Considering Temporal Preferences and Probabilities in Guideline Interaction Analysis

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Abstract. The treatment of patients affected by multiple diseases (comorbid patients) is one of the main challenges of the modern healthcare, involving the analysis of the interactions of the guidelines for the specific diseases. Practically speaking, such interactions occur in time. The GLARE project explicitly provides temporal representation and temporal reasoning methodologies to cope with such a fundamental issue. In this paper, we propose a further improvement, to take into account that, often, (i) the actions in the guidelines can be executed by physicians at different times with different *preferences*, and that (ii) the effects of such actions have a *probabilistic* distribution in time. In our approach, physicians may investigate what are the preferences of their choices on the execution-time of guideline actions, and the probabilities that their effects temporally intersect (interactions may occur only in case effects intersect in time).

Keywords: Comorbidities · CIG interactions · Temporal reasoning · Probabilities · Preferences

1 Introduction

Clinical practice guidelines are the major tool that has been introduced to grant both the quality and the standardization of healthcare services, on the basis of evidence-based recommendations. The adoption of computerized approaches to acquire, represent, execute and reason with Computer–Interpretable Guidelines (CIGs) provides crucial additional advantages so that, in the last twenty years, many different approaches and projects have been developed to manage CIGs (consider, e.g., the book [1] and the survey [2]). One of such approaches is GLARE (Guideline Acquisition, Representation and Execution) [3]. By definition, clinical guidelines address specific pathologies. However, comorbid patients are affected by more than one pathology. The problem is that, in comorbid patients, the treatments of single pathologies may interact with each other, and the approach of proposing an ad-hoc “combined” treatment to cope with each possible comorbidity does not scale up.

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In the last years, many approaches in the Medical Informatics literature have faced different aspects of the treatment of comorbid patients (see the survey in [4]). Some of them have focused on the *knowledge-based automatic detection* of possible interactions between CIGs [5, 6], considering (i) the actions in the CIGs and (ii) their effects. In particular, in GLARE-SSCPM [7], specific attention has been devoted to temporal data [8–10] and to the temporal analysis of interactions [11], taking into account complex forms of temporal reasoning and query answering about temporal constraints between events. However, the approach in [11] only considers "crisp" temporal constraints, while a more flexible analysis may be needed, considering the fact that:

(1) CIG may contain guideline preferences among the execution-time of CIG actions [12] and
(2) the effects of CIG actions may have a probabilistic distribution in time (derivable, e.g., from pharmacokinetic and a pharmacodynamic studies).

Consider, e.g., Example 1, about the interaction between calcium carbonate administration (CCA) and nalidixic acid administration (NAA), concerning gastric absorption.

Example 1. A patient is affected by gastroesophageal reflux (GR) and by urinary tract infection (UTI). The CIG for GR may recommend CCA, to be administered as soon as possible, and within three hours. Considering as granularity units of 15 min, and assuming preferences in a scale from 0 (minimum preference) to 1 (maximum preference) the administration can be in the first two units (first 30 min) with preference 1, in units 3 and 4 with preference 0.75, in units 5, 6, 7 and 8 with preference 0.5, units 9, 10, 11 and 12 with preference 0.25. CCA has the effect of decreasing gastric absorption (DGA). DGA can start after 1 unit with probability 0.4, after 2 with probability 0.4, and after 3, with probability 0.2. Additionally, the duration of DGA may be 4 units (probability 0.1), 5 (0.3), 6 (0.4), 7 (0.1), or 8 (0.1). The CIG for UTI may recommend NAA, to be administered within two hours, with decreasing preferences (preference 1 for the units 1 and 2, 0.75 for units 3 and 4, 0.5 for 5 and 6, and 0.25 for 7 and 8). NAA has as effect nalidixic acid gastric absorption (NAGA), starting after 1 unit (probability 0.4) or 2 (probability (0.6). The duration of NAGA may be 1 (probability 0.05), 2 (0.05), 3 (0.15), 4 (0.15), 5 (0.25), 6 (0.25), 7 (0.05), 8 (0.05). ■

In order to support physicians in the study of the interaction between CCA and NAA, one must take into account not only the temporal constraints, but also their preferences and probabilities. This is essential to answer physician's queries such as:

(Q1) *If I perform on the patient CCA in unit 1 or 2 (i.e., in the following 30* min*), and NAA in units 1 or 2, what is the guideline preference of my choices and what is the probability that the effects of such two actions intersect in time (i.e., what is the probability of the interaction between CCA and NAA)?*

The approach in [11] does not consider preferences nor probabilities on temporal constraints. Such an approach has been extended in [13] to consider *probabilities*. However, no work in the literature has proposed a comprehensive approach coping with both preferences and probabilities.

2 Managing Temporal Constraints with Preferences and Probabilities

Temporal Formalism. The first step of our approach is the definition of an extended temporal formalism, in which temporal constraints are paired with preferences and/or probabilities. We base our approach on STP (Simple Temporal Problem [14]). In STP, temporal constraints have the form $\boldsymbol{P_i[l, u]P_j}$, where P_i and P_j denote time points, and l and u (l <= u) are integer numbers, stating that the *temporal distance between* P_i *and* P_j *ranges between l and u*. Notably, in STP, pairs of time points may represent time intervals, to cope with durative facts/actions.

As discussed in the introduction, certain constraints are "purely" preferential, and others are "purely" probabilistic. Additionally, while performing the propagation of temporal constraints, "mixed" probabilistic+preferential constraints, which model probabilities and preferences along paths of events, can arise. To simplify the technical treatment, we choose to represent all types of constraints (preferential, probabilistic, and "mixed") in an homogeneous way. Thus, in our approach, each constraint has both a preference and a probability, and we use the special symbols "%" and "#" to denote undefined probability and preference, respectively.

Definition. Probabilistic+Preferential Quantitative Temporal Constraint (P+PQTC). Let

- let $t_i, t_j \in \mathbb{R}$ be time points
- let $p_1, \ldots, p_n \in \mathbb{R}$ be probabilities; $0 < p_1 \leq 1, \ldots, 0 < p_n \leq 1$ or $p_1 = \ldots = p_n = \%$
- let $P_1, \ldots, P_n \in \mathbb{R}$ be preferences; $0 \leq P_1 \leq 1, \ldots, 0 \leq P_n \leq 1$ or $P_1 = \ldots = P_n = \#$
- let $d_1, \ldots, d_n \in \mathbb{Z}$ be distances (between points)

A **Probabilistic+Preferential Quantitative Temporal Constraint (P+PQTC)** is a constraint of the form $t_i < (d_1, p_1, P_1), \ldots, (d_n, p_n, P_n) > t_j$ where $t_i, t_j \in R$ are time points and where either $p_1 = \ldots = p_n = \%$ or $p_1, \ldots, p_n \in [0, 1]$ and conforms a probability distribution. ■

The intended *meaning* of a constraint $t_i < (d_1, p_1, P_1), \ldots, (d_n, p_n, P_n) > t_j$ is that the *distance* $t_j - t_i$ between t_j and t_i can be d_1 with probability p_1 and preference P_1, or … or d_n with probability p_n and preference P_n (where preferences or probabilities may also be undefined, when they are denoted by # or %).

Example 2. The constraint between calcium carbonate administration (CCA) and the beginning of decreasing gastric absorption (DGA_S) in Example 1 can be represented by the following **P+PQTC**:

CCA <(1,0.4,#),(2,0.4,#),(3,0.2,#)> DGA_S

and the constraint in Example 1 about the calcium carbonate administration (CCA), relating it to a time point X_0 representing the starting time in the execution of the guideline, can be represented by the following **P+PQTC**:

X_0 <(1,%,1),(2,%,1),(3,%,0.75)(4,%,0.75),(5,%,0.5),(6,%,0.5),(7,%,0.5),(8,%,0.5),(9,%,0.25),(10,%,0.25),(11,%,0.25),(12,%,0.25)> CCA ■

Temporal reasoning. In STP, as well as in most AI approaches, temporal reasoning is based on two operations on temporal constraints: ***intersection*** and ***composition***. Given two constraints C1 and C2 between two temporal entities A and B, temporal intersection (henceforth $\cap$) determines the most constraining relation between A and B (e.g., A[20,40]B $\cap$ A[30,50]B $\rightarrow$ A[30,40]B). On the other hand, given a constraint C1 between A and B and a constraint C2 between B and C, composition (@) gives the resulting constraint between A and C (e.g., A[20,40]B @ B [10,20]C $\rightarrow$ A[30,60]C).

In STP, constraint propagation can be performed applying Floyd-Warshall's *all-pairs shortest path* algorithm, to repeatedly apply intersection and composition of temporal constraints. Floyd-Warshall's algorithm is *correct* and *complete* on STP [14], operates in cubic time, and provides as output the ***minimal network*** of the input constraints, i.e., the tightest equivalent STP, or an inconsistency.

In our approach, we extend such an approach to operate on the **P+PQTC** constraints. We propose a version of the general Floyd-Warshall's algorithm in which the operations of intersection and composition used for STP are extended to operate also on preferences and probabilities (our formal definition of intersection and composition is quite technical and long, and is omitted for the sake of brevity). The application of Floyd-Warshall algorithm (considering our new definition of intersection and composition) provides as output the minimal network of our **P+PQTC** constraints, i.e., the possible distances between each pair of time points, and the preference and probability of each distance.

Query Answering. To facilitate the interaction with physicians, we provide users with facilities to query such a minimal network, to ask for (i) the extraction (from the minimal network) of the temporal constraints between actions (or their endpoints), and their preferences and probabilities; (ii) Boolean queries, concerning whether a set of P +PQTC temporal constraints holds; (iii) Temporal interaction queries, devoted to the check of whether two events (effects of CIG actions) can interact in time, and what is the probability of such an interaction; (iv) Hypothetical queries, in which queries of types (i)–(iii) above are asked while assuming a set of temporal constraints. For example, query Q1 can be expressed in our approach as

IF{X_0<1,2>CAA, X_0<1,2>NAA}THEN Pref&Prob(INTERSECT(DGA, NAGA))?

The answer is <pref: **1**, prob: **0,9486**> (i.e., the choice of the execution time has an high preference, but there is a strong probability of interactions between the effects). Notably, after Q1, physicians might ask a query like Q2 (to check the probability of interaction in case NAA is executed in the first 30 min, and CAA between two and three hours from the current time, and the guideline preference of such a choice of the execution-time of the CIG actions):

(Q2) IF {X_0<9,10,11,12>CAA,X_0<1,2>NAA} THEN Pref&Prob(INTERSECT (DGA,NAGA))?

The answer is <pref: **0,625**, prob: **0,02455**>, suggesting to physicians that, delaying CAA, they can still comply with the CIG constraints (though obtaining a lower preference with respect to the choice in Q1), but sharply decrease the probability of interactions. Notably, considering our running example, using a "standard" temporal reasoner (i.e., not considering probabilities and preferences), physicians could only infer that an interaction may occur, both in case CAA is executed within the first 30 min, and in case it is executed after two or three hours.

3 Conclusions

We propose the first temporal reasoning approach in the AI literature coping with *both preferences and probabilities*. Our approach provides significant advantages to support physicians in interaction detection for comorbid patient. Future work regards the development of user-friendly interfaces, and an experimental evaluation.

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