:

$(A_S - B_S \leq 0 \ \wedge \ B_S - A_E \leq 0) \ \vee \ (B_S - A_S \leq 0 \wedge \ A_S - B_E \leq 0)$
(Condition 1)

where A_S (B_S) and A_E (B_E) indicate respectively the starting and ending points of A (B). On the other hand, the non-intersection is ascertained by checking the necessity of the following condition:

$(A_E - B_S < 0) \vee (B_E - A_S < 0)$
(Condition 2)

Notice that, since Condition (1) is the negation of Condition (2), we can easily verify the necessity of one of the two conditions by verifying the non-possibility of the other one and vice versa.

Example 1 (Solution Existence Verification). The minimal network resulting our example is shown in Table 1.

To ensure the interaction, the intervals $[AN2_S, AN2_E]$ and $[RM1_S, RM1_E]$ must overlap, thus the Condition (1) must hold, i.e.:

$$(AN2_S - RM1_S \leq \ 0 \wedge RM1_S - AN2_E \leq \ 0) \vee (RM1_S - AN2_S \leq \ 0 \wedge AN2_S - RM1_E \leq \ 0)$$

To ensure the non-interaction, the Condition (2) must hold, i.e.:

$(AN2_E - RM1_S < 0) \vee (RM1_E - AN2_S < 0)$

Given the minimal network, both the conditions are possible, but not necessary. Then, the answer of the system is `MAYBE`.

	RT	$W1_P$	$W2_P$	WT_S	WT_E	$AN2_S$	$AN2_E$	DEC_P	ET_S	$E1_P$	ET_E	$RM1_S$	$RM1_E$
RT	0	0	1	0	∞	2	6	0	1	2	∞	3	9
$W1_P$	0	0	1	0	∞	2	6	0	1	2	∞	3	9
$W2_P$	-1	-1	0	-1	∞	1	5	-1	0	1	∞	2	8
WT_S	0	0	1	0	∞	2	6	0	1	2	∞	3	9
WT_E	-1	-1	0	-1	0	1	5	-1	0	1	∞	2	8
$AN2_S$	-1	-1	0	-1	∞	0	4	-1	0	1	∞	2	8
$AN2_E$	-2	-2	-1	-2	∞	-1	0	-2	-1	0	∞	1	7
DEC_P	0	0	1	0	∞	2	6	0	1	2	∞	3	9
ET_S	0	0	1	0	∞	2	6	0	0	1	∞	2	8
$E1_P$	0	0	1	0	∞	2	6	0	0	0	∞	1	7
ET_E	0	0	1	0	∞	2	6	0	0	0	0	1	7
$RM1_S$	0	0	1	0	∞	2	6	0	0	0	∞	0	6
$RM1_E$	-2	-2	-1	-2	∞	0	4	-2	-2	-2	∞	-2	0

Table 1. Minimal network of the temporal constraints (after temporal reasoning)

4.4 Visualization of the Results

Our goal is to show to the physician how the interacting variations overlap (or do not overlap) in time. Thus, the system represents in two aligned timelines the intervals of existence of the interacting effects. In each timeline, two rectangles represent the intervals of existence of the endpoints of the respective variation: the upper rectangle represents the time interval in which the effect can start, while the lower one represents the time interval in which the effect can end. On the other hand, the time interval (if any) included between the ending point of the upper rectangle and the starting point of the lower one (represented with a colored line) represents the time when the effect certainly holds.

Example 1 (Visualization). In Figure 4, we show the graphical representation returned by the "Visualization" module to support

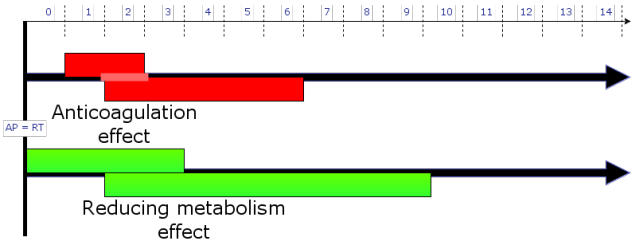

Figure 4. Graphical representation of the result of the analysis of interaction between the "*Anticoagulant*" effect of the warfarin administration and the "*Reducing metabolism*" effect of erythromycin.

the "MAYBE" answer (meaning that the interaction may occur in time, but it can also be avoided) to the query expressed by the physician. The upper timeline (red rectangles) represents the interval of existence of the Anticoagulation effect caused by the Warfarin administration W2, while the lower timeline (green rectangles) represents the effect Reducing metabolism of the Erythromycin administration E1. The intervals are drawn considering the reference time RT as aligning point (AP = RT). It is possible to observe that the Anticoagulation effect certainly holds in day '2'. On the other hand, the Reducing metabolism effect has no certain parts[2]. Thus, since there is no overlap between the certain parts, the interaction can be avoided (e.g., by discontinuing the Warfarin treatment and starting the Erythromycin in a time in which its effect starts on day '3'). On the other hand, it is easy to see that for some configurations the two effects can overlap and the interaction may occur. Notice how such a graphical representation can significantly help physicians in the study of the interactions and in the choice of the correct times in which executing CIG actions to avoid/obtain interactions.

5. RELATED WORK AND CONCLUSIONS

The treatment of comorbid patients is one of the main challenges for the modern healthcare, and several approaches are recently emerging to cope with the integration of CIGs to manage comorbid patients. Among them, the approach in [15] is the most similar to ours. It provides a conceptual model for medical actions and detects interactions using such a model and rules. However, it does not consider time. Other approaches, for instance [16] and [17], use constraint logic programming to identify and address adverse interactions between actions. In this solution, a constraint logic programming (CLP) model is derived from the combination of logical models that represent the CIGs, then a mitigation algorithm is applied to detect and mitigate interactions. On the other hand, Sánchez-Garzón et al. [18] propose an agent-based approach to guideline merging. Each guideline, considered as a physician expert in the treatment of a single disease, is represented by an agent with hierarchical planning capabilities. The result is obtained through the coordination of all the agents and respects the recommendations of each guideline. Riaño et al. represent guidelines as sets of clinical actions that are modelled into an ontology [19]. To combine two treatments, first they are unified in a unique treatment and then a set of "combination

[2] Notice that the absence of certain part in the Reducing metabolism effect is given by the uncertainty in the execution of E1. Indeed, constraining, for instance, E1 to be executed on day '1' would produce a different minimal network in which the effect certainly occurs on days '2' and '3'. In such a case, the answer of the system would be "YES" and the overlap of the certain parts would be evident from the graphical representation.

rules" is applied to detect and avoid possible interactions. A model-based automatic merge of CIGs is then proposed in [20] through the definition of a combining operator.

In general, all the approaches coping with comorbidities in literature do not consider time, or consider it in a very marginal way. However, temporal issues are pervasive in the CIG context, and many previous approaches have faced some of them (see, e.g., the survey in [5]). The approach in this paper is the *first* one that deeply takes into account the *temporal* dimension in the treatment of comorbid patients. This is, in our opinion, a crucial advance with respect to the state of the art: a non-temporal analysis can only consider *theoretically possible* interactions between actions (e.g., conflicts between their goals or effects) in different CIGs, while *actual* interactions occur *in time*, i.e., just in case that the considered goals or effects *overlap in time*. In this sense, we believe that our approach is somehow *complementary* with respect to the other approaches, so that an integration with some of them can be devised as a future work. Moreover, to devise an approach useful in practice, we aim at improving our methodology by extending it to manage inconsistencies between log and CIG constraints (e.g., through conformance analysis techniques). In addition, to return suitable results to physicians, also the possibility of recognize relevant interactions (exploiting, e.g., knowledge regarding the probability or the seriousness of interactions) would be useful. Finally, we plan to perform an extensive evaluation on real world cases and involving real users to validate our work.

6. REFERENCES

[1] Institute of Medicine, Committee on Quality Health Care in America, "Crossing the Quality Chasm: A New Health System for the 21st Century." Washington, USA: National Academy Press, Mar-2001.

[2] A. Ten Teije, S. Miksch, and P. Lucas, Eds., *Computer-based medical guidelines and protocols: a primer and current trends*, vol. 139. Amsterdam: IOS Press, 2008.

[3] M. Peleg, "Computer-interpretable clinical guidelines: A methodological review," *Journal of Biomedical Informatics*, vol. 46, no. 4, pp. 744–763, Aug. 2013.

[4] L. Anselma, P. Terenziani, S. Montani, and A. Bottrighi, "Towards a comprehensive treatment of repetitions, periodicity and temporal constraints in clinical guidelines," *Artificial Intelligence in Medicine*, vol. 38, no. 2, pp. 171–195, Oct. 2006.

[5] P. Terenziani, E. German, and Y. Shahar, "The temporal aspects of clinical guidelines," *Stud Health Technol Inform*, vol. 139, pp. 81–100, 2008.

[6] P. Terenziani, G. Molino, and M. Torchio, "A modular approach for representing and executing clinical guidelines," *Artificial Intelligence in Medicine*, vol. 23, no. 3, pp. 249–276, 2001.

[7] P. Terenziani, S. Montani, A. Bottrighi, G. Molino, and M. Torchio, "Applying artificial intelligence to clinical guidelines: the GLARE approach," *Stud Health Technol Inform*, vol. 139, pp. 273–282, 2008.

[8] L. Piovesan, G. Molino, and P. Terenziani, "An ontological knowledge and multiple abstraction level decision support system in healthcare," *Decision Analytics*, vol. 1, no. 8, pp. 1–24, 2014.

[9] L. Piovesan, G. Molino, and P. Terenziani, "Supporting Multi-Level User-Driven Detection of Guideline Interactions," in *Proceedings of the International Conference on Health Informatics (HEALTHINF-2015)*, 2015, pp. 413–422.

[10] R. I. Sato, D. R. Gray, and S. E. Brown, "Warfarin interaction with erythromycin," *Arch. Intern. Med.*, vol. 144, no. 12, pp. 2413–2414, Dec. 1984.

[11] R. Dechter, I. Meiri, and J. Pearl, "Temporal Constraint Networks," *Artif. Intell.*, vol. 49, no. 1–3, pp. 61–95, May 1991.

[12] M. Vilain, "A System for Reasoning About Time," in *Proc. of the National Conference on Artificial Intelligence. Pittsburgh, PA,* 1982, pp. 197–201.

[13] J. F. Allen, "Maintaining knowledge about temporal intervals," *Communications of the ACM*, vol. 26, no. 11, pp. 832–843, Nov. 1983.

[14] M. Vilain, H. Kautz, and P. van Beek, "Constraint propagation algorithms for temporal reasoning: a revised report," in *Readings in Qualitative Reasoning About Physical Systems*, D. S. Weld and J. de Kleer, Eds. San Francisco, CA, USA: Morgan Kaufmann Publishers Inc., 1990, pp. 373–381.

[15] V. Zamborlini, R. Hoekstra, M. da Silveira, C. Pruski, A. ten Teije, and F. van Harmelen, "A Conceptual Model for Detecting Interactions among Medical Recommendations in Clinical Guidelines," in *Knowledge Engineering and Knowledge Management*, vol. 8876, K. Janowicz, S. Schlobach, P. Lambrix, and E. Hyvönen, Eds. Cham: Springer International Publishing, 2014, pp. 591–606.

[16] M. Michalowski, S. Wilk, W. Michalowski, D. Lin, K. Farion, and S. Mohapatra, "Using Constraint Logic Programming to Implement Iterative Actions and Numerical Measures during Mitigation of Concurrently Applied Clinical Practice Guidelines," in *Proc. of AIME*, Springer Berlin Heidelberg, 2013, pp. 17–22.

[17] S. Wilk, W. Michalowski, M. Michalowski, K. Farion, M. M. Hing, and S. Mohapatra, "Mitigation of adverse interactions in pairs of clinical practice guidelines using constraint logic programming," *J Biomed Inform*, vol. 46, no. 2, pp. 341–353, Apr. 2013.

[18] I. Sánchez-Garzón, J. Fdez-Olivares, E. Onaindía, G. Milla, J. Jordán, and P. Castejón, "A Multi-agent Planning Approach for the Generation of Personalized Treatment Plans of Comorbid Patients," in *Artificial Intelligence in Medicine*, vol. 7885, N. Peek, R. Marín Morales, and M. Peleg, Eds. Berlin, Heidelberg: Springer, 2013, pp. 23–27.

[19] J. A. López-Vallverdú, D. Riaño, and A. Collado, "Rule-Based Combination of Comorbid Treatments for Chronic Diseases Applied to Hypertension, Diabetes Mellitus and Heart Failure," in *Process Support and Knowledge Representation in Health Care*, vol. 7738, R. Lenz, S. Miksch, M. Peleg, M. Reichert, D. Riaño, and A. ten Teije, Eds. Berlin, Heidelberg: Springer, 2013, pp. 30–41.

[20] D. Riaño and A. Collado, "Model-Based Combination of Treatments for the Management of Chronic Comorbid Patients," in *Artificial Intelligence in Medicine*, vol. 7885, N. Peek, R. Marín Morales, and M. Peleg, Eds. Berlin, Heidelberg: Springer, 2013, pp. 11–16.