Artificial Intelligence in Medicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Artificial Intelligence in Medicine

journal homepage: www.elsevier.com/locate/aiim

Analyzing interactions on combining multiple clinical guidelines☆

Veruska Zamborlini[a,b,*], Marcos da Silveira[b], Cedric Pruski[b], Annette ten Teije[a], Edwin Geleijn[c], Marike van der Leeden[c,d], Martijn Stuiver[e,f], Frank van Harmelen[a]

[a] Department of Computer Science, Vrije Universiteit Amsterdam, The Netherlands
[b] Luxembourg Institute of Science and Technology – LIST, Luxembourg
[c] Department Rehabilitation Medicine, VU Univ. Medical Centre, Amsterdam, The Netherlands
[d] Amsterdam Rehabilitation Research Center – Reade, Amsterdam, The Netherlands
[e] Department of Physiotherapy, Netherlands Cancer Institute, Amsterdam, The Netherlands
[f] Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 21 March 2017
Accepted 28 March 2017

Keywords:
Clinical knowledge representation
Combining clinical guidelines
Multimorbidity
Comorbidity
Interactions among guidelines

ABSTRACT

Accounting for patients with multiple health conditions is a complex task that requires analysing potential interactions among recommendations meant to address each condition. Although some approaches have been proposed to address this issue, important features still require more investigation, such as (re)usability and scalability. To this end, this paper presents an approach that relies on reusable rules for detecting interactions among recommendations coming from various guidelines. It extends a previously proposed knowledge representation model (TMR) to enhance the detection of interactions and it provides a systematic analysis of relevant interactions in the context of multimorbidity. The approach is evaluated in a case study on rehabilitation of breast cancer patients, developed in collaboration with experts. The results are considered promising to support the experts in this task.

1. Introduction

Accounting for patients with multiple health conditions is an important and complex task that requires analysing potential interactions among recommendations meant to address each condition. The medical community has signaled the need for methods to support healthcare professionals in dealing with multimorbidity [2]. On the medical front, some methodologies have been proposed to support this analysis [3,4], but it remains a very knowledge intensive manual task that falls short in scalability (combining more than two guidelines) without suitable computational support. On the medical informatics front, existing Computer Interpretable Guideline (CIG) languages (e.g. Asbru, Proforma, etc.) also do not support this issue, since they have been mainly designed for the purpose of executing a CIG (as part of a treatment), and they have limited power to formally express care actions [5]. Therefore, a family of approaches (e.g. [6–10]) has emerged that aims to enhance the reasoning capabilities of computer systems to combine clinical guidelines in order to address the multimorbidity challenge.

In previous work [10], we investigated a number of related works. Firstly, we categorized them according to the moment at which multimorbidity is addressed: (i) before, (ii) during, (iii) after CIG execution, or (iv) during treatment execution. Accordingly, we positioned our work into class (i). For this class, we highlight the following important requirements that are not properly addressed: (1) **rules (re)usability**: defining a small set of **generic** rules that can be applied to detect several recommendation interactions independently of the guideline or disease at hand – such an approach is preferable to having a large quantity of manually modelled rules to cope with each specific guideline; (2) **scalability** *in number of guidelines*: allowing the combination of any number of CIGs, i.e. detecting interactions among any number of recommendations – which is preferable to considering only pairwise interactions; (3) **knowledge reusability**: allowing the reuse of existing clinical knowledge (complementary to the CIG) as well as providing reusable knowledge.

We started addressing the aforementioned features in our previous work [10–12]. Ref. [10] focuses on providing a conceptual model covering core concepts underlying clinical recommendations, in the form of the TMR (Transition-based Medical Recommendation) model, and [11] extends this model in order to

☆ Invited submission as extension of [1].

* Corresponding author at: Department of Computer Science, Vrije Universiteit Amsterdam, The Netherlands.
E-mail address: v.carrettazamborlini@vu.nl (V. Zamborlini).

http://dx.doi.org/10.1016/j.artmed.2017.03.012
0933-3657/

detect Interactions. It provides reusable FOL (First Order Logic) rules to identify interactions among recommendations when guidelines need to be combined to deal with multimorbidity scenarios. In addition, the model and rules are implemented using Semantic Web technologies and reusing available clinical knowledge sources. In [12] we provided improvements to the model together with reusable rules for exploring more external medical sources available as Linked Open Data.

The overall goal of our research on multimorbidity is to investigate how clinical knowledge can be formally represented to detect interactions between recommendations so that the formal representations of clinical guidelines and interaction rules are reusable and scalable in the number of guidelines. To this end we adopt the methodology of splitting the problem into smaller subproblems. This methodology leads to an iterative process so that we can gradually increase the complexity of the knowledge representation and evaluate the solution in small steps. In the iteration step presented in this paper, we address the following research questions: How can we refine the TMR model to be more flexible and to represent more closely the way clinical knowledge is produced and used in practice? How do our TMR refinements affect the detection of interactions? Does the approach stand up in a realistic case study developed with experts?

Therefore, the main contributions of this paper are: (i) an improved version of the TMR model (Section 2.2); (ii) a systematic analysis of the interaction types that can be detected with this model (Section 3.3); (iii) formal rules that enable the automated detection of interactions, including strengths of the interactions (Section 3.4); and (iv) an evaluation in a realistic scenario in collaboration with domain experts from VUmc and the Netherlands Cancer Institute (Section 4).

This paper is structured as follows: Section 2 introduces concepts and relations related to guideline recommendations through a running example, and these concepts and relations are subsequently defined and formalised. Then, in Section 3, the same running example is used to illustrate the interaction types, which are also further defined, analysed and formalised. Section 4 evaluates the application of our approach to a realistic case study developed in collaboration with experts. Section 5 discusses related and future work and presents conclusions.

2. Guideline recommendations

This section first presents an intuitive description of concepts and relations underlying clinical guidelines, then gives their formal definitions and finally explains a graphical schema to help understanding the cases studied in this paper.

2.1. Concepts and relations through a running example

This section discusses some concepts and relations underlying clinical recommendations that play a role in the task of detecting interactions. These concepts and relations will be incorporated into the TMR model in Section 2.2. To illustrate our approach we provide a running example on combining parts of three guidelines, namely Diabetes (DB), Osteoarthritis (OA) and Hypertension (HT). This example is inspired by a case study from the literature [6], but is intended for illustration purposes only. See Section 4 for our work on a realistic case study).

Table 1 describes some of the recommendations from the three guidelines. For instance, consider the recommendation *R4* for Hypertension: 'Administer thiazide' should be performed because it often has a positive contribution to the patients well-being by decreasing the blood pressure (high confidence), although it often has a negative contribution by increasing the blood sugar level (high confidence). In line with our iterative research methodology, some information, such as dosage and time have been simplified or omitted and will be addressed in future work. On the other hand we make explicit, for means of formal reasoning, other information that is often implicit in the guidelines, such as the contribution of an effect to the overall goal. As a result, the text describing the R4 may look more detailed than it would be in a typical guideline.

In the given example (R4) we analyzed the (rephrased) text and we identified the following components: a *positive* **recommendation** (*should*) about the execution of the **care action type**[1] '*administer thiazide*', justified by a **causation belief** on the promotion of the **transition type** '*decreasing the blood pressure*' with a certain **probability** (*often*). It has a *high* **belief strength** (evidence level), which means it is supported by good medical evidence. Achieving this **transition** is considered a *positive* **contribution** to the overall goal of the *patient wellbeing*. Moreover, it is also acknowledged as a *negative* **contribution** (or side-effect) due to the **causation belief** that *it increases the blood sugar level* with a *high evidence level*.

By empirically analysing guidelines, we observed that different guidelines can have similar beliefs contributing to either positive or negative transitions. For instance, '*NSAID/Aspirin reduces the blood coagulation*' is seen as a positive contribution in the Diabetes and Stroke Guidelines, while it is seen as a negative (side-effect) or neutral contribution in the Osteoarthritis and Ulcer Guidelines. We assume that each positive recommendation points to at least one causation with a positive contribution, and similarly that each negative recommendation points to at least one causation with a negative contribution.

Another relevant feature that we observed in the guidelines is the "negative causation", or negated causation assertions. For example, the Dutch Breast Cancer Guideline [13] says: '*Breast reconstruction is recommended for improving the breast aesthetics and it will NOT increase the risk of cancer recurrence*'. The negative causation '*does NOT increase the risk of cancer recurrence*' is considered as an additional contribution to that recommendation. It is mainly stated as complementary information to highlight the safety of certain recommendations with respect to an effect. A similar example is provided in recommendation R8 in Table 1: *'Administer Clopidogrel should be performed because... although it never negatively contributes by increasing the blood pressure'*. Observe that this can be rephrased as *'it does NOT increase the blood pressure'* (see also our further discussion in Section 2.2). Consequently, causation beliefs can be twofold: positive (i.e. it is believed that *Clopidogrel* does cause *decrease of blood coagulation*) or negative (i.e. it is believed that *Clopidogrel* does NOT cause *increase of blood pressurel*).[2]

Finally, care action types can be organised in **hierarchies** according to a 'grouping criterion', i.e. a feature that defines a certain action type as a category for other types. For example, *pharmacotherapy* is an action type (category) that groups (or subsumes) action types in which *pharmacological drugs* are administered, i.e. administration of pharmacological drugs is the grouping criterion. Similarly, '*administer NSAID*' subsumes all action types involving the administration of *non-steroidal drugs* that have an *anti-inflammatory* effect, i.e. a combination of two criteria. As an example, '*administer Aspirin*' and '*administer Ibuprofen*' are both subsumed by the action type '*administer NSAID*'.

[1] The need for distinguishing action and action types is discussed in [10]. However, for sake of simplicity, hereafter we refer to both *care action types* and *transition types* as simply *care action* and *transition/effect*.

[2] Notice that the negative causation is different from prevention. The formal definition of the latter is outside the scope of this work.

Please cite this article in press as: Zamborlini V, et al. Analyzing interactions on combining multiple clinical guidelines. Artif Intell Med (2017), http://dx.doi.org/10.1016/j.artmed.2017.03.012