Analyzing Differences in Operational Disease Definitions Using Ontological Modeling

Linda Peelen[1], Michel C.A. Klein[2], Stefan Schlobach[2], Nicolette F. de Keizer[1], and Niels Peek[1]

[1] Dept. of Medical Informatics, Academic Medical Center, Amsterdam
{l.m.peelen,n.b.peek,n.f.keizer}@amc.uva.nl
[2] Dept. of Artificial Intelligence, Vrije Universiteit Amsterdam
michel.klein@cs.vu.nl, schlobac@few.vu.nl

Abstract. In medicine, there are many diseases which cannot be precisely characterized but are considered as natural kinds. In the communication between health care professionals, this is generally not problematic. In biomedical research, however, crisp definitions are required to unambiguously distinguish patients with and without the disease. In practice, this results in different operational definitions being in use for a single disease. This paper presents an approach to compare different operational definitions of a single disease using ontological modeling. The approach is illustrated with a case-study in the area of severe sepsis.

1 Introduction

In medicine, many diseases cannot be unequivocally defined by etiology or anatomical localization, but are instead described by a combination of signs and symptoms that are common in patients believed to be suffering from that disease.

An example of such a disease is the syndrome of *severe sepsis*. In this disease the immune system of the patient overreacts to an infection. If untreated, the patient becomes severely ill, which may result in organ failure and eventually death. The cause of severe sepsis is largely unknown, and the disease is not restricted to an exact anatomical localization, which hinders the precise characterization of the patient.

In daily patient care and in communication between health care professionals such a lack of precision is often not problematic. However, when the purpose of describing patients is to select patients for medical research or to automatically reason with patient data (e.g., in triggering computerized guidelines) a crisp disease definition is required, which unambiguously distinguishes patients with the disease from persons without the disease. In practice, this often results in ad hoc, operational definitions that largely cover the intended patient group.

It is questionable to which extent patients selected by different definitions can be compared. This is an important issue in, for instance, statistical aggregation of data, meta-analysis of medical scientific evidence, and in the design of clinical studies.

In previous work we have shown that nine recent clinical trials in the area of severe sepsis all used different operational definitions. Applying these definitions onto real clinical data resulted in the selection of patient groups with different outcome characteristics [1].

In this paper we present an approach to systematically compare different operational definitions of a single disease using *ontological modeling*. First we present a general abstraction hierarchy which indicates the levels at which the concepts related to the operational definitions are expressed. Subsequently we propose a method that uses this hierarchy to compare complex definitions at different levels of abstraction.

Throughout the paper we will use two operational definitions of severe sepsis as an example, which are depicted in Table 1. When comparing these definitions, we note that both definitions have *polythetic* aspects: a list of signs and symptoms is given, of which a particular number has to be fulfilled, and some of which are necessary conditions.

Table 1. Definitions for severe sepsis used in the PROWESS[2] and Kybersept[3] trial

PROWESS		
Known or suspected infection or signs of pneumonia	At least three of the modified SIRS criteria: 1)temperature $\geq 38°$C or temperature ≤ 36 °C 2) heart rate ≥ 90/min 3) respiratory rate ≥ 20/min or $PaCO_2 \leq 32$ mmHg or mechanical ventilation 4)leukocyte count $\geq$12,000/mm^3 or leukocyte count $\leq$4,000/mm^3 or >10 % immature neutrophils	At least one out of: 1) pH ≤ 7.3 or base deficit ≥ 5.0 mmol/L with plasma lactate > 1.5 times higher than normal 2) urine output < 0.5 mL/kg/hr 3) thrombocyte count $< 80 \cdot 10^3$ /mm^3 4) $PaO_2/FiO_2 \leq 250$ or ≤ 200 if no other organ dysfunction present 5) systolic blood pressure < 90 mmHg or mean arterial pressure ≥ 70 mmHg or use of vaso-active medication
Kybersept		
Suspected infection	temperature > 38.5°C or temperature < 35.5 °C AND leukocyte count >10,000/mm^3 or leukocyte count <3,500 /mm^3	At least three out of: 1) heart rate > 100/min 2) respiratory rate >24/min or mechanical ventilation 3) plasma lactate higher than normal or pH < 7.30 or base excess -10 mmol/L 4) urine output < 20 mL/hr 5) thrombocyte count <100 $\cdot 10^3$/mm^3 6) systolic blood pressure < 90 mmHg or use of vaso-active medication

2   Analyzing Differences in Definitions

This section describes the abstraction levels that can be distinguished in operational disease definitions (Section 2.1), and explains how these levels are used in comparing different definitions (Section 2.2).

2.1   Levels of Operationalization

When describing a disease which is considered a natural kind, in fact, operationalization takes place at different levels. These levels form an abstraction hierarchy for concepts that are used in operational disease definitions, which is depicted in Table 2. Four different levels are distinguished. On the first, most abstract, level, concepts are expressed in terms of the *condition* of the patient. The second level focuses on *signs and symptoms*. Signs and symptoms are further operationalized using terms related to *measurements* that are performed in the patient. On the fourth, most concrete, level, terms are used to describe the *threshold value* for measurements, which distinguishes patients with the sign or symptom from patients without.

When moving through the hierarchy from top to bottom the concepts become more explicit. In daily patient care, it mostly suffices to use terms from the 'Condition' and 'Sign / Symptom' levels. Instead, in operational definitions used for purposes of selection, concepts are mostly expressed in terms of the measurements with their threshold values.

2.2   Using the Operationalization Hierarchy in Comparing Definitions

Differences between operational definitions occur at different levels of operationalization. Identifying differences at the Threshold level is relatively straightforward, e.g., both severe sepsis definitions use the Measurement 'Thrombocyte count', but Kybersept uses '< 100' as a cut-off value, whereas PROWESS requires the thrombocyte count to be lower than $80 \cdot 10^3/mm^3$. It is however much more complicated to see to which extent a definition that requires two specific criteria to be present relates to a definition that requires three out of a list of four criteria, such as in our example. Our approach helps to compare the definitions not only at the lowest level of operationalization, but also at higher levels.

The approach consists of three steps. First, a 'disease ontology' is created, which describes all possible operationalization choices for a specific disease in a formalized way. Concepts for similar conditions that are operationalized in different ways

Table 2. Abstraction hierarchy for concepts that are used in the operational definitions of medical conditions

Level	Description	Example
Condition	A collection of symptoms and/or signs of which a given number has to be present for the condition to be present.	Severe sepsis
Sign / Symptom	A characteristic of the patient which is experienced by the patient or can be measured by the physician.	Platelet disorder
Measurement	Result of a measurement performed by the physician.	Low thrombocyte count
Threshold value	Threshold which determines whether the result of the measurement indicates the sign / symptom to be present.	Thrombocyte count $\leq$ 80,000 mm^3

in the definitions are given different names, e.g., KS-Thrombocytopenia and PW-Thrombocytopenia. As formalization language we have used OWL DL, a language recently recommended as a standard for ontology modeling based on Description Logics [4], because it is able to 1) formalize concepts and complex relations (e.g. number restrictions); 2) reason and query at different levels; 3) be used in combination with real patient data. A detailed description of the formalization of the severe sepsis definitions is found in [5].

Second, each disease definition is formulated in terms of the disease ontology. For each element of the definition is determined at which level it is specified, and the appropriate concept from the disease ontology is chosen. In this step, we also specify the polythetic conditions using number restrictions, e.g., KS-SevSepsis ⊑ conditionOf.(> 3 hasSymptom.(or KS-Thrombocytopenia KS-Hypotension KS-AbnormalHeartRate KS-AbnormalRespiratoryState KS-Oliguria KS-Acidosis)).

In the third step we compare the reformulated definitions automatically. The question, "can the definitions be considered similar", is easily answered by checking for equivalence between the disease definitions. As this is often not the case, in the second phase further comparisons aim to discover in which parts of the definitions the differences are located. This comparison is based on enforcing equivalence between concepts from different definitions and checking for inconsistencies. This can be done at different levels. To verify whether the thresholds are similar, equivalence is enforced at the Measurements level. This will lead to an inconsistency when the definitions make use of different thresholds. To investigate whether the problem is located at the threshold level only, the ontology can be 'pruned' unto the level of Measurements (i.e., at the threshold level the concepts in both definitions are forced to be equivalent) and again checked for equivalence of the definition and for inconsistencies. These comparisons can be repeated at the higher, more abstract, levels.

For example, Figure 1 depicts a part of the ontology with some elements of the Kybersept and PROWESS definitions of severe sepsis. When we test for equivalence of the PROWESS and Kybersept concepts of 'severe sepsis' we will find that these two definitions are not equivalent (cf. Table 1). To find out which concepts or relations cause the differences, we start at the lowest level. When enforcing equivalence between both 'Low TC count' measurements, we will find an inconsistency, as the trials use different threshold values.

3   Discussion

In this paper we present an approach to systematically compare different operational definitions of a single disease using ontological modeling. Its use has briefly been illustrated with an example in the area of severe sepsis. More extensive examples of reasoning possibilities are given in [5].

The approach we have presented can be applied for several purposes. We are implementing a web-service which assists trial designers in operationalizing
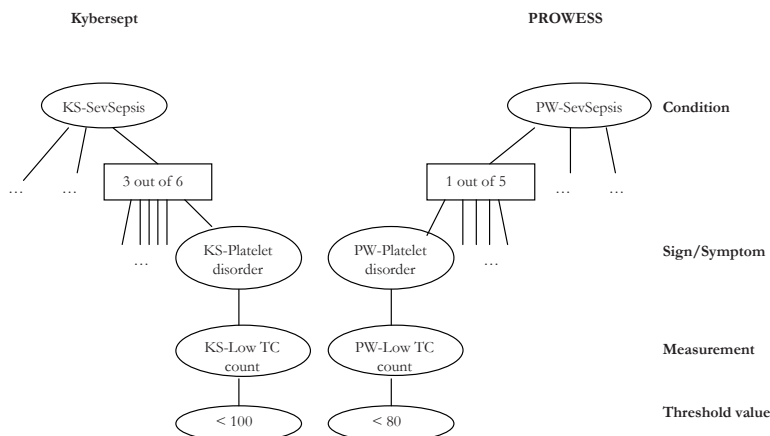
Fig. 1. Part of the disease ontology with some elements of the Kybersept and PROWESS definitions of severe sepsis. (TC count = thrombocyte count).

disease definitions.[1] Current decision-support systems for trial designers focus mainly on procedural, safety, and ethical aspects of the trial protocol (e.g, [6]), whereas in our approach the focus is on the operational definition of the disease. The approach can also be used in meta-analysis of scientific medical results, and in the area of development of computerized versions of clinical guidelines.

In the current DL model we did not use datatype properties to model the 'Threshold' level, but instead created artificial concepts which were in a subsumption relation (e.g., we used VeryLowTCCount-lt80, which is a subclass of LowTCCount-lt100) . In future work we will enhance our approach to allow for more complex reasoning at this lowest level. Furthermore, we will extend the current model with an A-box with real patient data to combine querying the knowledge-based model with querying patient data.

References

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[1] The user-interface of the web service is found at `http://prauw.cs.vu.nl/sepsis-trials/`. We are currently implementing the connection to the reasoning engine.

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