UiT THE ARCTIC UNIVERSITY OF NORWAY

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Semantic and Perceptual Models for Clinical Decision Support Systems

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Semantic and Perceptual Models for Clinical Decision Support Systems

To Estela, your love made this PhD possible.

Abstract

The current vision of healthcare is evolving in directions towards the secondary use of health data for producing new evidence, rapidly assimilating new knowledge, including the patient as an active component in decision-making and developing communication strategies to coordinate different areas of health care, among others. The work in these directions heavily relies on the appropriate use of different technologies. Among these technologies, Clinical Decision Support Systems (CDSS) implement validated evidence as computable artifacts that enable access to medical knowledge at the point in time when it is needed to make a decision about a person's health. During the last two decades CDSS standards and technologies have progressed significantly to develop them as more robust and scalable systems. However, the current context of medicine sets high demands in aspects such as interoperability to enable the use of EHR data in CDSS, the need to establish communication challenges to include the patient as an active component in decision making, collaborative learning and sharing CDSS across institutional borders, to name a few.

In this thesis I tackle some of these challenges. In particular, I evolve previous conceptual computerized decision support frameworks and I postulate a CDSS environment where different models interact to enable:

- **Secondary use of data for CDSS:** The dissertation presents a model to leverage different developments in data access and standardization of medical information. The result is an openEHR-based Data Warehouse architecture that enables access, standardization and abstraction of clinical data for CDSS. The architecture allows: a) to access heterogeneous data sources; b) to standardize data into openEHR to grant interoperability of data; and c) to exploit an openEHR repository as a Data Warehouse that allows querying data in a technology-independent format (the Archetype Query Language).
- **CDSS semantic specification:** The semantic model proposed exploits the paradigm of Linked Services to unambiguously describe CDSS in a machine-understandable fashion. This grants ontological descriptions of functional, non-functional and data semantics. These descriptions facilitate to overcome some of the barriers in CDS functionality sharing. In particular, the semantic model proposed allows using expressive queries to discover CDS services in health

networks, and analyzing CDSS interfaces to understand how to interoperate with them.

- **Effective patient-CDSS interaction:** the dissertation proposes a method to evaluate the communication process between patients and consumer-oriented CDSS. The method aims for detecting if important human-computer interaction barriers that could lead to negative outcomes are present in CDSS user interfaces.

The methods and developments presented are framed in the context of the CDSS *er du syk*. *Er du syk* (in English, are you ill) is a symptom checker that allows users to record data regarding their symptoms and demography. These data are combined with epidemiology information from regional Laboratory Information Systems to provide patients a list with the likelihoods of the diseases that may be affecting them.

Acknowledgements

The work summarized in this dissertation was only possible thanks to the collaboration of many people and organizations.

I am grateful to Helse Nord for funding my PhD and the Norwegian Centre for e-health Research (previously the Norwegian Centre for Integrated Care and Telemedicine) that provided me with a nice work environment.

I thank Prof. Johan Gustav Bellika, my main supervisor, who has provided not only research advice but also he has taught me how to look at research challenges with an open critical mind. He has helped me in my life in Tromsø introducing me to its nature and culture. Furthermore, he has granted me freedom to choose which fields to explore, respecting my decisions so I could mature as a researcher. An important part of my PhD has been carried out in collaboration with the good friends of ITACA at Universidad Politécnica de Valencia. I thank my co-supervisors Jose Alberto Maldonado and Vicente Traver for all the inestimable advice and help provided during my PhD. I also thank David Moner who came to Tromsø as guest researcher and provided very valuable help in the first stage of my research. I acknowledge Diego Boscá, also from ITACA, for all the inspiring conversations and advice in technical deployments. I would also like to thank my co-supervisor Rong Chen from Cambio Healthcare systems for the case study and guidance provided in the field of openEHR Clinical Decision Support Systems. I am grateful to Randi Karlsen and Gro Berntsen for the time devoted to my supervision.

During the PhD I spent three months at the Knowledge Media Institute (the Open University) in Milton Keynes. I thank all KMI researchers for the wonderful time I spent there, and specially Carlos Pedrinaci who guided me in the developments regarding Semantic Web technologies crucial to this PhD. I found his conversations and perspective from the Semantic Web research point of view particularly rewarding.

In addition to research institutions, private held companies have provided both technologies and ideas with the only motivation of their passion for technological advances. I am grateful to Marand d.o.o. for providing me technologies and support that significantly accelerated my research. Specifically, I thank Fabian Borut for all the time devoted to discuss about different health informatics topics and the best way of applying latest technological advances in the medical domain. I also acknowledge Bostjan Lah for the time devoted to clarify details about their technologies. The help of Marand transcends this PhD and was also crucial for the success of my supervised Master student´s work.

I acknowledge the National Editorial Group for Archetypes, in particular Rune Pedersen and Silje Bakke, for the advice in archetype management and the availability of national resources to guide the development of my clinical models. Rune Pedersen also provided me with valuable insights about the Norwegian healthcare system that were important to ground my work.

Very specially, I thank the openEHR community in general, and the openEHR foundation, in particular, which has always been supportive. The foundation, led by Ian McNicoll, has helped my research group with advice, contacts and support to research projects. They were also responsive when I organized the *Arctic Conference on Dual-Model based Clinical Decision Support and Knowledge Management*. That experience gave me a privileged overview about the different developments in openEHR implementations around the world. Some of the participants were mentioned above, but I would also like to thank Thomas Beale, Heather Leslie, DIPS ASA, Pablo Pazos and Alfonso Pérez for their participation. I also acknowledge Indizen technologies for providing me with full access to their terminology server.

Several researchers have provided feedback on different parts of this dissertation. I thank my friend emeritus Prof. Rafael Romero for the statistical advice and spiritual counseling that he has provided. I am grateful to Cristina Soguero, Torje Henriksen and Joseph S. Hurley for the revision provided to some sections of this dissertation.

The validation of the methods presented has required demanding computational resources and deployment frameworks. I thank Øystein Hansen and Inge-Håvard Hunstand for their help in systems deployment.

Additionally, many researchers have answered different enquiries about health informatics topics during this time. I am grateful to: Catalina Martinez-Costa, Nils Kolstrup, Daniel Karlsson, Margarita Sordo, Carlos Cavero, Arturo González, Stein Olav Skrøvseth, Dipak Kalra, and David E. Shields.

During my time in Tromsø, many friends and colleagues have contributed to make my life better. I thank Elia Gabarron, Andrius Budrionis, Kassaye Yitbarek, Meskerem Asfaw, Torje Henriksen and the rest of my colleagues and friends for this.

Finally, I would like to thank my wife Estela and my parents Luis and Mª Teresa. They have always supported me in all the good and bad moments of my life. I cannot express how fortunate I feel to have such an incredible family.

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Abbreviations

ADL	Archetype Definition Language
AQL	Archetype Query Language
CDS	Clinical Decision Support
CDSS	Clinical Decision Support Systems
CEM	Clinical Element Models
CIG	Computer Interpretable Guidelines
CIM	Clinical Information Models
CMO	Clinical Models Ontology
DB	Data Base
DIKW	Data-Information-Knowledge-Wisdom
DW	Data Warehouse
EBM	Evidence Based Medicine
ECA	Event-Condition-Action
EHR	Electronic Health Record
ERA	Extended Relational Algebra
GDL	Guideline Definition Language
GUI	Graphical User Interfaces
HCI	Human Computer Interaction
HIPAA	Health Insurance Portability and Accountability Act
HIS	Health information system
IDL	Interface Definition Languages
IoT	Internet of Things
KM	Knowledge management
LHS	Learning Healthcare System
LIS	Laboratory Information Systems
LKB	Linked Knowledge Base
LOD	Linked Open Data
MSM	Minimal Service Model
NLP	Natural Language Processing

OCL	Object Constraint Language
PC	Principal components
PCA	Principal Components Analysis
RDBMS	Relational Data Base Management System
RM	Reference Model
SWS	Semantic Web Services
TAM	Technology Acceptance Model
VMR	Virtual Medical Record
WADL	Web Application Description Language
WSDL	Web Service Description Language
WSMO	Web Service Modeling Ontology

1. Introduction

Summary: This chapter presents the introduction to the dissertation. First, it provides an overview of the challenges that Evidence Based Medicine is currently facing and how the concept of the Learning Healthcare System aims to approach these challenges. Secondly, it introduces the requirements that Clinical Decision Support Systems need to fulfill to become effective tools to enable agile knowledge assimilation in the Learning Healthcare System. Thirdly, the chapter introduces the hypothesis and objectives to fulfill the requirements presented. Finally, the chapter explains how this dissertation is organized.

1.1. The Learning Healthcare System

Healthcare sector in western economies is currently facing several challenges both externally and internally[1–4]. The main external challenges are [1,5]:

- Increasing aging population that needs assistance not only for health but also in their daily life. For example, many citizens that nowadays suffer a stroke will survive from it but will need assistance on a daily basis [1].
- Lack of enough workforces to cover all healthcare and social care needs. At the moment, while the demand of workforce to perform caring tasks is increasing; the availability of it in many European countries is diminishing [1,5].
- Insufficient coordination of the different services involved in people care such as healthcare services, social services and others to provide integrated care for, for example, old citizens living with chronic conditions or multi-morbidities [1].

The internal factors are related to the limitations of the current operation of Evidence Based Medicine (EBM) that translates to difficulties in providing the best care available. Main internal challenges are [3,4]:

- Assimilation of the evidence produced. Two factors are determinant for this challenge. The first one is that currently there is a time lapse of circa 17 years since new knowledge is produced until that knowledge is applied in healthcare [6–8]. The second one is that the amount of evidence growing in real time is overwhelming and it is nearly impossible for health professionals to keep up to date [9].

- Reductionism in the scientific method. EBM does not deal with the complexity of medical cases [10]. EBM guidelines are often restricted to a narrow group of patients with only one condition. As a consequence, EBM is today practiced as a set of rather inflexible rules. In some cases, these rules are influenced by management decisions rather than patient needs, thus hampering the treatment of complex cases (e.g. patients with multimorbidity) [4].

- Inclusion of the patient as decision maker. Patients should feel empowered and demand evidence that is explained to them and personalized to their case [3,4]. The most efficient treatment for a patient may be one that causes secondary effects that disturb his life. However patients may prefer to find a balance between condition control and quality of life. For example, a patient with hypertension may prefer a less effective treatment that does not produce impotence.
- Consideration of tacit knowledge. EBM relies in public evidence to decide what are the best interventions. However, it neglects the evidence that each professional develops over the years of practice [3] and the experience and knowledge that each patient has about his/her own condition.

Internal limitations show that EBM still needs to, first, demonstrate that it improves patient outcomes and, second, develop an appropriate theoretical framework for effective problem solving [3]. Several studies have proposed directions to overcome these challenges [4,5]. Some studies put a stronger focus on the need to grant the patient an active role in decision making and designing public health interventions [4]; while other studies put a stronger focus on the need for enabling the development of new evidence, the rapid assimilation of it, and accelerating the adoption of that evidence when delivering healthcare [5]. These two visions are well balanced in the proposal to redesign biomedical research and healthcare delivery proposed by the IOM Roundtable on Evidence-Based Medicine in 2007. The IOM Roundtable proposed to evolve current healthcare into the so-called Learning Healthcare System (LHS)[2]. The LHS defines explicit directions of work to overcome EBM challenges, evolving EBM into a paradigm where the healthcare system uses clinical data to produce new evidence, rapidly assimilates and provides access to that evidence and where the patient is considered an active component in decision making [2]. Work towards the LHS involves political, legal and organizational processes redefinition, but also relies heavily on the appropriate use of technology as enabler of the changes needed [1,5,11].

On the technology side, overcoming current health challenges requires to work in different parallel tracks. These tracks aim for [1,5]: a) facilitating secondary use of data to generate new knowledge; b) implementing that knowledge to exploit latest evidence at several levels (patients, citizens and populations); c) establishing communication channels that include patients to make them active participants in decision making; d) providing the tools for communication across different health services. Technology must allow to inter-communicate Health Information Systems[1] (HIS) and actors, thus allowing for exploiting highly contextualized information. That requires research in standardization, terminologies and usability, governance and practitioner identification, among others [1].

All these directions of work have as a final goal to exploit data from different views to generate knowledge that will, in the end, improve patients' health. For health professionals to be able to use new knowledge in an effective way, that knowledge must be provided in the appropriate context, at the exact time when it is needed [12]. Among the different HIS that interact to support health services, the explicit implementation of computable knowledge accessible at the point of care is covered by Clinical Decision Support Systems (CDSS)[2]. Typically CDSS are considered as tools that support clinicians, but the inclusion of the patient as an active component in decision making is changing that perception [1,2]. Considering this scenario, CDSS can be defined as computer systems designed to support decision making about a person's health at the point in time when that decision is made.

1.2. Clinical Decision Support in the Learning Healthcare System

Enabling Clinical Decision Support (CDS) involves major legal, political, organizational, privacy and technical challenges [13,14]. CDSS have typically been embedded into the Electronic Health Record (EHR). However, in order to be an efficient tool that helps to overcome the challenges presented, CDSS need to become more flexible platforms that operate across different EHRs by sharing knowledge implementations [13–16] and bringing knowledge into practice. Furthermore, new knowledge must be provided not only for clinicians but also for citizens [2]. In this context, CDSS researchers have a path to walk for allowing CDSS to become effective systems that provide support for the LHS. In particular, this has implications for their interfaces of communication with both systems and users. In order to reliably provide improvements to patient's health, there

[1] Health Information System is the generic term to encompass any system that processes, stores or manages health information. Examples are Electronic Health Records, Laboratory Information Systems, Radiology Information Systems, Clinical Decision Support Systems etc.

[2] In this dissertation the term CDSS refers to computerized CDSS.

must exist a smooth communication among the actors and technologies involved in CDS. As the IOM points, while healthcare is often seen as a data problem, it is in fact a communication problem among many systems and actors, including the patient [2]. CDSS, as a part of the health information infrastructure, are no exception to this. Therefore an appropriate computational framework must be established to design the mechanisms that will allow the communication among the different actors involved in decision making. A recent review of Budrionis and Bellika shows that three directions of work are currently involved in the LHS implementation[17]: 1) secondary use of data; 2) patient reported outcomes; and 3) collaborative learning. These three directions have direct influence on the requirements needed to implement CDS in a LHS environment that are only partially covered by previous CDS frameworks [18]. This dissertation aims to tackle three of the main challenges that directly affect CDS in the LHS:

- **Challenge:** Regarding secondary use of data, its influence on CDSS comes from the need of binding data stored in the EHR to decision algorithms. The concepts referenced from inference models are often abstractions (e.g. high blood pressure) derived from raw EHR data (e.g. systolic 158 mm Hg, diastolic 95 mm Hg) that may be stored in heterogeneous data sources. Nowadays there is a large availability of decision algorithms that are constantly adapted and retrained to implement new knowledge or infer it from data sets [19–21]. Previous studies have covered the problem of abstracting data by using a standard Virtual Medical Record (VMR)[22–25]. However the connection of the VMR with the EHR has often been performed as ad-hoc queries to a single source. The data sources may be distributed or they may require applying privacy preservation techniques. Moreover abstraction mechanisms are usually coupled with one technology. This introduces a problem of re-implementing abstraction queries/mappings if the technology changes, which for environments where algorithms are in continuous evolution represents an important burden.
  Requirement for data perception (R1): There is a need for dynamic architectures that allow access to heterogeneous data sources, transform the data accessed into a common standard and provide technology independent abstraction mechanisms [26–28].

- **Challenge:** Collaborative learning is a rather unexplored field. Budrionis and Bellika only identified one paper related to it discussing the benefits of interchange of historical information and experiences about practice. When it comes to the CDS arena, collaborative learning is needed in the elicitation of clinical knowledge that is used to implement CDS artifacts [29]. That is a complex and resources demanding process that requires multidisciplinary teams making the CDSS development costs very high [29–32]. Thus, sharing CDS artifacts is adequate in order to avoid duplicating costs in CDSS developments. Sharing knowledge in the form of computational artifacts has been an aspiration of CDS research for a long time [15] since it is the way towards the broad adoption of CDSS [13][29]. Sharing CDS functionality requires methods for the interoperation of clinical information across HIS [33], but also the interoperation of other CDSS properties so professionals can assess the reliability and validity of the CDSS. This involves the specification of properties such as which organization issued the CDS artifact, when it was issued, which literature supports its algorithm etc. For these properties to be interpreted across organizations they cannot be only human interpretable, but they also need to be machine computable [34].

Requirement for semantic description (R2): CDSS functionality, Knowledge Management (KM) properties and data interfaces need to be unambiguously specified in a way that allows the alignment of different formats. Therefore CDSS interfaces and properties need to be specified in common machine-interpretable formats that allow computers processing equivalence, subsumption and other types of semantic relationships among concepts.

- **Challenge:** The provision of outcomes by the patient involves the inclusion of a new actor (the patient) who provides valuable data for decision-making [1,2,17]. This is a source of information that may help to personalize health but also to enhance decision making quality [17]. For data to be used by decision algorithms, it must be reliably gathered and formalized in terms of clinical information standards and terminologies [33]. However, the patient needs to be able to interpret medical concepts to report his data. This introduces a problem of Human Computer Interaction (HCI) between the patient and the CDSS.

  Requirement for human-computer perception (R3): when patients communicate their health data, methods that guarantee that the patient is able to accurately record his health status are needed. This involves the evaluation of CDSS Graphical User Interfaces (GUIs) to ensure that the communication process is successful.

1.3. Hypothesis

1. Regarding the first requirement (R1), data warehousing methodologies can be combined with EHR information standards to define an architecture that enables the integration, standardization and abstraction of data for its use in CDSS. If used in the appropriate way, that architecture can provide access to heterogeneous data sources and abstraction mechanisms based on clinical information standards.

2. Regarding the second requirement (R2), the Linked Services paradigm, i.e . Semantic Web Services (SWS) that exploit Linked Data principles, can be used to produce semantic descriptions of CDSS to enable their publication, discovery and analysis based on machine-interpretable ontological descriptions.

3. Regarding the third requirement (R3), usability techniques can be appropriately leveraged to evaluate consumer oriented CDSS, thus detecting usability problems that may lead to incorrect advise.

1.4. Objectives

With the objective of overcoming the challenges presented in the previous sections, firstly, I build on the models proposed by Rector et al.[35,36] and Sheth et al. [37,38] to define a CDS framework encompassing the 3 computational models that illustrate the hypothesis presented. The framework, depicted in Figure 1, represents a CDSS deployment framework with an algorithm on its core (pink circle), and defines semantic and perception mechanisms to generate CDS outcomes. Secondly, I develop specific models to enable the implementation of such framework in openEHR environments by developing:

1-A **data perception model** that enables the secondary use of health data for CDS by allowing the integration of disparate data sources, contextualizing it with an information standard (openEHR) and allowing performing abstractions through standard queries (represented by the arrow on the top of the yellow circle).

2-A **semantic model** (orange circle) that allows the publication, search and analysis of CDSS based on linked data principles. This way CDSS can be discovered and analyzed by different organizations regardless of the standards used in their implementation. Thus opening the door for sharing CDSS distributed across different organizations.

3-A **human-computer perception model** so CDS GUIs can be evaluated to detect HCI barriers that may lead to negative outcomes (represented by the cloud in the yellow circle).

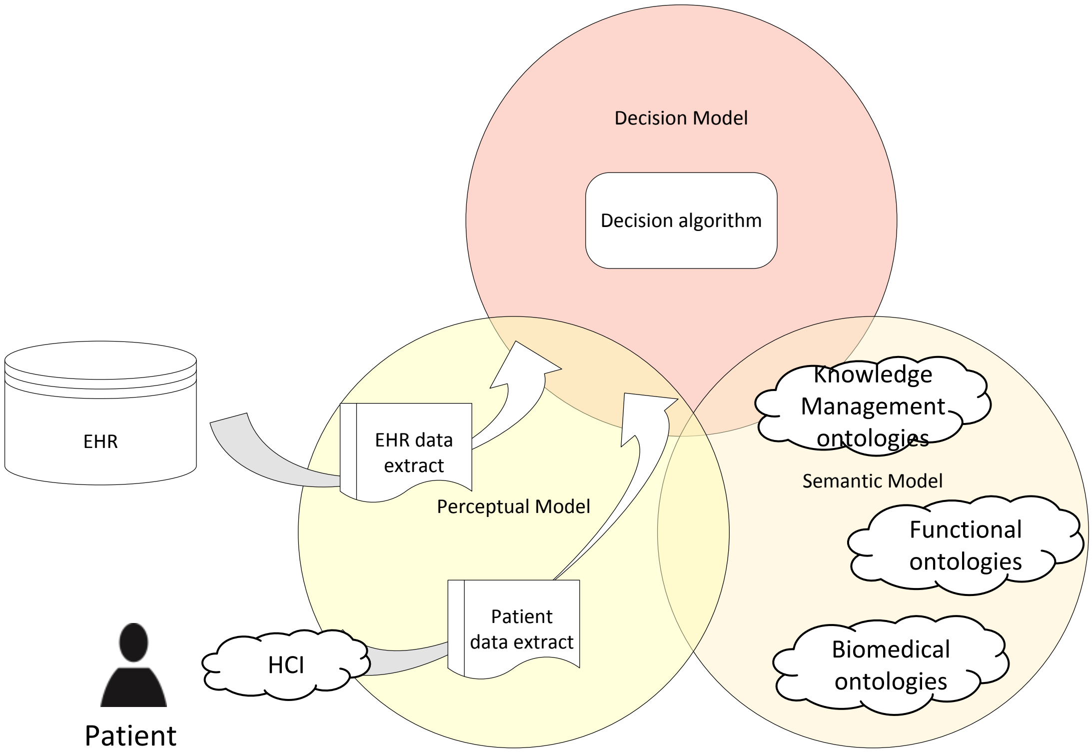

Figure 1. CDS Computational models overview.

1.5. Dissemination and exploration

During my PhD I have published the different results of my research. Following there is a list with the different communications I have authored.

1.5.1. Journal papers

- **PAPER 1:** Marco-Ruiz L, Moner D, Maldonado JA, Kolstrup N, Bellika JG. Archetype-based data warehouse environment to enable the reuse of electronic health record data. International Journal of Medical Informatics. 2015 Sep;84(9):702–14. (Published)

  My contribution: I had the original idea to define a method for building archetype-based Data Warehouses (DW). I led the study and developed the RESTful micro-services architecture to create an openEHR DW. I also led the drafting of the manuscript.

- **PAPER 2:** Marco-Ruiz L, Pedrinaci C, Maldonado JA, Panziera L, Chen R, Bellika JG. Publication, discovery and interoperability of Clinical Decision Support Systems: A Linked Data approach. Journal of Biomedical Informatics. 2016 Aug;62:243–64. (Published)

  My contribution: I had the original idea and I led the developments and the drafting of the manuscript. I developed the ontologies for CDSS semantic specification and deployed the infrastructure for the use case.

- **PAPER 3:** Marco-Ruiz L., Bønes E., de la Asunción E., Gabarrón E., Avilés-Solis J.C., Lee E., Traver V., Sato K, Bellika J.G. Combining Multivariate Statistics and Think Aloud to Asses Human-Computer interaction barriers in Symptom Checkers. (Submitted to the Journal of Biomedical Informatics)

  My Contribution: I had the original idea and I led the developments and drafting of the manuscript. I performed the statistical analysis and led the qualitative analysis stage.

1.5.2. Conference papers

- **PAPER 4:** Marco-Ruiz L, Maldonado JA, Traver V, Karlsen R, Bellika JG. Meta-architecture for the interoperability and knowledge management of archetype-based clinical decision support systems. In: 2014 IEEE-EMBS International Conference on Biomedical and Health Informatics (BHI). 2014. p. 517–21(published)

  My Contribution: I had the original idea and I defined the architecture described. In addition, I led the developments and drafting of the manuscript.

- **PAPER 5:** Marco-Ruiz L, Maldonado JA, Karlsen R, Bellika JG. Multidisciplinary Modelling of Symptoms and Signs with Archetypes and SNOMED-CT for Clinical Decision Support. Studies in health technology and informatics. 2014;210:125–129. (published)

  My Contribution: I had the original idea, I led the modeling tasks and drafted the manuscript. I defined a project in the National CKM and coordinated the review process where different clinical reviewers participated. I modeled the ontology presented.

- **PAPER 6:** Marco-Ruiz L, Budrionis A, Yigzaw KYY, Bellika JG. Interoperability Mechanisms of Clinical Decision Support Systems: A Systematic Review. In: Proceedings from The 14th Scandinavian Conference on Health Informatics 2016, Gothenburg, Sweden, April 6-7 2016 [Internet]. Linköping University Electronic Press; 2016 [cited 2016 Jun 3]. p. 13–21. Available from: http://www.ep.liu.se/ecp/article.asp?issue=122&article=003 (Published)

  My Contribution: I had the original idea, performed the literature review and drafted the manuscript.

1.5.3. Other communications

In addition to the publications in scientific journals and conferences during my PhD I have also participated in several tutorials and communications. In 2014 I organized the first *Arctic Conference on Dual-Model based Clinical Decision Support and Knowledge Management* where the majority of openEHR vendors and researcher met in Tromsø to explain they latest developments and challenges. At Medinfo 2015, I organized the tutorial *Enabling Clinical Data Reuse with openEHR Data Warehouse Environments* about the data perception methodology presented in chapter 4 [39]. In the same conference I participated as speaker at the tutorial *Design and Implementation of Clinical Databases with openEHR* [40]. In addition, I am the main editor of www.thedatavineyard.com, a personal blog where I discuss the topics related to my research in medical informatics with other colleagues. I use it to extend certain topics of interest that cannot be fully covered in papers or that require special attention. The blog intends also to provide a space for presenting the importance of medical informatics to the general public with simple examples and interviews to my co-authors.

1.6. Research Context

I carried out my thesis as part of the Norwegian Centre for e-Health Research (NSE), previously the Norwegian Centre for Integrated Care and Telemedicine. Helse Nord funded my PhD under the grant HST1121-13. My PhD was attached to the PhD program offered at the Faculty of Health Sciences belonging to the University of Tromsø - The Arctic University of Norway. My PhD started on September 2013 and during its time I have collaborated with different organizations in both academia and industry.

ITACA/UPV (Spain): Dr. J. Alberto Maldonado and Dr. Vicente Traver were my co-supervisors. Both belong to the ITACA institute at Universidad Politécnica de Valencia where I have spent several periods as visiting researcher. Our collaboration provided me important feedback and led to the publication of several scientific papers. Additionally, David Moner from the ITACA institute visited NSE in 2014, providing important advise in openEHR data transformation, which was used for transformation stage of the Archetype-based DW, presented.

Knowledge Media Institute/The Open University (UK): I spent 3 months in a research stay at the Knowledge Media Institute (The Open University) in Milton Keynes. During my time there I developed the method for the application of SWS and Linked Data to CDSS. Dr. Carlos Pedrinaci supervised my work and helped me to get immersed in the field of Semantic Web technologies.

Marand d.o.o. (Slovenia): The company Marand provided me with the technologies needed for openEHR persistence. Additionally, I have regularly shared opinions and views with Fabian Borut and Bostjan Lah about different health informatics topics that have significantly enriched my work.

Cambio Healthcare Systems (Sweden): Cambio Healthcare Systems supported my research proving me with CDS modules as case study for the development of the methodology for applying SWS to CDSS. Dr. Rong Chen, from Cambio Healthcare Systems, was also my co-supervisor and assessed my work by clarifying aspects of the Guideline Definition Language (GDL) and CDSS KM technologies.

NRUA: I collaborated regularly with the National Editorial Group for Archetypes to develop the archetypes that were used in my PhD. Dr. Rune Pedersen and Silje Ljosland Bakke helped me setting up a repository for my project in the National CKM and provided me with a holistic overview of the challenges and advances in interoperability in the Norwegian scenario.

openEHR community: the openEHR community in general, and the openEHR foundation, in particular, with Dr. Ian McNicoll as director, were crucial to this PhD. From the very beginning I found support for my research in the form to access to technologies, discussions and advice. With the support of the openEHR foundation I organized in June 2014 the first *Arctic Conference on Dual-Model based Clinical Decision Support and Knowledge Management* were most of the vendors and researchers involved in openEHR and ISO 13606 participated sharing their views. The conference provided a valuable overview of the state of the art in CDSS and interoperability technologies for my PhD.

1.7. Dissertation Overview

This dissertation is organized as follows:

• Chapter 1 has presented the Learning Healthcare challenges, the role of technology in overcoming them by providing effective CDS, the hypothesis and the objectives to cover.

• Chapter 2 provides a selective literature overview, gaps in prior research and the contributions of this thesis.

• Chapter 3 presents the conceptual framework that encompasses the models developed.

• Chapter 4 presents the contribution to enable the data perception model to gather data from HIS, transform it into openEHR compliant instances, and allow performing abstractions to feed CDS algorithms using the Archetype Query Language (AQL).

• Chapter 5 presents the development of the semantic model to enable ontological descriptions of CDSS interfaces and KM properties compliant with Linked Data principles.

• Chapter 6 presents the human-computer perception model that allows evaluating the patient-CDSS communication. In particular, the chapter presents a method for the evaluation of consumer-oriented CDSS GUIs to deal with complex interfaces evaluation in a cost-effective manner.

• Chapter 7 presents a summary of the accomplishments and contributions; assessment of the methods developed and their generalizability; the limitations and future work, and the conclusions.

2. Background and State of the Art

Summary: The previous chapter argued that the Learning Health System requires CDSS to develop mechanisms for data processing (integration, standardization and abstraction), semantic descriptions, and user interfaces evaluation methods that guarantee the absence of human-computer interaction barriers when patients provide their data to a CDSS. This chapter presents a summary of the standards and technologies used to develop interoperable CDSS. The end of the chapter presents the state of the art and limitations of CDSS technologies and standards; and the research gaps that this thesis aims to cover.

2.1. Standards and technologies in CDS

The previous section presented that the LHS requires working in three directions to provide CDS outcomes. The data perception model for CDS must allow for data to be captured from different sources preserving its context and assuring the consistency and meaningfulness of the decision model inputs. The semantic model must, first, provide unambiguous descriptions of that data in commonly accepted ontologies and, second, express without ambiguity the functionality, KM properties, inputs and outputs of decision algorithms. The human-computer perceptual model needs to guarantee that data reported by patients is complete and that no barriers exist to its communication. This implies that seamless interaction across different computational models must be established. For these models to interact a high level of interoperability is needed.

Currently, from a technical point of view, there are five mechanisms that are leveraged to enable CDS interoperability [41]: medical logic specification formalisms, Clinical Information Models (CIM), semantic web technologies, medical terminologies and web services. In addition to these mechanisms, as presented in the previous chapter, it is also important to consider the patient communication model. Figure 2 shows an overview of the components that conform the CDS architecture. In orange the figure represents each of the mechanisms that allow the interoperation of the CDSS. On the left, the patient is represented as an active component in the decision making process. This introduces the requirement for allowing patients to communicate their data through the appropriate mechanisms (represented by the cloud).

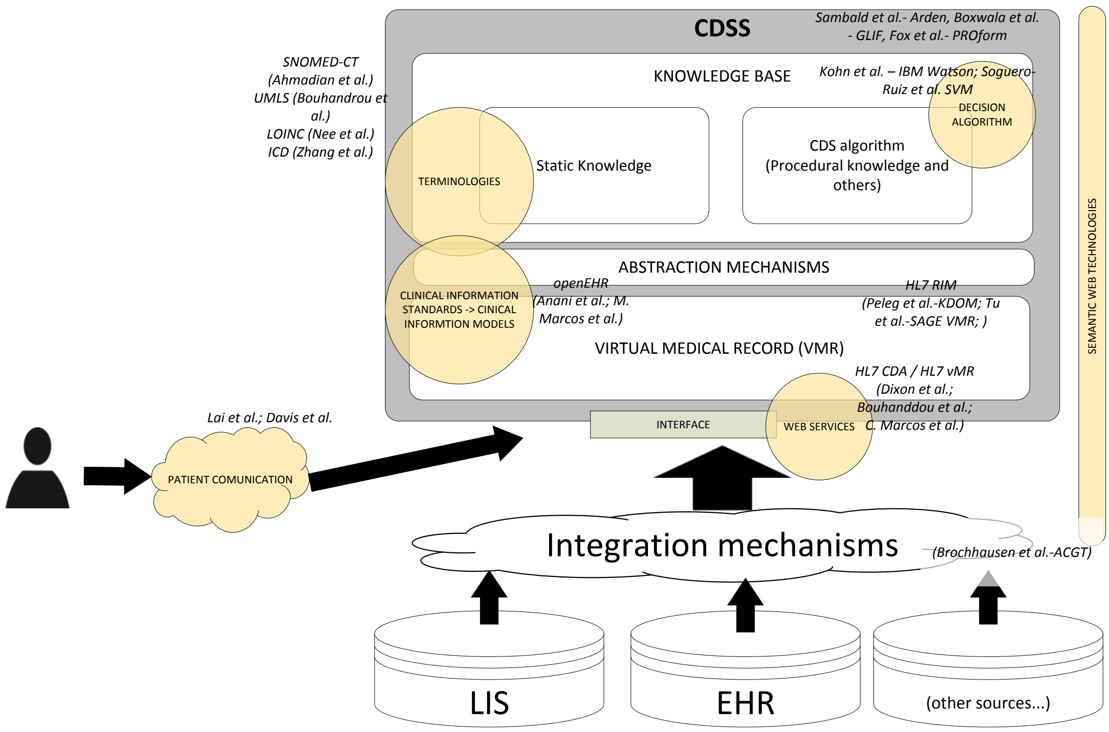

Figure 2. Interoperability mechanisms of CDSS.

Binding of data to decision algorithms

Binding data to decision algorithms involves the integration and abstraction of health data from the data sources where it was originally stored (EHR, LIS etc.) so it can be consumed by decision algorithms. Two main types of operators are used for this, namely horizontal and vertical [42]. Horizontal operators allow integrating heterogeneous sources of data (see integration mechanisms in Figure 2). Vertical operators (see abstraction mechanisms in Figure 2) provide functionality to combine background knowledge with data to produce abstractions (e.g. *if (systolic blood pressure > 140 mmHg) -> hypertension present*). The top right part of Figure 2 shows the CDS algorithm. In the CDSS field, most standards for CDS specification have focused on providing medical logic specification formalisms. These formalisms emerged in the 90s as a mean for specifying decision logic as CDS modules independent from the EHR. The first approach to encapsulate CDSS as modules was the Arden Syntax that allowed the definition of Event-Condition-Action (ECA) rules and queries to the EHR Data Base (DB) inside CDS artifacts [43,44]. In the 2000s, new formalisms aimed for defining more complex CDSS such as Computer Interpretable Guidelines (CIGs). Some examples of those formalisms are PROforma [45], EON[46], GLIF[47] or SAGE[31]. Those formalisms do not only allow the development of simple logic modules for alarms or reminders, but also clinical guidelines that support full workflows and provide methods to improve the integration with the EHR. Data integration mechanisms evolved in those models from simple queries embedded in logic modules to standard-based data schemas that allowed CDS modules to reference standard EHR entities. That approach was defined as the VMR [48]. The main advantage introduced by VMRs was that medical logic does not need to be mapped to the EHR DB schema. Rather it references VMR entities, which were often defined using a standard Reference Model (RM) (e.g. HL7 RIM). This allows defining abstractions from the VMR rather than from proprietary DBs. Therefore abstractions remain unchanged across different deployments since only the VMR needs to be mapped to the EHR DB, thus avoiding replicating abstraction mappings. Such replication is risky provided that it may introduce changes in the semantics of the data referenced by the algorithm. Nowadays, the VMR approach has been accepted by most CDS architectures. Originally VMRs were defined directly from RIM classes as in Peleg et al. [22] and Tu et al. [31]. More recently CDA has been used by Dixon et al. [14] and Bouhaddou et al. [49]. Since the VMR works at a higher abstraction level than the EHR, researchers from the HL7 CDS work group have defined a specific VMR standard that simplifies the classes involved in EHR content model definitions from RIM [50,51]. An example of the use of HL7 vMR can be found in the project Mobiguide by Marcos et al. [25]. At the moment, the reference architecture openCDS [52] is implementing a CDS generic framework that allows the interoperation of Drools logic modules with data schemas compliant with HL7 vMR, HL7 CDA and HL7 FIHR. Although most VMR developments and integration architectures have come from HL7, the openEHR community (openehr.org) has also proposed the definition of scalable VMRs at different abstraction levels by using archetypes [23]. When used in combination with GDL [53] (a rules and data constraint language for openEHR CDS artifacts definition) its integration with the EHR is seamless since GDL is designed to directly reference archetypes and bind logic to terminologies [53,54]. CIMs such as archetypes are at the moment a corner stone in the development of CDSS interfaces and interoperability across models. Nowadays, all modern CDSS implementations rely on clinical information standards to define their data models and interfaces. A VMR defined with CIMs does not only allow to reference standard entities from the decision algorithm, but also represents the nexus with terminologies that are used to attach semantics to data entities.

Clinical Information Models

The appropriate organization of clinical information is needed in order to allow HIS to maintain, scale, query and share clinical data. CIMs are currently the main trend for representing clinical data. Several standards have been developed to define the information architecture of clinical data [55]. The most spread standards (HL7 CDA, openEHR and ISO13606) follow an approach that divides models in 2 levels to shape clinical content. In this two level modeling, the first level defines a core set of generic classes and relationships common to all clinical content models. In essence, it represents a canonical clinical information ontology[3] that is constant across application domains. In the second level, the RM in combination with a constraint language is used as a metamodel to define application domain clinical content models (e.g. archetypes in openEHR can be used to define the content of the EHR). Examples of those content models are the EHR document structure, messages schemas, VMR models etc. Figure 2 represents CIMs on the left side.

CIMs represent how data elements are composed for an application domain, the binding of their elements to terminologies to attach semantics and constraints definitions [56]. CIMs therefore become a corner stone to drive the implementation of enterprise HIS that can effectively share, process, query and exploit clinical data. Provided that CIMs are defined as a consensus among clinicians and information architects; they represent generic models of an application domain that are independent from local implementation features (e.g. software or database technology, data models, indexes or constraints). Depending on the standard, CIMs may be known as archetypes, templates or detailed clinical models. The generality of CIMs allows the definition of regional or national libraries that implementers can access [57]. This enables, on the one hand, the appropriate governance of those models to ensure their validity and generality; and, on the other hand, the promotion of semantic interoperability since the same set of CIMs is common to different implementations. Examples of CIMs governance frameworks and libraries are the Intermountain Clinical Element Models (CEMs) [58], the Norwegian CKM [59], the international openEHR CKM [60] or the opencimi.org initiative [61].

In the CDS arena, regarding to the CDSS interoperability mechanisms presented aforementioned, it is possible to see how CIMs glue many of those mechanisms together. Architecturally, Web services encapsulate the CDSS and CIMs provide a standard structure to the content in the messages payload. At the same time, CIMs provide the linkage of each element in those messages with standard terminologies attaching semantics. Inside the internal implementation, CIMs allow logic to reference standard entities contained in CIMs that are, in turn, bound to terminologies facilitating their integration with different data sources or contexts.

[3] Here the word ontology is used in the figurative sense, it should not be confused with the meaning in computer science. Reference models define a general data model which classes define a sort of data ontology. However, their definition in languages such as ADL or XML Schema does not grant reasoning capabilities as ontologies in computer science often do.

Biomedical terminologies and ontologies

The upper left part of Figure 2 shows the static knowledge contained in CDSS knowledge bases. Static knowledge corresponds to entities of the domain of discussion that represent invariable knowledge. An example is SNOMED-CT that represents clinical concepts constant across application domains and time. Terminologies and medical ontologies, in CDSS developments, have been used to annotate CIMs (note the overlap of orange circles in the figure) with standard vocabularies [49,62–64], thus allowing the logic to reference standard concepts; integrate heterogeneous data sources or map different terminology systems [49]. This can be used to ease the mapping tasks among entities in different information standards, map them to other terminologies, or provide a *lingua franca* to integrate data from several sources [14,49]. Several challenges are related to their adoption in CDSS including the cost of mapping to other terminologies, the cost of annotating CIMs and the limitation to process pre- and post- coordinated expressions [41].

Web services

Web services (represented by the interface in the lower part of Figure 2) have been used to enable the complete decoupling of CDSS from the EHR. Encapsulating CDSS in Web services allows CDSS to be used and shared among several clients that may be hosted in different institutions [14,65]. The Service Oriented Architecture (SOA) has been proposed as an approach to implement national frameworks to share CDS systems in order to enable their broad adoption [13]. The work in SOA for CDSS has led to the definition of the HL7 DSS Implementation Guideline that specifies the SOA architecture to combine information standards for defining the VMR with the use of terminologies [66]. This way a CDS service can be available in a health network for any HIS (Web service client) with the appropriate access rights. This allows sharing the same CDS artifact deployment. In SOAs, CIMs provide the information schema of the data carried as SOA payload that the CDS service will use to produce outcomes [14,67].

Semantic Web technologies

Semantic web technologies, represented by the cross sectional vertical ellipse to the right in Figure 2, have occupied a transversal role in CDSS implementations [41]. They have been used to cover requirements that other implementation mechanisms could not fulfill [41]. Nevertheless, the most prominent use has been to provide implementations for the concept models of ontology-based biomedical terminologies such as SNOMED-CT. In some cases, Semantic Web technologies have also been used in the definition of guidelines specification formalisms [68]. Furthermore, their use has been very significant in semantic data integration where ontologies are used to represent the global schema to mediate across heterogeneous data sources. Finally, some works have used them to develop mapping frameworks from fine-grained VMR to generate abstractions that the decision algorithms can consume [22].

Knowledge Management

Another aspect often omitted but of paramount importance for CDSS is knowledge management (KM). An appropriate framework for the elicitation, maintenance and deployment of CDS artifacts is needed. Rocha et al. [29] define how such a framework should be organized. Recently the HL7 standard for Knowledge Artifacts has defined a complete set of properties for KM of CDS artifacts and it has harmonized existing mapping and VMR models [69]. Part of KM is the process for knowledge elicitation where tools such as Natural Language Processing (NLP) or machine learning predictive models from Cognitive Computing may be supportive [20,21].

Patient-computer interaction

The former paragraphs have described the elements described for the interoperability of CDSS concerning data processing and semantic enrichment in CDSS. However, when data come from subjective measures provided by a patient through an interface (e.g. symptoms or pain description), the CDSS perceptual model needs to provide the human-computer interaction mechanisms that guide the patient in recording health data (cloud in Figure 2). The usability of CDS patient interfaces is a relatively unexplored area. Davis and Jiang used a mixed method where they combined objective measurements[4] such as errors rates and time for completion, with subjective measures from usability questionnaires to capture the patient usability perception [70]. Lai et al. combined usability heuristics and think-aloud for testing user interfaces for chronic patients [71].

[4] It is important to differentiate between measurements of health data and measurements of usability tests. Here the text refers to the objective/subjective measuremetns of data that result from a usability test (e.g. eye tracking, TAM, heuristics etc.). However, in chapter 6 the text will refer to objective/subjective measurements about patient health data (e.g. a glucose measurement, symptom reporting etc.).

Privacy and security

Although it is not a central topic in this dissertation, one must be aware that in any CDS intervention providing the appropriate security and privacy preserving framework is a must. Privacy and security are transversal to each of the models that manage patients´ data. Currently the threat to privacy and security is constant [72]. Security is often treated at a software and network level as a vertical layer that crosses other application layers (user, service, business, persistence etc.) [73]. Depending on the scenario of application, security and privacy can be managed in different ways. For example, Dixon et al. describe the communication and legal framework that were established to share patient data from the organization where the patient is treated to the organization where the CDS service was available [14,74]. As recommended by the Health Insurance Portability and Accountability Act (HIPAA), in their deployment the patient data shared across organizations was a subset that did not contain sensitive information such as patient name, EHR number or date of birth. Communications were secured by using Secure Socket Layer and encrypted HTTP. The CDSS was placed in a secure environment at the organization providing CDS. A different context appears when the information is not provided by an EHR or enterprise system, but it is provided by a sensor or submitted by a patient directly into a website or app. Mobiguide dealt with that problem by projecting chunks of guidelines in the patients cell phone [75,76]. Therefore, the decision algorithm rather than the patient information was transmitted, thus overcoming security and privacy issues.

2.2. General overview

Figure 3 provides an overview of the different studies covering the interoperability and KM of CDSS and how they fit in the decision, perceptual and semantic models introduced in chapter 1. In the intersection of the three models lays the combination of SOA principles with CIMs to express VMRs that are annotated with standard terminologies. SOA provides the execution architecture that can serve many clients while CIMs establish the structure of the information inside messages exchanged that is semantically described by their annotation with terminologies. Those messages may come from several sources including the EHR, the patient or other sources.

Irrespective of the CDSS architecture, perception, semantics and CDS artifacts governance are needed. This makes the three computational models presented common across implementations. For example, both the work of Dixon et al. and Mobiguide used HL7 CDA and vMR respectively to represent clinical information; medical terminologies to provide semantics and both needed CDS algorithms development frameworks. Nevertheless, one must note that although data perception, patient communication and semantics may be present, the technical infrastructure to support them may vary significantly as the examples of Dixon et al. and Mobiguide show.

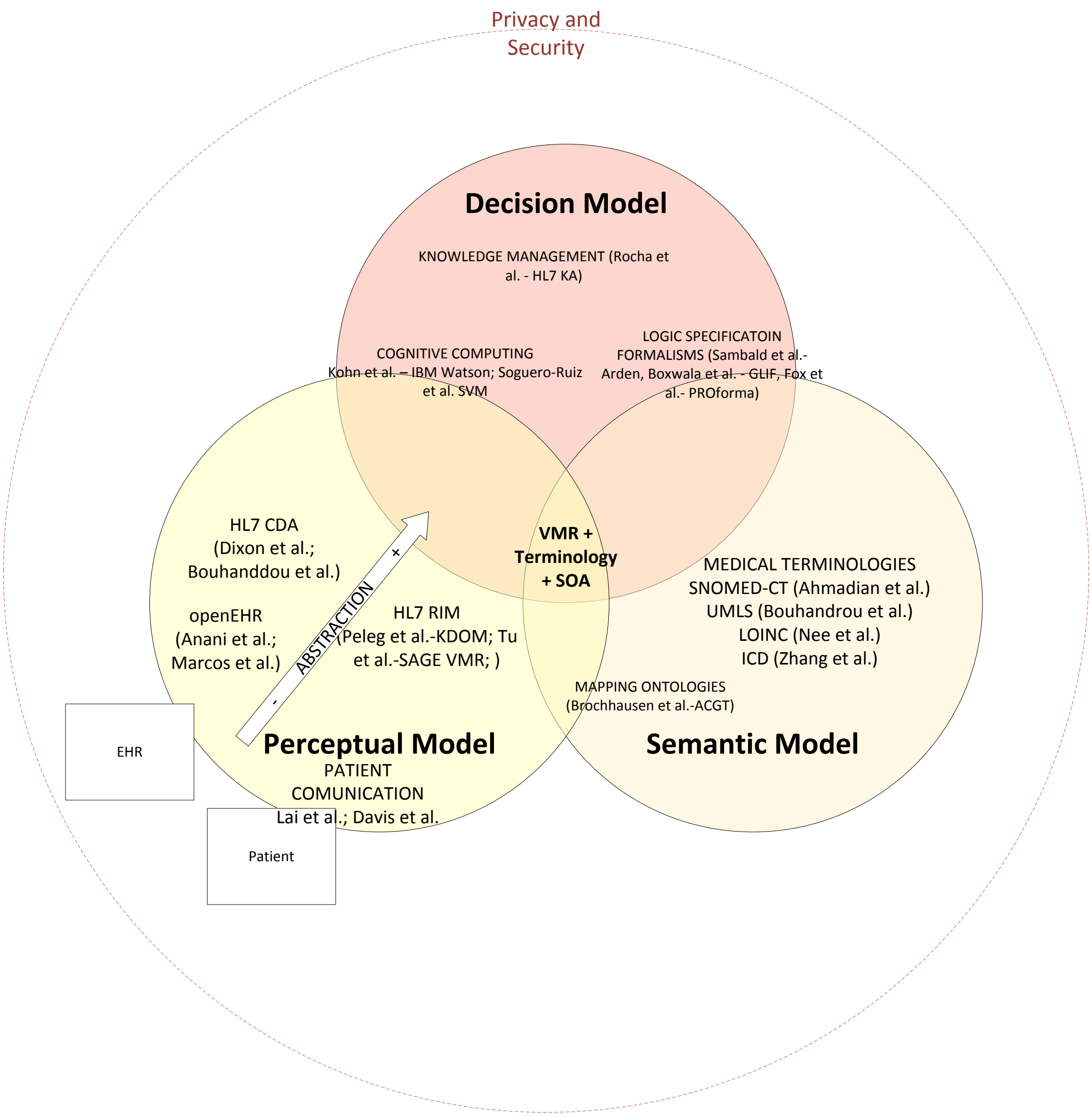

Figure 3. Approaches for interoperability and KM in relation with Semantic, Perceptual and Decision models.

2.3. Context: The Learning Healthcare System in Norway

CDS implementation is considered as one of the milestones to reach in national e-Health infrastructures after the adoption of clinical information standards [77]. Nowadays openEHR and ISO 13606 are the two archetype-based standards. OpenEHR has been exploited in several countries and projects for clinical modeling. In Australia, NEHTA maintains a complete set of clinical models based on openEHR [78]. The UK and Slovenia count on instances of the openEHR CKM to define clinical models [79,80]. In Norway, openEHR is currently the standard adopted by 3 out of 4 health regions, covering 82% of the hospital´s EHR market share [81]. From 2012 several projects have been evaluating and implementing the new openEHR-based EHR [81]. First stages in its adoption were marked by overlapping activities in clinical modeling and software implementation that resulted in uncertainty and a lack of archetypes to drive the development of the EHR [81]. Nevertheless, in the last two years, original problems have been overcome by accelerating the publication of archetypes thanks to the joint venture between the National ICT board, responsible for archetypes development, and the international openEHR CKM [82]. As a result the number of published[5] archetypes has increased from one in 2014 to 47 in 2016. The current set of published archetypes provides the core of the data structures to define the EHR content. Additionally, at the moment of writing, there are other 173 archetypes in draft or review status that cover more specialized contents.

Besides clinical models development, Norway is currently involved in several initiatives to unify all the information related to each patient [83], to allow patient-centered medicine [84,85], to enable data secondary use [84], and to elicit and evaluate clinical guidelines [86,87]. In addition, several research projects are working towards establishing the symbiosis between the clinical view and patient preferences to enable shared decision making [88,89]. Altogether those projects and initiatives are gradually moving Norway towards a LHS. In order to provide the tooling necessary to accomplish those objectives, in particular rapid knowledge assimilation in the form of CDSS, the experience and modeling in clinical data provided by archetypes can provide the basis for making the decision model, the perceptual model and the semantic model interact, thus enabling CDS.

2.4. Gaps

Although the role of CIMs in organizing EHRs content is well established, that is not the case in the CDSS field. On the data side, several studies [14,23,25,54,65] and standards [51,53,66,90] are defining how CIMs can be leveraged with other mechanisms of interoperability to solve some of the CDS communication barriers. However, despite the advances in information specification that CIMs annotated with standard terminologies have provided, there are still strong barriers when sharing CDSS across organizations [14,65]. When other than the clinical data dimensions are explored, the situation is even more challenging. In the LHS context, the decision model includes many data streams

[5] A published archetype is a CIM that has gone satisfactorily through all the stages established in order to be accepted as a generic model at a national level.

from different actors and sources: knowledge engineers, domain experts, CDS developers, data from the EHR, from the patient etc. that need to be specified. Relating them to the computational models previously presented, several research gaps can be identified:

Data perception model: In order to prepare data to be exploited by the decision model, the data perception model must explore and gather data from heterogeneous sources. Data gathered from displays, sensors and physical objective measures has been treated elsewhere using ontologies such as the W3C Semantic Sensor Network ontology [91] that enables interoperability among sensors for the Internet of Things (IoT) [37]. However, in the LHS context, the main sources of data that contain most of the information needed in patient centered medicine are contained in the EHR [11] or are provided by the patient as subjective information about their condition[1,2]. Regarding CDS access to EHR data, several studies have proposed different methods to map and abstract data from the EHR to the CDS. Saez et al. [92] proposed a pragmatic approach to map CDA documents to Jess rules, but did not performed abstraction. Marcos et al. [23] used layers of archetypes where the first layer was mapped to the EHR and the others gradually increased the level of abstraction by using transformation functions to map one layer to the layer above. Peleg et al. [22] proposed a mapping ontology able to automatically generate SQL queries over the HL7-RIM based VMR in order to create abstractions consumed by clinical guidelines. CDS abstractions mechanisms typically focus on vertical operators [42] (used by the abstractions mechanisms represented in Figure 2) and they are often dependent on one persistence technology (e.g. XML, SQL etc.). Thus, if the underlying persistence technology changes, the abstraction mechanisms will have to be re-implemented. Besides defining abstractions, data extraction mechanisms need to deal with the problem of integrating the VMR with the local EHR model which may be represented with a different set of CIMs or, even worse, in a different standard or with no standard at all. However, data is in many cases stored in distributed data sources that have different access policies. Horizontal operators (used by the integration mechanisms represented in Figure 2) that integrate these data sources are also necessary. Often data integration techniques are more mature in the field of secondary use of data for research. These techniques often rely on Data Warehousing techniques that provide robust horizontal operators [42] to integrate heterogeneous data sources. Nevertheless, they usually do not support clinical information standards and they are dependent on a particular persistence technology. In the LHS environment, where decision models are under continuous evolution, methods that take the best of both approaches (CDS and Data Warehousing) are needed in order to rapidly assimilate data for new decision models. This introduces the need to provide architectures supporting more powerful horizontal operators and abstraction mechanisms (vertical operators) based on clinical information standards to guarantee technology independence **(GAP 1)**.

Semantic model: Standards such as HL7 CDS Service IG [66] have provided architectures that leverage Web services with the use of CIMs and terminologies. However, although terminologies linked to CIMs provide some semantics in the form of a code that has an external definition, these semantics are not contextualized in the application domain within the CIM. Thus, the CDSS service interface and CIMs provide a syntactical description where relationships among CIM elements cannot be formally explored. This disallows to evaluate if two concepts are equivalent, if one is a specialization of another, or if one concept is defined by constraining others (union, intersection etc.). As a consequence of these limitations, barriers in enabling Semantic Interoperability (SIOp) with CIMs annotated with terminologies have been detected when sharing CDSS functionality across organizational boundaries [14]. In order to share CDSS across EHRs, the relationships among concepts need to be not only human readable but also machine computable [34]. In addition, these issues are not only limited to data models. As it was discussed before, the decision model requires the interaction of knowledge engineers, data modelers, domain experts etc. Therefore accurate specifications to indicate the version of the system, the institution issuing it, the maintenance responsible, the evidence it is based upon etc. are needed. The semantic model must provide the framework to unambiguously specify functionality, KM metadata and CIMs in order to reliably locate, understand, and invoke decision models **(GAP 2)**.

Human-computer perceptual model: Another important source of data in LHS is the patient. Previous projects [93–96] have provided insights into how to collect data for CDS from the patients using mobile platforms. Nevertheless these projects retrieve physical objective measures that can be gathered with sensors or mobile displays. This is useful to follow-up some diseases but other information crucial for medical decision making is actually subjective and expressed by the patient during consultations. The rise of importance of the patient in decision-making involves patients registering data about their health condition. For patients to effectively record their health conditions, they need to understand and interpret their symptoms and signs and report them through a user interface that will be the entry point to the perceptual model. However, record that information with the level of detail required to be used for CDS inference engines can be very challenging for patients. In fact, how patients understand health information or characterize their condition in comparison with clinicians is unclear [2,97]. The challenge is therefore to evaluate complex interfaces ensuring that users understand what the system is asking to allow them effectively registering their health data. **(GAP3)**.

2.5. Contributions

Enabling CDS in the LHS involves major legal, political, organizational, privacy and technical challenges. This dissertation tackles some of the challenges in the technical dimension. In particular, this thesis aims to provide a technical framework where national developments for standardization can be exploited together with semantic web and human-computer interaction developments to enable CDSS in the LHS context. The main contributions of this thesis are:

1) An archetype-based DW methodology to build a data integration and abstraction pipeline that allows: a) to deal with heterogeneous data sources; and b) to enable the definition of technology-independent abstractions using the AQL [98,99]. This contribution aims to cover the first research gap presented **(Contribution 1).**

2) A method to drive the definition of CDSS metadata with unambiguous machine-interpretable semantics using the common body of knowledge provided by the Linking Open Data Cloud. This grants unambiguous definitions of CDSS functionality, data interfaces and KM properties. These descriptions allow to discover and analyze systems using formal models to overcome current CDS SIOp limitations [14,65]. This contribution aims to cover the second research gap presented **(Contribution 2).**

3) A method to measure the user technology acceptance and usability of the CDS patient interfaces, thus identifying barriers in the patient-CDS interaction. This contribution aims to cover the third research gap presented **(Contribution 3)**.

3. Conceptual Framework for CDS

Summary: The previous chapter presented a selective literature review and introduced the research gaps that this thesis aims to cover. This chapter presents a conceptual framework of the different models that are involved in the Learning Healthcare System context to enable CDS. This chapter builds on previous conceptual frameworks to define CDS generic models that contextualize the technical developments presented in the following chapters.

In the previous chapter I have presented a literature review of the available technologies to implement the components and application layers needed to enable CDS interventions. I have briefly introduced three main computational models namely perceptual, semantic and decision model. The perceptual model unfolds into two main functionalities: a) data binding (integration and abstraction) between heterogeneous sources and the decision algorithm; and b) data capture from patients ensuring completeness and HCI barriers detection. The semantic model aims to describe unambiguously CDSS functionality, KM and data properties to enable their discovery, analysis and interoperability. The decision model frames the mechanisms and actors that elicit new knowledge and implement it as decision algorithms.

This chapter presents a theoretical framework to understand how the models proposed interact to enable CDS. This framework will help to understand the relationship among the different technical developments explained in following chapters.

3.1. Previous conceptual frameworks for CDS

One of the first works documenting at a high level the different models interacting to produce CDS outcomes was presented by Rector and colleagues in 2001 [35,36]. In their works they analyzed the interfaces between different models that interact in medical information systems [35,36]. Figure 4 shows the models identified by Rector et al. namely the information model, the inference model and the concept model [35]. The information model represents the information structures in the EHR. That information can be specified using information standards such as openEHR or HL7 CDA that represent EHR content as CIMs [55]. The inference model represents logic and statistical models used by CDSS that exploit contextualized data from the EHR to produce an outcome that supports decision-making. The concept model represents the terminologies and ontologies that provide semantics to the entities referenced by medical logic or the EHR. The interface of the information model and the inference model represents the connection of the EHR with the decision algorithm through data views. The interface between the concept model and the information model represents the annotation of information structures with biomedical terminologies. The interfaces between the concept model and the inference model represent the conceptual entities that are used to identify the data structures referenced by the decision algorithms.

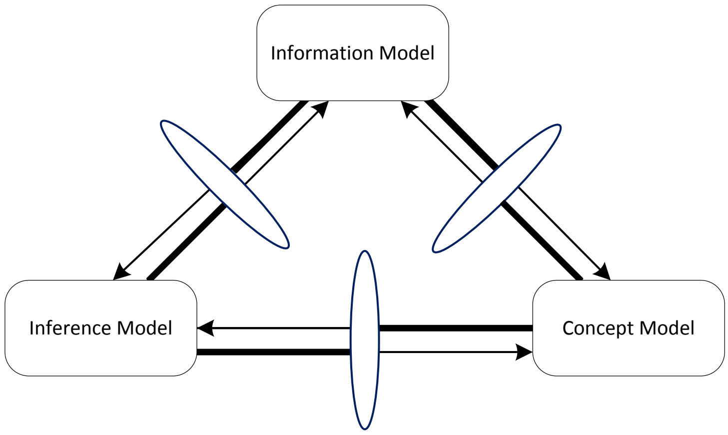

Figure 4. Interfaces between information, terminology and inference models from Rector et al [35,36].

Rector's model comprehends the three main enterprise models involved in the production of CDS outcomes in EHR centric health information architectures. These models are constant in most large CDS deployments. The LHS relies in a seamless integration of those models to produce knowledge and accelerate its use in clinical practice. However, the LHS also introduces a more holistic view that requires the consideration of other actors and systems that need to be involved to produce CDS outcomes. As explained in previous chapters, communication channels with the patient need to be established, and semantics need to go beyond biomedical ontologies to cover contextual properties of the system such as the author, the institution issuing it etc.

Recently, another conceptual framework that includes some of these characteristics has been proposed from the IoT perspective by Sheth and colleagues [37,38]. Their framework proposes the distinction of three computational paradigms namely Semantic Computing, Cognitive Computing and Perceptual Computing. These paradigms interact towards enabling human-centric computing by processing and analyzing large amounts of heterogeneous data to support decision making [37,38]. This separation can be very useful for the CDS arena since it allows isolating the different computation models that interact when CDS is provided in the LHS context.

In Sheth´s model, Semantic Computing provides mechanisms to identify entities and abstractions from Perceptual Computing. Perceptual Computing iteratively explores the cyber, social and physical domain [42] to gather observations that are used to generate abstractions. Cognitive Computing helps to process and analyze large amounts of multimodal data useful for decision-making.

An example of Semantic Computing is the use of ontologies to attach semantics by linking an entity of a data model to a medical terminology (e.g. laboratory tests coded with LOINC). An example of how Perceptual Computing works is presented in Sheth et al.´s work [37,38]. There, Perceptual Computing explores the EHR iteratively locating the topic of interest and contextualizing it so it can be used in decision-making. For example, they exemplify how raw data related to an asthma patient can be gathered from sensors and the EHR to infer concepts useful for decision making such as disturbed sleep, low activity, night cough etc. [38]. Cognitive Computing provides the algorithms to analyze complex data and discover knowledge hidden by complex relations, correlations and high number of variables. An example of Cognitive Computing is provided by Soguero et al. that use machine-learning techniques to analyze data from surgery patients to predict anastomosis leakage [20].

Although those models fit with the IoT vision, the Cognitive Computing role is not so clearly defined. For Cognitive Computing, Sheth envisions the use of NLP of scientific literature to provide evidence to the clinician and states that advanced statistical models could be used to analyze complex data sets and derive knowledge from them. Although in essence this is correct, from a functional point of view, the clinician would hardly ever perform that exploration during consultations provided that average times per consultation go from 11 to 21 minutes [100–102]. Typically the process of knowledge elicitation is performed by multidisciplinary teams of clinicians and knowledge engineers that distill it from scientific literature and national guidelines [29]. That knowledge is then implemented in the form of a CDS artifact deployed in an integration architecture [103] that seamlessly integrates it with the EHR so it can be exploited at the bedside. This way, CDS can be rapidly delivered in the appropriate context and time with a minimum interference with the physician, which is a key factor for its success [12].

Gutierrez-García and López-Neri performed a review on the different approaches to Cognitive Computing [104]. Among the definitions presented, the one of Clark is the closest to the application of Cognitive Computing in CDS: "One of the central tenets of cognitive computing is that there exist suitable ways to abstract detailed behavior, and to talk about goals, plans, constraints and methods at a high level"[105]. DARPA also provides a vision more centered in the requirements defining a cognitive system as one that is able to "reason, use represented knowledge, learn from experience, accumulate knowledge, explain itself, accept direction, be aware of its own behavior and capabilities as well as respond in a robust manner to surprises"[106]. DARPA´s vision is also followed by Sheth [37]. When looked as a whole, the complete framework that allows the elicitation and deployment of CDS artifacts behaves similarly to a cognitive system since it uses represented knowledge (e.g. ontologies), learns from experience (is maintained and monitored), is context aware [31,94] and allows to specify goals and plans at a high level [107]. However, in CDS deployment frameworks, intelligence emerges not directly from a machine learning algorithms, but also from the interaction among different human agents and their symbiosis with technologies [108]. Therefore, if the definition of Sheth for this model is generalized to include all the actors and components of such frameworks, Cognitive Computing may fit in this paradigm. But even so, in the Cognitive Computing milieu there is not a clear consensus over what Cognitive Computing encompasses. Several alternative definitions can be found, sometimes related to machine learning algorithms, and other times related to hardware architectures emulating the brain cellular physiology [104]. For the sake of clarity, this dissertation will identify the CDS algorithm implementation, maintenance and deployment framework with the broader term *Decision Model*. Additionally, since models are proposed to realize those computation paradigms, I will use the terms *Semantic Model*, *Perceptual Model* and *Decision Model* to refer to them. A constrained definition of those models elaborating the ideas originally proposed by Sheth et al. [37,38] and Rector et al. [35,36] from a LHS point of view follows.

3.2. Proposed conceptual framework

3.2.1. Decision model

The decision model encompasses all mechanisms and actors involved in the elicitation and management of medical knowledge for enabling the deployment and evolution of one or more CDS algorithms. These algorithms may be based on different methods such as logic, Bayesian etc. The decision model includes many processes and roles such as knowledge engineers, knowledge modelers, terminology specialists, developers and tooling supporting them[29,103]. Part of that tooling can be provided by Cognitive Computing in the way described by Sheth, thus augmenting the cognitive capabilities of domain experts by helping them to explore scientific literature and extract new clinical knowledge. Another use of Cognitive Computing can be to provide advanced cognitive algorithms in the core of the inference model when Bayesian models are needed, for example, to make complex classifications or predictions. Examples regarding the use of cognitive algorithms can be found in Soguero et al. [20] for prediction of post-surgery complications or in García-Gomez et al. for classification of brain tumors using magnetic resonances [109]. Also the IBM Watson architecture is an example of how many of those algorithms can be applied to support several clinical tasks [21]. One must be aware that although these algorithms provide ways for analyzing complex data sets, all of them need human supervision to be deployed, used and maintained. The decision model must provide a human-centric approach where technology acts as an extension of human cognitive abilities to assist persons in complex decision making tasks [37,110,111].

In the core of a decision model lays one or more inference models that process data abstractions provided by the perceptual model. The result of such process can be a prediction (e.g. stroke risk, survival rates in the next 5 years etc.), an alarm (e.g. possible drug interaction), a classification of the patient into a group (e.g. pre-operative risk), a recommendation for a treatment etc. Those outcomes facilitate decision making tasks by analyzing multimodal data that otherwise would be hard to consider in a timely manner.

3.2.2. Semantic model

Semantics are needed in order to manage and interpret data correctly. The large amount of multimodal data present in today´s information systems need to be formally represented in order to allow its unambiguous interpretation. This is even more appealing in the medical context due to the large amount of hierarchical concepts with subtle differences in their meaning.

The semantic model provides machine-understandable models that unambiguously represent the meaning of the entities involved in generating a CDS outcome. A formal representation of semantics allows for reasoning over concepts and their relationships, inferring new knowledge, establishing equivalences with concepts from other models (e.g. terminology mapping) and keeping track of the transformations performed from a semantic point of view to avoid loss of meaning. The semantic model allows representing concepts and relationships as knowledge models that identify the entities used in the other models in an unambiguous machine-understandable way. For example, ontology models such as the SNOMED-CT concept model allow expressing in formal semantics that a *Prostate cancer* is a subtype of *Primary malignant neoplasm of prostate*; which, in turn, is a type of disorder that is located at the *prostate structure*. This is very useful to unambiguously establish what is the meaning of CDS properties (data entities, KM attributes, functionality etc.) since it is possible to determine if two entities are equivalent, if one is a subtype of the other etc. The semantic model encompasses but it is not limited to biomedical ontologies such as SNOMED-CT. The semantic model must also provide the infrastructure to provide the unambiguous definition of the system properties such as functionality, authorship, conditions of execution etc. The different types of semantics described by the semantic model can be classified in three categories [67,112]:

- Data semantics: describe the semantics of the information that the CDSS accept as input and provides as output. For example, the representation of the semantics contained within archetypes [113] as machine-understandable models.
- Functional semantics: describe the functionality of the CDSS as a taxonomy that allows the annotation of the system specifying both the clinical target task and the clinical domain focus [67]. For example, CDSS for the prevention and screening (clinical target task) focused on pneumococcal infections (clinical focus).
- Non-functional semantics: define the semantics not covered by the previous sections. In most cases they concern the specification of KM properties such as author, issuer, references supporting the implementation etc.

The presented types of semantics allow describing the properties of a CDSS that one needs to evaluate to search the system, analyze it to determine whether it is appropriate for a given context and understand how to interoperate with it.

3.2.3. Perceptual model

The perceptual model concerns all the processes involved in iteratively exploring, capturing and processing data to feed the decision model. It may encompass disparate domains and processes to capture different types of data. In the LHS, the main sources will be the EHR and the patient. When enabling data perception from the EHR (data perception model) it will need to cover access to the EHR data. When data is captured from the patient, it will need to enable proper human-computer interaction mechanisms to allow patients recording accurate data (human-computer perception model). Once captured from one system or another, the perceptual model will exploit clinical information standards to ensure the proper contextualization of the information. When dealing with clinical information, contextual properties that indicate how data was recorded (e.g. arm cuff to record blood pressure), when it was recorded (e.g. last blood pressure measured 3 hours ago), who recorded it (e.g. the nurse) or where it was recorded (e.g. recorded in the emergency department) are paramount. Otherwise it may not be possible to know if that data is useful for decision-making or not.

3.2.3.1. Data perception model

The data perception model, first, uses horizontal operators to integrate heterogeneous sources of data into a canonical data model. Data in the canonical model are then transformed into clinical information standards (e.g. openEHR) to ensure proper contextualization. That model is then used to derive abstractions using vertical operators allowing climbing positions in the Data-Information-Knowledge-Wisdom (DIKW) triangle [42,114]. Adapting the vision in [42], Figure 5 shows how data in the EHR is complemented with background knowledge becoming information, knowledge and finally wisdom that leads to a decision about a treatment. In the example, Blood pressure is interpreted with medical knowledge to infer that there exists a hypertension problem. Hypertension in combination with other data allows the calculation of the CHADS2 score. This score provides knowledge about the risk for stroke in the next year. At the top of the triangle, stroke risk and the knowledge about anticoagulants effect may be used by the decision model to recommend prescribing an anticoagulant drug. Some of the data (e.g. presence of diabetes) may have been inferred in the same way by another iteration of the perceptual model. Therefore, depending on the context an entity may be used as data, information or knowledge. For example, in one iteration, Atrial Fibrillation or Hypertension may be derived as knowledge interpreting electrocardiograms and blood pressure measurements respectively. But in another iteration Hypertension may be used as data to estimate the CHAD2DS2 score (information). The striped area between decision and perceptual models represent algorithms that sometimes derive data that is needed by another algorithm. For example, the rule *If CHADS2>=2 then risk="high"* derives a concept that is used later to recommend treatment (i.e. *if risk=="high" then "Consider treatment with Warfarin"*).

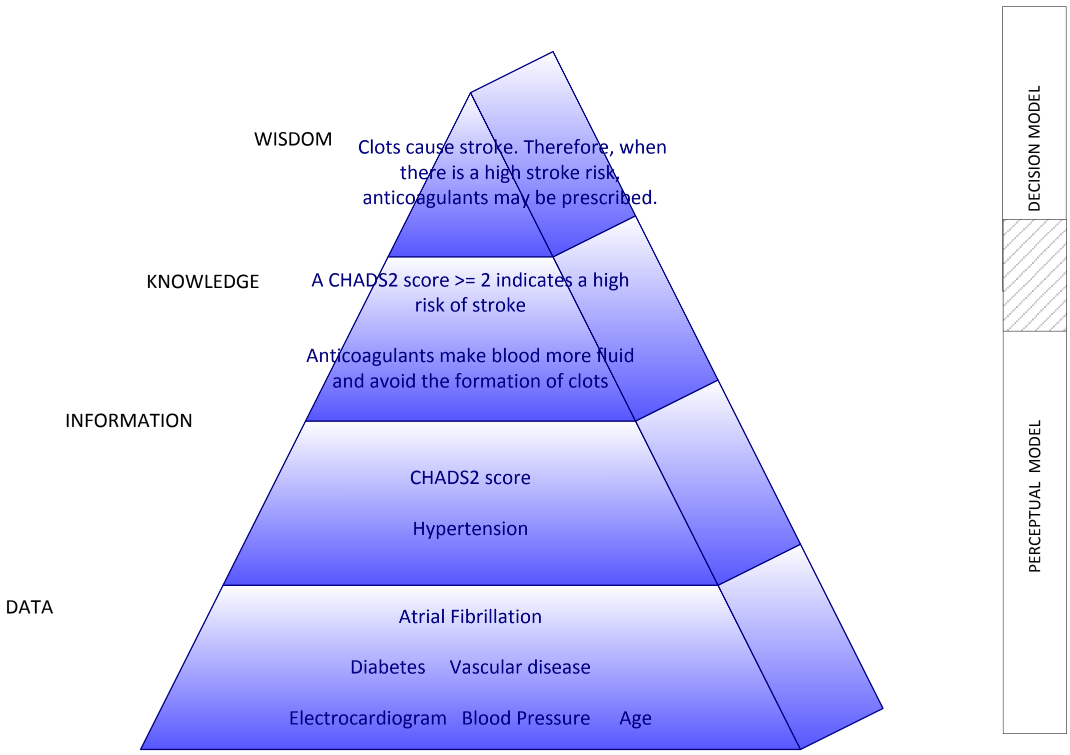

Figure 5. DIKW triangle adapted from Sheth et al. [42].

3.2.3.2. Human-computer perception model

When not only EHR or clinicians reported data is managed, the human-computer perceptual model needs to deal with patients data capture before representing information with clinical information standards and performing the operations presented in the previous example. Recently, several projects have approached this problem at a technical level developing Patient Health Records and web apps to allow patients storing their health data [76,95,115,116]. However, patient provided data does not only include objective measures (e.g. sensors data, blood glucose levels etc.) but also subjective patient observations such as symptoms or pain. In that case, the perceptual model transcends the pure technical dimension and it provides efficient mechanisms to allow the interaction of patients with the decision model, i.e. a human-computer perceptual model. This communication is a cornerstone of the LHS and involves not only technical challenges but also a patient-computer communication challenge. This communication needs to be performed in such a way that the patient understands the information requested by the system. The perceptual model must guarantee the seamless communication of health data between patients and CDSS. Patients must understand the system´s interfaces in order to provide data that is coherent with the expectations of the system. Otherwise the system will not be able to produce accurate outcomes.

This dissertation constrains the perceptual model to the EHR and patient data capture for the reasons explained. However, it is important to note that it is a generic model that may include many other sources coming from the Cyber, Physical and Social spheres [37,42].

3.3. Comparison with previous conceptual frameworks

There are several differences between the model presented and those proposed by Rector et al.[35,36] and Sheth et al.[37,38].

Firstly, the reader must note that abstraction carried out by the perceptual model rather than the semantic model is a difference from Sheth´s paradigm [42,114]. Semantic technologies offer very efficient ways of integrating, transforming and abstracting data. However, if CIMs are fully represented using semantic technologies the resulting model may not be tractable [117] depending on the properties used in its specification. This means that the ontology reasoners that process the model may not be able to finish the computation in polynomial time. Those issues will be explained in detail in Chapter 5. Since CIMs are a central point in interoperability, this forces us to treat information abstraction as a functionality performed by the perceptual model.

Secondly, the IoT vision of perceptual computing includes the Cyber, Physical and Social spheres [42], but it is focused mainly in capturing knowledge from the Web. However the model presented in this dissertation puts the focus on including EHR standards and capturing patient´s subjective measures that need human-computer communication [38]. This is a difference in Perceptual Computing when looked from the LHS perspective rather than from the IoT perspective. The communication with patients, and the study on how it should be performed become crucial to success in including them as active participants in decision-making.

Thirdly, the differences between the model proposed and Rector et al.´s framework are mainly a matter of perspective. While their framework presents three models constant across enterprise architectures, the one proposed in this dissertation presents them from a more holistic perspective considering the interaction with other actors and components. The perceptual model in order to contextualize data by means of information standards uses the information model of Rector et al. Nevertheless, the EHR rather than being the central source of information, it remains as one of the many possible sources. The concept model proposed by rector occupies the central core of the semantic model presented. However, it is not considered only a model of meaning to attach clinical semantics to data structures. Rather, its realization as semantic model acts as an application layer that merges biomedical ontologies with other types of ontologies and technologies to describe data, functional and non-functional semantics. Regarding Rector et al.´s inference model, it lays in the core of the decision model presented. But, as described before, the decision model also concerns knowledge elicitation and management processes.

Figure 6 depicts the decision model, the semantic model, the perceptual model and their overlap. It is important to remark that the processes involved in the communication and evolution of those models are not mere static algorithms, medical ontologies or health records mapped to the other models. These models involve processes that iteratively adapt and develop new decision algorithms, gather data from heterogeneous data sources (EHR, patients, web etc.) and evolve conceptual models including new knowledge from different domains in the form of interlinked ontologies. The perceptual model provides the mechanisms to gather and abstract data from the EHR and patients. The decision model, with an inference model within its core, involves the decision algorithm and the framework to maintain and adapt it allowing learning from previous experiences. The semantic model encompasses a core of the basic biomedical ontologies that can be constrained or augmented to represent more complex entities that index the EHR, patient and inference model entities.

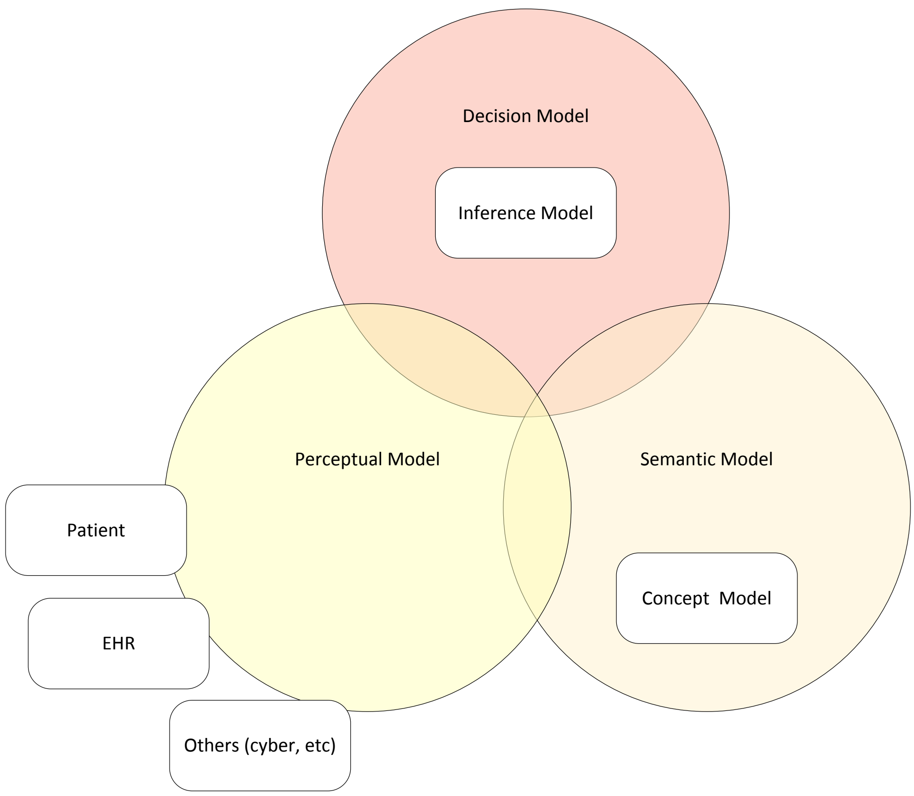

Figure 6. Computational models in CDS.

3.4. Interaction between computational models

As mentioned in chapter 1, healthcare is often seen as a data problem, but it is in fact a communication problem among many systems and actors [2]. CDSS, as a part of the health information infrastructure, are no exception to this. The role of CDSS in learning health needs to effectively communicate and leverage the semantic model, the perceptual model and the decision model to produce outcomes. Therefore their interfaces must be carefully defined and developed with mechanisms that ensure that data is captured, transformed and communicated with minimal loss of meaning and preserving its context. The perceptual model needs to provide mechanisms that allow capturing and processing data coming from EHR and patients to feed inference models. The semantic model must unambiguously represent the metadata and entities produced and consumed by the system, its functionality and its execution requirements to ensure that the system is used in the appropriate context.

There are significant areas of overlap among the three models. For example, the core of the decision model in most cases will encompass a decision algorithm, but the model may overlap in some cases with the perceptual model in areas such as NLP where knowledge can be directly derived at the moment of perception. The interface between CDS and the semantic model will encompass the use of semantic relations by algorithms to identify the entities involved in its execution. The overlap of the perceptual model and the semantic model will contain the annotation of information captured with ontologies and the use of knowledge from these ontologies to derive new abstractions.

Figure 7 shows a minimal example of the interactions between these three models. The figure depicts how the decision model encompasses a group of knowledge engineers, developers and domain specialists that study guidelines and literature to elicit knowledge of respiratory diseases. When the knowledge, data and terms needed have been identified, the team develops and deploys a CDS artifact with one rule. The CDS artifact is designed to recommend performing an X-Ray when a patient has had early morning productive cough. The algorithm (rule) needs 2 abstractions namely *early morning cough* and *productive cough* in order to be able to produce a recommendation. Those entities are not directly available in the EHR/PHR. The perceptual model needs to gather the necessary data to infer them. In first place, the human-computer perceptual model needs to deal with the interaction with clinicians and patients that record data into an EHR or PHR respectively. The human-computer perceptual model needs to enable efficient mechanisms of HCI in order to gather the data regarding symptoms. Different mechanisms can be used for that. To capture data from patients, apps or websites have been used [95,115]. To capture data from clinicians, the EHR deployed in a hospital will offer an appropriate interface [118]. The data perception model stores that data and its contextual metadata using a clinical information standard (e.g. openEHR) to guarantee quality and interoperability. With data represented in a rich and robust format, the data perception model can exploit it to perform abstractions. The data perception model uses the onset and cessation dates of the coughing episodes to infer new abstractions, i.e. *early morning cough*. The data perception model also explores the EHR/PHR and detects the presence of sputum, which, in combination with the presence of cough, is used to infer the abstraction *productive cough*. This way the perceptual model infers the entities that the algorithm can exploit to produce a recommendation. In that framework, the semantic model allows the algorithm to reference standard concepts independently from the information model used by the perceptual model. The algorithm references abstractions through a place-holder that links the entities referenced to a concept provided by a medical terminology and the data entity. This is an approach followed by, for example, openCDS [52] and openEHR GDL [53]. The link of entities used in the algorithm to ontologies provided by the semantic model allows attaching a meaning in a standard terminology. For example, the entity *early morning cough* may be bound to the concept *62618004]Early morning cough* in SNOMED-CT. The same is done when the semantic model provides meaning by tagging data entities and abstractions. For example, in the EHR/PHR, ontologies are used to tag the content of the archetype element onset with *405795006]Time of symptom onset*. The role of the semantic model is paramount since it is the way of identifying every entity at any stage of the abstraction process. Therefore, it allows defining the semantics of the interface between the decision model and the perceptual model. The semantic model does not only serve data entities identification, but also can help in providing standard ontologies for KM indexing the metadata needed in the CDS artifact development process. Metadata ontologies such as the Dublin Core can be used to express the KM data of a CDS artifact. For example, the properties dc:creator, dcterms:hasversion, dcterms:bibliographiccitation may be used to indicate the author, the version and the literature that supports the development of a CDS artifact.

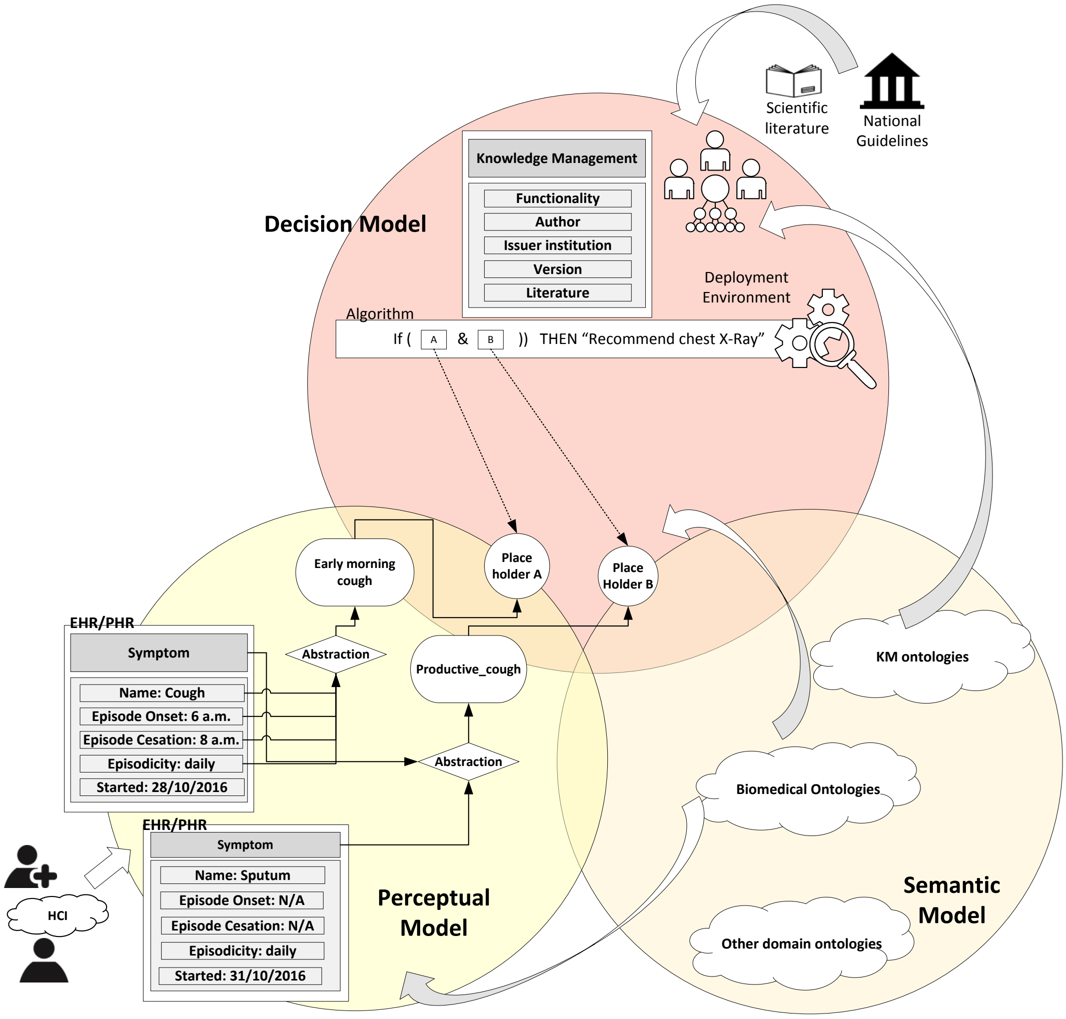

Figure 7. Interaction of computational models.

3.5. The symptom checker *er du syk*

At the moment, most symptom checkers are in their first generation [119]. This means that their outcomes are recommendations or diagnoses that implement static algorithms that only take into account fix knowledge. Therefore they do not adapt for example to seasonal changes, epidemiology or specific populations.

Er du syk is a symptom checking service for respiratory and gastrointestinal diseases[120]. Since 2012 it has been running in north Norway covering Troms and Finnmark regions. *Er du syk* evolves the first generation of symptom checkers by using a disease query engine [121] that leverages epidemiological data, extracted from Laboratory Information Systems (LIS), with symptoms and demographic information provided by patients. Its outcome is a list of the possible diseases affecting the patient linked to an estimation of the probability of each of them. This allows the patient to make an informed decision on whether to visit or not to visit a GP rather than directly assessing an action.

As presented in previous sections, Norway is involved in several initiatives that together advance towards the LHS. One of these initiatives is the adoption of openEHR as clinical information standard and the evaluation of SNOMED-CT as a reference terminology [122]. These initiatives involve challenges for CDS implementers that concern the adoption of openEHR archetypes for CDS, the adoption of semantic technologies that can exploit SNOMED-CT to describe the system data interfaces, and enable the seamless interaction with patients that need to record clinical information based on archetypes.

When it comes to *er du syk,* this arena brings both challenges and opportunities. Opportunities come from the set of nationally approved archetypes by the national CKM [59] and the advantages in adopting a reference terminology. If CDSS were based on such set of archetypes, the quality of information would be guaranteed since domain experts nationally agree on them. In addition, with the proper use of ontologies with SNOMED-CT as the reference one the interoperability of the system can be granted and its maintenance facilitated [123].

The remaining chapters present the developments to build a perceptual, semantic and human-computer interaction model. The development of a complete decision model will remain out of the scope of this thesis. The reason is that currently, to the best of my knowledge, national frameworks for CDSS artifacts development do not exist in the Norwegian context and, additionally, a perception and semantic model are a precondition for developing such frameworks [13,18,67]. The developments presented in this dissertation are framed by the case study of *er du syk*. Chapter 4 presents the data perception model built to extract, standardize and abstract data from HISs. Chapter 5 presents the semantic model to describe its data, functional and non-functional semantics. Chapter 6 presents the human-computer perceptual model developed to evaluate human-computer interaction when capturing data from patients. Finally, Chapter 7 presents the conclusions and final remarks.

4. Data Perception Model

Summary: The previous chapter introduced the conceptual framework where the decision, perceptual and semantic models interact to produce CDS outcomes. This chapter covers the challenge of data perception. In particular, it presents an openEHR-based architecture to integrate, standardize and abstract data for er du syk. The contribution lays in the combination of different approaches to build a DW environment that provides: a) a robust data integration method to deal with heterogeneous data sources; and b) technology-independent abstraction mechanisms. The contents of the chapter are based on the results of PAPER 1.

4.1. Background

The data perception model is the one that enables the access, integration, transformation and aggregation of data instances so they can be exploited by the decision model. Figure 8 shows the figure already presented in chapter 1 to integrate fine grained data from several data sources and, using background knowledge, define some abstractions that climb positions in the DIKW triangle [37,42]. On the top of the triangle a person (a practitioner or a user in the case of consumer oriented CDS) uses aggregated data to make informed decisions. This way, the data perception model assists decision making by allowing the decision model algorithms to analyze multimodal data that otherwise would not be possible to consider in the decision making process.

Multimodal data perception models have been previously treated by using semantic web technologies to integrate, transform and abstract data [114]. However, as explained in Chapter 2, many of the data constraints specified in clinical models in general, and archetypes in particular, are not fully tractable by today´s ontology reasoners [117]. Therefore, it is adequate to perform data integration and abstraction as part of the perceptual model rather than the semantic model.

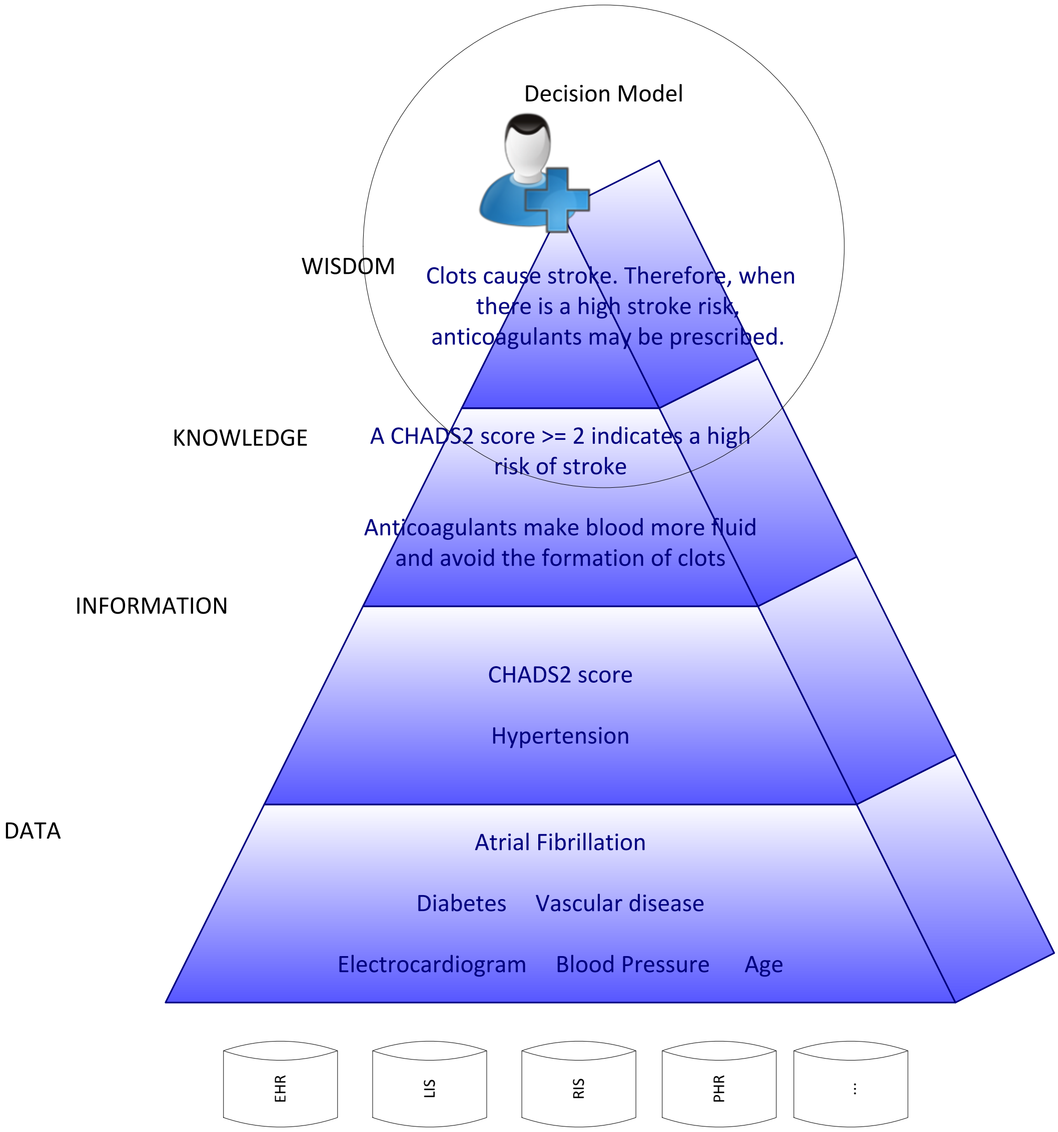

Figure 8. Abstraction in data perception for CDS adapted from [42].

4.1.1. Data perception operators

There are two types of operators involved in the data perception model [42]: horizontal and vertical.

From the clinical data point of view, horizontal operators allow to integrate data from heterogeneous HIS (LIS, EHR, RIS etc.) into an integrated standard view. This ensures that the information will be represented retaining its context and with a maximum level of completeness by means of a clinical information standard (openEHR archetypes in this thesis). An example of horizontal operator functionality is the integration and standardization into an openEHR-based EHR of data from two different sources, for example, a Radiology Information System (RIS) and a LIS each with a proprietary data model.

Vertical operators provide the mechanisms necessary to transform granular data contained in a HIS (e.g. EHR) to generate the abstractions exploited by the decision model. For example, a vertical operator may infer from a white cell count with value $15x10^9$/L a moderate leukocytosis. In this case, the vertical operator exploits clinical knowledge that allows for interpreting a white cell count in the range [$11x10^9$, $17x10^9$]/L as the abstract concept "moderate leukocytosis present".

4.1.1.1. Horizontal operators

One of the first documented approaches to develop decision models detached from the EHR was the Arden syntax [124]. The Arden syntax defined the concept of Medical Logic Modules as CDS artifacts that encapsulated logic decision rules. MLMs allowed embedding SQL statements inside its data section to retrieve data from the EHR. In order to access data in the EHR it allowed embedding database queries between curly braces inside the MLM data section. This direct reference to the EHR database led to the "curly braces problem". This problem can be explained as the need to adapt the data access sections when moving the system among different production environments. Aiming to relief the dependency from the original DB schema, CDS researchers proposed the use of VMRs [125,126]. Among the different approaches to map the EHR schema to the VMR, there are some differences in the way mappings are developed. Some studies define DB views from relational or other types of databases directly with some data manipulation language. For example, Peleg et al. used database views to define a RIM based VMR[22]. Boeaz and Shahar used a wrapping interface that mapped terminologies, units and data schemas to the common VMR using different languages depending on the DB model of the database to be queried (e.g. SQL for relational, XPath for XML etc.)[24]. In Mobiguide a view was also created using SQL and DB scripts [25]. Other studies rely in some sort of mapping languages that are later translated automatically to queries. For example, Sujansky and Altman proposed the Extended Relational Algebra (ERA) to define mappings between a global canonical schema and each data source [127]. A more recent example of this approach is the proposed by Marcos et al. that defines declarative mappings with the LinkEHR tool that are translated to XQuery expressions that transform EHR instances into an openEHR VMR [23].

4.1.1.2. Vertical operators

Many of the frameworks presented in the previous section also provide vertical operators to abstract data. Several options have been considered. Some frameworks for data integration and normalization allow the definition of mappings to generate abstractions. Marcos et al. [23] relied on archetypes and the LinkEHR tool to generate an

EHR view. LinkEHR was originally designed for standardizing clinical data. For that purpose, it provides a complete set of transformation functions. However, in CDSS scenarios, these functions may not suffice to generate the abstractions consumed by the decision model. To overcome this challenge, Marcos et al. propose defining additional layers of archetypes that gradually increase the level of abstraction, thus chaining small transformations between layers until the desired abstract concept is generated. Other abstraction frameworks are based on mapping ontologies such as Peleg et al.[22] and Henson et al. [114]. In the case of Peleg et al., the mapping ontology (KDOM) instances are translated automatically to SQL queries executed against a RIM-based VMR. KDOM was also used to abstract data in Mobiguide [25]. Boeaz and Shahar explored advanced deductive reasoning to interpret which abstraction must be inferred [24]. It is important to note that these approaches are not standard in the sense that they have not been agreed and adopted by a community of implementers. Currently, to the authors knowledge, the only existing standards to define constraints for abstracting data are openEHR GDL[53,54] and its HL7 counter part GELLO [90,128]. Both GDL and GELLO are expression languages that allow defining data constraints over a VMR that may be developed with archetypes, in the case of GDL, or Object Oriented (OO) model in the case of GELLO. GDL defines its own data constraint functions while GELLO relies on the Object Constraint Language (OCL) to specify data constraints in OO models [90].

4.1.2. Advances in data integration and abstraction from Data Warehouses

The approaches presented have provided advances to decouple the CDS artifact from other HIS databases. However, research in abstraction mechanisms has often been centered in providing powerful vertical operators and less focused on providing horizontal operators. Horizontal operators presented are able to integrate a set of EHRs but do not allow to deal with distributed access and privacy policies that may change from one source to another. Most of them rely in database views of scripts to extract data from one database. However they do not define a scalable architecture to access distributed data sources that may have different privacy policies. Moreover, vertical operators have remained in the academic sphere and studies testing their scalability in complex enterprise environments where speed must be guaranteed to ensure CDS effectiveness are scarce [12]. Although these solutions integrate the EHR with the VMR, their application is usually over a limited set of source DBs with limited control over privacy policies.

Another field that has evolved very rapidly in the last decade are the architectures to enable secondary use of clinical data. The developments to enable secondary use of clinical data in areas such as clinical research or public health have provided important advances in the integration and abstraction of data.

It is interesting that the requirements of data management in secondary use environments for research and public health are mostly the same as in CDS. If one thinks of a statistical model for clinical research, it becomes evident that they behave as a decision model. Horizontal operators for secondary use of clinical data are often more powerful since they need to integrate heterogeneous data sources. Therefore, they are designed to deal with data and policy divergences. In the case of vertical operators, they need to be dynamic (e.g. queries rather than static scripts) to allow defining different views from the same data set depending on the scenario.

Most techniques proposed for secondary use of data are inspired by Data Warehousing techniques from the Business Intelligence arena. For example, Danciu et al. [129] present an in-house DW to drive data from clinical notes to inference models for clinical research. The SHARPn consortium adds to this approach by transforming data not only in structured proprietary formats but in CEM compliant extracts allowing to query data using the HL7 Health Quality Measure Format [28]. DW4CR develops a powerful ontological framework to integrate data from existing ontologies used in research, terminologies and data models [130]. The data model is based on HL7 RIM.

A platform being widely adopted for data reuse is Informatics for Integrating Biology and the Bedside (i2b2). I2b2 is a framework to enable data warehousing for clinical research [131]. It provides tooling for NLP, genomic information management and ontology management, among others. Its persistence model is based on a relational data model based in the Star Schema proposed by Kimball et al. [132]. Its open source license is accelerating its adoption across many organizations worldwide.

In the Norwegian scenario, the SNOW system has provided an architecture to enable the distributed access to heterogeneous data sources that may have different policies [133]. SNOW has been used for epidemiology control monitoring the evolution of gastrointestinal and respiratory diseases [134]. In parallel, the adoption of openEHR in Norway has provided a full set of published archetypes. These archetypes can be exploited to drive the definition of data perception models with the appropriate use of technology. This requires leveraging different openEHR tooling to build an archetype-based DW environment.

Conveniently, most of the tooling needed to design an architecture that realizes an openEHR data perception model already exists. For example, the SNOW system abilities to access distributed health databases complying with their privacy policies can be used as horizontal operator to define an integrated view of data. That view can be transformed into openEHR valid instances using the mapping abilities of LinkEHR to map non-standard data views to archetypes as Marcos et al. [23] did in their first data integration layer. Once data is in openEHR compliant format, an openEHR DB such as ThinkEHR [135] can be used to enable transactional control over data and perform queries over the standard model using AQL as vertical operator to abstract data [98,99].

The objective of this chapter is to present a data perception infrastructure by building on previous research. This chapter describes the architecture developed to combine them into an openEHR DW environment for data integration and abstraction. The following of the paper presents the results PAPER 1 [26].

4.2. Methods

Most of the technologies that could provide the benefits of both CDS abstraction mechanisms and DW techniques are available. However, they have not been combined in an architecture that allows exploiting all their potential as an integrated solution. This chapter proposes an architecture where each technology is used to execute the task it performs optimally. Specifically, a data perception model is presented by combining the developments performed in openEHR into an archetype-based DW environment. The methodology starts by extracting data in health databases and integrating it into a common data view. Later, this data is transformed into openEHR compliant extracts and loaded into an openEHR database. Over this database, AQL [98,99] can be used to aggregate data raising the level of abstraction to invoke the service.

To build the DW environment for data perception, this chapter proposes a micro services architecture that divides into stages the different operations that need to be performed in order to prepare data for an inference model. The different stages are integrated by a RESTful services architecture that chains the output of one stage with the input of the next one. For data access and integration the architecture relies on the SNOW system that acts as horizontal operator to define a canonical integrated data view[133,134]. For transforming data into openEHR archetypes-compliant instances, the architecture relies on the transformation operators that LinkEHR provides. Finally, for persistence and abstraction the architecture relies on the openEHR persistence platform ThinkEHR to enable querying standardized data with AQL. The architecture aims for providing a methodological framework to define an archetype-based DW that enables CDS data perception in openEHR environments.

The scenario where the openEHR DW environment has been verified is the extraction of LIS extracts to feed the symptom checker *er du syk. Er du syk* uses a combination of laboratory data about test results of infectious diseases and symptoms provided by the patient to estimate the likelihood of the diseases that may be affecting the patient. LIS data is used to perform counts of the positive tests in a given time range to estimate the incidence of diseases per geographical areas.

4.3. Results

The design of openEHR clinical DW environments for data perception involves a challenge related to the use of archetypes. Often, industrial DW environments divide data processing into 3 stages named[132]: Extract, Transform and Load. In addition, DW usually store data in the form of OLAP cubes to enable the secondary use of data for decision making [132]. However, in the case of openEHR, clinical data is represented using the openEHR RM and archetypes to specify the information schema. This involves the need of relying on existing archetypes to maximize interoperability. Thus, the proposal to implement a data perception model as an openEHR DW adds an additional stage to encompass the activities related to archetypes modeling [26]. This leads to four stages: Model, Extract, Transform and Load.

4.3.1. Model

Model concerns the identification of existing archetypes or modeling of new ones to drive the standardization of data into openEHR [123]. These archetypes will be used to specify the information schema of the DW that will be referenced by queries in the abstraction process. By referencing openEHR archetypes rather than proprietary DB schemas, the dependencies on proprietary formats are eliminated.

In order to maximize the level of interoperability, national repositories such as the Norwegian CKM[59], or international repositories such as the International CKM [136], should be checked identifying the most adequate archetypes to use on each scenario. The archetypes identified to cover each data perception use case should be combined in an openEHR template defining the final structure of the DW information schema. In the case of *er du syk*, the Norwegian and international CKM were checked identifying three archetypes named: lab_test.v1, lab_test_microbiology.v1 and lab_test_microscopic_finding.v1.

Provided that archetypes are designed to structure EHRs clinical content, DW infrastructures for integration and abstraction of data may need to perform some modifications on them so they cover the information model requirements. That was actually the case in the case study presented. In *er du syk* demographic data such as that related to the patient requester and patient municipality are needed. Additionally, the way of representing laboratory tests varies since a request may encompass a material, requester and patient with a battery of tests where each test aims to detect an infectious agent. This made it necessary to remodel some sections of the archetypes to fit *er du syk* data needs. When modifications or new archetypes are defined, the process needs to be coordinated with the national CKM. This guarantees their accessibility and appropriate governance [123].

4.3.2. Extract

Extraction is an extremely sensitive stage since in some cases the CDSS may be outside the system where data was originally stored. Therefore, it must be carried out complying with every privacy policy established by data sources. Therefore, depending on the scenario, this stage may need to deal with simple de-identification techniques or, in the most restricting scenario, extract only results of aggregations performed inside the data source. In the architecture for data perception proposed the SNOW system is used to overcome these challenges. SNOW is an agent-based system that works as a peer to peer network to allow distributed computations over different data sources [133,134]. Its distributed nature avoids the need for extracting data to perform computations over it. SNOW integrates with several specific export modules that allow access to data stored in different information systems. An example is the Medrave library that provides an interface to access primary care EHRs. The libraries that SNOW encompasses are used to extract data. After extraction, SNOW presents data as a single integrated schema. That integrated schema can be mapped to openEHR archetypes in the transformation stage.

SNOW provides computation capabilities that can be used as vertical operators. However, the data perception model presented uses SNOW as a horizontal operator to define an integrated canonical view of de-identified data. This way it is possible to exploit its distributed data integration mechanisms. In this architecture abstraction is performed at later stages relying on openEHR. This allows to maximize the number of different abstractions that can be created later using the AQL. Nevertheless, scenarios with higher demands on privacy preservation may decide to apply aggregations before transformation. In those cases, the openEHR view will have some abstraction. Therefore, the amount of different abstractions that will be possible to perform will be more limited. For example, instead extracting fine-grained data at a patient level, if more privacy is required, it is possible to extract data accounting results per patient groups. An adequate trade-off between privacy preservation with aggregation and flexibility of data reuse in several scenarios must be found depending on the privacy requirements of each deployment.

In the case study presented, the canonical view of data was generated using one of the export modules that SNOW implements to extract data from the LIS DB. Then a cache is built and exposed through a RESTful service so it is available on demand for the transformation stage. A sample marshaling of one laboratory result contained in the cache is displayed in Figure 9. That view is a plain representation of the tests in the LIS DBs ready to be mapped to openEHR archetypes defined in the Model stage.


```xml
<microlabresult>
  <id>2350459475284566896</id>
  <registrationDate>2013-02-24T12:56:00+01:00</registrationDate>
  <analysisDate>2013-02-25T15:35:20+01:00</analysisDate>
  <resultSentDate>2013-02-25T15:39:30+01:00</resultSentDate>
  <testRequesterId>68C1C359608B3C5HF3355544DBD9357A9D927EC6</testRequesterId>
  <analysisName>Nasopharynx-Chlamydophila pneumoniae DNA</analysisName>
  <analysisType>VNX-CPP</analysisType>
  <originalTestResult>NEGATIV</originalTestResult>
  <material>Nasopharynx</material>
  <requesterMunicipalityCode>1905</requesterMunicipalityCode>
  <gender>K</gender>
  <patientMunicipalityCode>1902</patientMunicipalityCode>
  <patientId>18E87T6711779EFE0X2V4T717D335A3A0F5422AD</patientId>
  <patientBornYear>1972</patientBornYear>
</microlabresult>
```


Figure 9. Marshaled extract of one laboratory test result in canonical view.

4.3.3. Transform

The transform stage concerns the conversion of the data contained in the integrated view built using SNOW into instances compliant with the openEHR archetypes defined in the model stage. This transformation is carried out by means of the LinkEHR tool. Using LinkEHR, the XML Schema of the canonical model and the openEHR archetype are mapped. Mappings vary in type and purpose. Figure 10 shows some the most representative mappings used to standardize some of the data processed by *er du syk*. The simplest type of mapping regards the transformation of one value into another. For example, the mapping represented by blue arrows and ellipse indicates that when the analysis name in the canonical model is *´Nasopharynx-Chlamydophila pneumoniae DNA´* the node analysis type of the archetype should be set to the value 10652-6 that is the code for identifying that type of test in the LOINC terminology. Other type of mappings are those that infer new values of the archetype nodes that did not exist in the original schema by combining the information of the canonical schema with background domain knowledge. An example of this type of mapping is the mapping represented by green arrows and ellipses. That mapping infers the value of the *symptom group* node by applying the knowledge that VNX-CPP is the code of an infectious agent of the respiratory system that causes respiratory symptoms. Finally, another type of mapping often needed are structural mappings for specifying how data in the plain canonical model must be grouped to comply with the hierarchical structure of the archetype. Figure 10 represents with gray arrows and ellipse the set of attributes that must be used to specify groupings. In particular, the mapping specifies that all single tests with common values of *registration date*, *test requester id*, *material*, and *patient id* must be grouped inside the same tests battery.

Once all mappings have been defined, LinkEHR processes them. The outcome of that processing is an XQuery script. When the script is executed over the canonical model, it performs the transformations specified in the mappings and returns a data instance compliant with the openEHR archetype.

In the DW environment that transformation must be integrated with the other stages. Placing the XQuery script in a REST service allows its execution on demand. Therefore, when the service is invoked for a particular hashed patient id, it processes the canonical view and applies all mappings returning instances corresponding to that patient that comply with the openEHR archetype.

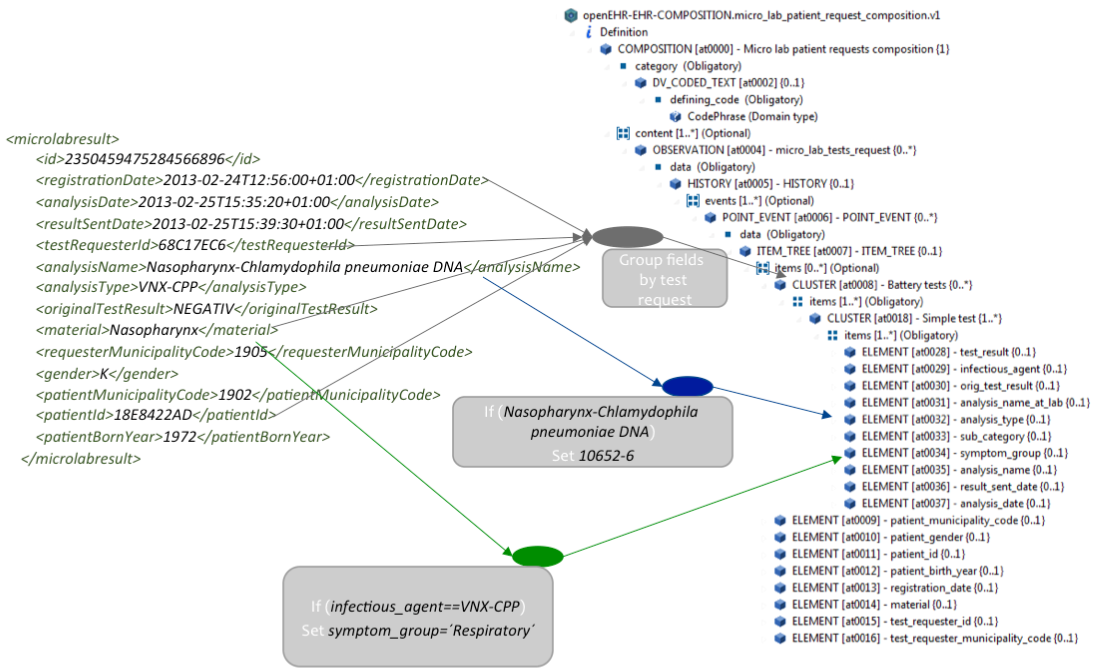

Figure 10. Mapping between the canonical integrated view and the openEHR archetype.

4.3.4. Load

With the transformation service deployed, it is possible to invoke it and get compliant openEHR extracts, thus granting interoperability based on the archetypes defined. However, in order to dynamically query data for defining abstractions, a platform that enables ACID properties and high throughput queries over the openEHR instances is needed. In the architecture proposed, the openEHR persistence platform is used for that purpose. The platform is loaded with openEHR instances by sequentially invoking the transformation service. For each invocation the transformation service returns the openEHR serialization result of transforming the canonical view into openEHR. That extract is then analyzed by the load service to apply some reconciliation in its format and it is submitted to the openEHR persistence platform. After the load stage, the openEHR persistence platform enables: 1) transactional control over openEHR instances; 2) high throughput in queries; 3) independence from the underlying persistence technology. Querying data with AQL enables the later. AQL allows defining queries that reference archetypes rather than a technology dependent persistence schema. For example, if a relational or XML DB is used instead of an openEHR persistence platform, queries will have direct dependencies on the DB technology such as the SQL queries over tables in the case of relational DBs, or XQuery queries in the case of XML DBs. Therefore, if at some point it is decided to migrate to another technology such as NoSQL DB, all the queries will need to be re-implemented. Since many technologies can be used to persist openEHR instances with different performances and capabilities [137] it is appropriate to rely on a persistence core that provides a standard way of querying data (e.g. with AQL). By relying on AQL new technologies can be adopted without affecting the queries used for data aggregation.

Table 1 and Table 2 contain several queries used to estimate diseases incidence and prevalence by er du syk [26].

Table 1. Pertusis monitoring queries.

PERTUSSIS MONITORING	
Count positive tests of Pertussis for the day specified in the parameter (e.g. 2013-01-04)	SELECT count(o1/data[at0001]/events[at0002]/data[at0003]/items[at0022]) - - count (patientId) FROM EHR e CONTAINS COMPOSITION c CONTAINS (OBSERVATION o1[openEHR-EHR-OBSERVATION.micro_lab_test.v1] and OBSERVATION o2[openEHR-EHR-OBSERVATION.micro_lab_test.v1]) WHERE (o1/data[at0001]/events[at0002]/data[at0003]/items[at0010]/items[at0043]/items[at0036]/value='Kikhoste'and o1/data[at0001]/events[at0002]/data[at0003]/items[at0010]/items[at0043]/items[at0037]/value='Positiv') and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value >= '2013-01-04' and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value < '2013-01-05'
Count negative tests of Pertussis for the day specified in the parameter(e.g. 2013-01-04)	SELECT count(o1/data[at0001]/events[at0002]/data[at0003]/items[at0022]) FROM EHR e CONTAINS COMPOSITION c CONTAINS (OBSERVATION o1[openEHR-EHR-OBSERVATION.micro_lab_test.v1] and OBSERVATION o2[openEHR-EHR-OBSERVATION.micro_lab_test.v1]) WHERE (o1/data[at0001]/events[at0002]/data[at0003]/items[at0010]/items[at0043]/items[at0036]/value='Kikhoste'and o1/data[at0001]/events[at0002]/data[at0003]/items[at0010]/items[at0043]/items[at0037]/value='Negativ') and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value >= '2013-01-04' and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value < '2013-01-05'
Total tests of Pertussis (in Norwegian 'Kikhoste') performed for the day specified in the parameter(e.g. 2013-01-04)	SELECT count(o1/data[at0001]/events[at0002]/data[at0003]/items[at0022]) FROM EHR e CONTAINS COMPOSITION c CONTAINS (OBSERVATION o1[openEHR-EHR-OBSERVATION.micro_lab_test.v1] and OBSERVATION o2[openEHR-EHR-OBSERVATION.micro_lab_test.v1]) WHERE (o1/data[at0001]/events[at0002]/data[at0003]/items[at0010]/items[at0043]/items[at0036]/value='Kikhoste') and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value >= '2013-01-04'

	and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value < '2013-01-05'

Table 2. Salmonella monitoring queries.

SALMONELLA MONITORING	
Salmonella cases in the specified municipality (same as patient just confirmed) in the first 2 weeks of January	SELECT count(o1/data[at0001]/events[at0002]/data[at0003]/items[at0022]/value) - - count (patientId) FROM EHR e CONTAINS COMPOSITION c CONTAINS (OBSERVATION o1[openEHR-EHR-OBSERVATION.micro_lab_test.v1] and OBSERVATION o2[openEHR-EHR-OBSERVATION.micro_lab_test.v1]) WHERE (o1/data[at0001]/events[at0002]/data[at0003]/items[at0010]/items[at0043]/items[at0036]/value='Salmonella'and o1/data[at0001]/events[at0002]/data[at0003]/items[at0010]/items[at0043]/items[at0037]/value='Positiv') and o1/data[at0001]/events[at0002]/data[at0003]/items[at0020]/value='1917' and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value >= '2013-01-01' and o1/data[at0001]/events[at0002]/data[at0003]/items[at0024]/value < '2013-01-15'

<table>
<tr><td>Positives in the whole region to plot evolution per day (# abbreviates the path to the CLUSTER)</td><td>SELECT
  count(o1/data[at0001]/events[at0002]/data[at0003]/items[at0022])
FROM EHR e
CONTAINS COMPOSITION c
CONTAINS (
  OBSERVATION o1#micro_lab_test and
  OBSERVATION o2#micro_lab_test)
WHERE
  o1#battery/Simple_test/infectious_agent='Salmonella' and
  o1#battery/Simple_test/test_result='Positiv' and
  o1#registration_date>='2013-01-01' and
  o1#registration_date<'2013-01-15'</td></tr>
<tr><td>Negatives in the whole region to plot evolution per day(# abbreviates the path to the CLUSTER)</td><td>SELECT
  count(o1/data[at0001]/events[at0002]/data[at0003]/items[at0022])
FROM EHR e
CONTAINS COMPOSITION c
CONTAINS (
  OBSERVATION o1#micro_lab_test and
  OBSERVATION o2#micro_lab_test)
WHERE
  o1#battery/Simple_test/infectious_agent='Salmonella' and
  o1#battery/Simple_test/test_result='Negativ' and
  o1#registration_date>='2013-01-01' and
  o1#registration_date<'2013-01-15'</td></tr>
</table>

4.4. Discussion

The architecture to realize an openEHR-based data perception model has been described. The approach presented intends to use the strengths of each tool to design a DW environment that can integrate, standardize and abstract data for decision models.

SNOW libraries provide the horizontal operators to extract and define a canonical integrated view of data. LinkEHR allows transforming that canonical view into openEHR compliant archetype instances. The openEHR persistence platform Think!EHR enables persistence and abstraction of openEHR instances. The archetypes that define the information schema provide a robust model available and governed at a national level.

Most of the approaches to define abstractions up to date are based on mappings that provide vertical operators but limited integration capabilities [22–24,138]. The DW environment presented tries to adapt techniques from data warehousing to improve data integration capabilities and enable abstraction using standard-based dynamic queries.

Regarding integration, the main advantage with respect to CDS abstraction techniques are the powerful horizontal operators provided by the data access libraries and distributed access functions that SNOW provides. Distributed data sources can be accessed respecting the privacy restrictions of each of them. Although the case study presented in *er du syk?* only uses one library from one data source (the regional LIS), nowadays SNOW integrates 5 GP offices and 7 microbiology laboratories. Another advantage with respect to other DW environments is the dynamic management of data based on standard queries using AQL. AQL allows performing queries over the standard model defined by archetypes regardless of the underlying technology. This allows for managing the complexity of clinical data by relying on models that were developed for that purpose (e.g. openEHR). Otherwise OLAP cubes or Snow flaked schemas that warehouses implement would explode in complexity to represent clinical information instances. Moreover, the use of openEHR allows for representing all the contextual information linked to clinical data instances.

The architecture presented has benefits but also limitations. The first limitation concerns transactional control over ETL stages. The openEHR persistence platform grants ACID properties once data has been loaded. However, while data is extracted into the canonical view or loaded into the persistence platform some of the operations may abort. This could lead to wrong inferences at the query stage. At the moment, the correct functioning of these operations needs to be checked manually. A way to overcome this issue could be to endow the architecture with a global transaction management system such as the Java Transaction API [139] in combination with the openEHR Extract model. This would allow treating each information instance as a "versioned object". However, the combination of a global transaction system with the use of the openEHR Extract model versioning control remains as future work. Another limitation comes from the nature of AQL. While the approach presented attempts to maximize the flexibility in in the definitions of abstractions relying on AQL, this also ties the solution to AQL limitations. AQL was originally designed for querying openEHR-based EHRs, but not as a general-purpose query language to support the definition of complex abstractions for CDS. For the same reason it does not have manipulation operations since every modification in the EHR must become a new version of an existing object rather than be deleted. Therefore the number of functions to abstract and manage data is limited. While some functions such as count or sum are supported, to the best of my knowledge, more complex functions such as subqueries have not been yet included in the specification nor implemented. In the case of *er du syk,* the functions necessary to cover the case study were sufficient. However, other scenarios may need more abstraction power requiring to chain queries or rules to create the concepts needed by the decision model. Some studies have proposed to transform openEHR entities into semantic web representations to apply semantic web technologies in the abstraction process [140]. This would allow performing conceptual abstraction queries. For example, analyze subsumptive relationships to perform a general query to retrieve any patient diagnosed with any subtype of diabetes (type I, II, gestational etc.). However, this introduces a new layer and increases the level of complexity. Furthermore, there is no guarantee that the resulting models are tractable for the reasons explained in the next chapter. From a practical point of view, it seems more reasonable to deal with such scenarios by using GDL or GELLO on top of AQL to infer complex abstractions with operations such as conditions, complex arithmetic operations etc. GDL can reference archetypes directly and GELLO can treat them as an object model. Both models provide advanced abstraction mechanisms without the need of performing further transformations into semantic models.

Other DW infrastructures have been proposed oriented to enable the reuse of data for clinical research. Hu et al. proposed a DW that enabled secondary use of data for research [130]. Their approach exploited standard terminologies such as SNOMED-CT. However it did not rely on clinical information standards. Another related project is the SHARPn consortium. The SHARPn approach followed an strategy similar to the one presented here by using Intermountain CEMs rather than openEHR archetypes [28]. SHARPn is oriented to provide health quality measures in HL7 HQMF. A difference is that rather than using an openEHR persistence platform, queries over the models created are done by translating HQMF to the DB query language.

Haarbrandt et al. partially relied on openEHR to enable secondary use of clinical data by proposing a mapping methodology from openEHR to i2b2 [27]. That is a powerful strategy since it allows to place i2b2 on top of openEHR-based systems and exploit all the functionalities that i2b2 provides for clinical research. However most VMR are defined using clinical information standards such as openEHR or HL7 VMR in order to represent the clinical information preserving its contextual properties. Therefore, using the i2b2 star schema which was designed for phenotyping in clinical research is not an appropriate option for CDS perceptual model developments. Additionally it adds another transformation layer into another schema that leads to some information loss since not all the entities in openEHR can be transformed into the i2b2 star schema[27].

openEHR has been documented to be a scalable standard to build VMRs [141]. Its combination with AQL allows to have a rich clinical information model with an abstraction mechanism independent of the underlying technologies used in the implementation. Although AQL has some aggregations limitations, they can be overcome by combining it with standards such as GDL or GELLO without introducing further mapping layers into different models that may provoke information loss.

A problem regarding the use of archetypes to build the VMR is that most, if not all, published archetypes available on CKMs are designed to model the content model of the EHR. In many cases the VMR defines a summary with some abstraction level with respect to the EHR. That involves a problem since archetypes from the CKM may need some modifications to comply with the requirements of the VMR. An example of this was shown in the results section were only some of the sections of the archetypes from the CKM for laboratory tests were useful to model the laboratory request in the VMR of *er du syk*. This problem was discussed at the tutorial *Enabling Clinical Data reuse with openEHR DW environments* at Medinfo 2015 between openEHR developers and CKM editors [39]. Since this is a problem likely to appear in many data reuse and CDS developments, the recommended way of dealing with it for developers is to be in contact with their national CKM or the international CKM (if no national CKM is available). In the case of *er du syk,* the resources developed were uploaded to a project in the Norwegian CKM [123]. This allows placing the resources in a public repository with an appropriate governance framework. Additionally, interacting with the CKM provides feedback to CKM editors that may discover requirements for future versions of archetypes.

5. Semantic Model

Summary: The previous chapter presented an openEHR data perception model that needs to process data to allow the decision model exploiting it. This chapter is concerned with the specification of the CDSS. Specifically, it tackles the problem of extending CDSS specifications with semantic annotations. The aim is to enable CDSS exposed in a health network to be discovered and analyzed to understand how to interoperate with it in an unambiguous way. Several ontologies will be leveraged to specify data, functional and non-functional semantics using the Linking Open Data cloud as a common Knowledge Base. The annotation of er du syk will be used to exemplify how these models allow describing its interfaces and properties in a machine-understandable fashion. The contents of the chapter are based on the results of PAPER 2.

5.1. Background

The representation of information and knowledge in medicine involves many challenges inherent to the complexity of the biomedical domain. When health information systems are developed as conventional enterprise software they tend to become information silos [142]. This means that information cannot be easily shared, queried or analyzed outside the system boundaries since there is no common format to specify its structure, context and meaning. In previous chapters the importance of CIMs for providing content models to structure clinical information has been explained. However, although CIMs provide common scalable information schemas to enable interoperation, the specification of meaning in CIMs with rich semantics is also needed. Semantics need to unambiguously identify the meaning of exchanged information with an application independent *lingua franca*. Building semantic models of medical knowledge is a difficult task since complex relationships such as specializations and many concepts with subtle variations in their meaning are common. This involves the need of formalizing such specifications in a way that allows maintaining and scaling knowledge models that are constant across applications (i.e. background static knowledge) [143].

The need of building semantic models is not something only related to the clinical domain, but common to all domains that manage complex heterogeneous data such as the WWW. In the last decades the need of the Web to count on meaningful annotations to manage large amounts of multimodal data has led to the development of standards for specifying knowledge models by Semantic Web researchers [144]. These standards allow for defining models with a logic foundation (e.g. relying on Description Logics) as ontologies. Inspired by philosophy, the term ontology in computer science was first introduced by Grubber as conceptualization of a universe of discuss [145]. More formally, an ontology is described as a "formal, explicit specification of a shared conceptualization"[146]. The formal specification of a model means that it is expressed without ambiguity in a mathematical fashion, thus making it machine-understandable. This means that computers can process the concepts and relationships expressed inferring new knowledge without human intervention. Ontologies provide a semantic layer that allows for associating meaning with data regardless of the underlying information structure or syntax [37]. Chapman et al. summarize the three main features provided by the Semantic Web [147][chapter1]:

- Building knowledge models capable of representing complex domains making them easier to process and maintain. For example, the Gene Ontology provides a model with the concepts and relationships necessary to define gene functions. These concepts include gene products, cellular components, molecular functions and relationships among them.
- Computing with knowledge: the formal specification of ontologies allows computers to reason over represented knowledge inferring new knowledge and deriving conclusions. This facilitates the management of complex models. An example is the management of massive ontologies such as SNOMED-CT that contains around 300,000 concepts and more than 1 million relationships. Reasoning over a reduced set of assertions allows deriving and managing all the concepts present in the distribution files [143]. Also the SNOMED-CT´s ontology (concept model) provides the compositional grammar to define new concepts by combining others (post-coordination). When this happens, reasoners can be used to classify the new concept in its corresponding hierarchy.
- Exchanging information: counting in a common model to specify semantics plays an important role in interoperability and integration of disparate knowledge models. For example, heterogeneous medical terminologies can be mapped using the semantic web establishing equivalence relationships. An example is the UMLS Metathesaurus that integrates a large amount of terminologies [148] and the architecture caCore for the integration of resources in cancer research [149].

So far the use of semantics in CDS systems has been mostly limited to the definition of background knowledge as reference ontologies (SNOMED-CT, Gene Ontology, Uniprot etc.) [143] and some ontology based models for the specification of the decision algorithms (e.g. SAGE)[68]. Nowadays the trend towards encapsulating the CDS artifacts behind a web service [13,14,66,150] makes the effective binding semantics to CIM elements even more appealing. Medical ontologies (e.g. SNOMED-Ct or GALEN) and terminologies (LOINC, ICPC) are used for that. SOA principles for CDS promulgated by Kawamoto and Lobach [150], and later implement by Dixon et al. [14] and openCDS [52], decouple the CDS artifact from any other HIS allowing to make it available for any client. For the exchange of information between clients and CDS services this approach relies on messages defined by CIMs and annotated with standard terminologies as canonical models to identify the entities that the service consumes [66]. However, although terminologies provide some degree of semantics to CIMs they are not contextualized; meaning that they link to an external knowledge model that has not direct relationship with the semantics implicit in the CIM. This has implications in the automatic analysis of their interfaces, the search in CDS repositories and the mapping to other conceptual models as described in the next section.

5.1.1. Limitations of SOA and CDS specification standards

Encapsulation of CDS systems into Web services implies delegating development, maintenance and governance to a third party. However, this delegation involves challenges since the client does not have any control over the system deployed. This translates into difficulties to find services and determine their behavior to decide, for example, if they are suitable to perform a particular task. The technologies used to implement Web services provide Interface Definition Languages (IDLs) such as the Web Service Description Language (WSDL), Web Application Description Language (WADL) or Swagger. IDLs provide information about how a service must be invoked and the structures of input and output messages. However, these technologies operate at a syntactic level requiring the intervention of developers to manually search services, identify compositions of services and, in many cases, to dive into the implementation details to determine the functionality of the service [151]. In health applications, these limitations become even more prominent due to the complexity of the domain. Dixon and Wright documented some of the limitations found when sharing CDS services across organizational boundaries[14,65]. Those problems are related to several limitations that appear when operating those services across health networks [67]:

- First, it is not possible to discover the service using expressive queries. For example, it is not possible to search for CDS services for heart diseases prevention and retrieve stroke risk prevention CDS because it is a subtype of heart disease prevention.
- Second, when a service is discovered and its properties need to be explored to determine if it is suitable to perform a particular task, the lack of unambiguous specifications does not allow to automatically determining the precise meaning of the interface concepts. This involves difficulties in establishing SIOp between the client and the service as reported by Dixon et al. [14]. For example, it is not possible to automatically infer that two concepts expressed in different terminologies are semantically equivalent. Another example comes from the inability to explore the semantics implicit in the archetype structure. Let us consider an archetype for family history of diseases, which contains one element coded with Diabetes. The intended semantics are that the patient has a relative with diabetes but they is not necessarily suffering the condition. To know the exact meaning, the hierarchy would need to be explored but this cannot be done automatically in a machine-understandable way provided that the archetype is expressed at a syntactic level.
- Third, it is not possible to explore systems independently from the standard that was used in their implementation. For example, a CDS service operation may receive an input message conforming an openEHR template. That input may be semantically equivalent (but syntactically different) to a document conforming HL7 CDA in the client system. Therefore, if the client system supports a different standard from the service (e.g. HL7 CDA), it will need to know both standards in detail to understand how to interoperate with the service.
- Fourth, it is not possible to explore the relationships among the concepts used in the shared messages and those in other public ontologies. This disallows to understand the service operations without ambiguity and explore its relation with other models. For example, if one attempts to invoke a system for recommendation of treatments for liver cancer, it is not possible to automatically infer that any subtype of liver cancer (hepatocellular carcinoma, cholangiocarcinoma etc.) is a valid input; or if there is a CDS for drug dosing automatically infer that both Xarelto® and Aldocumar® are valid inputs because they are trade names of anticoagulant substances. Furthermore, on the server side, it is not possible to exploit the information available in public ontologies to, for example, determine what mutations make a treatment better than another in certain types of cancer. This lack of connection with other knowledge models hampers to combine several ontologies to define fine grained semantics for example combining the time ontology with SNOMED-CT [67].

Not only the limitations intrinsic to the syntactic technologies are a problem in exploring and sharing CDS functionality. To make it worse, the syntactic models used to specify CDSS are not common to all CDS developers. There is a huge variety of standards and terminologies for different purposes overlapping in functionality [41,67]. For example, for the definition of CIMs openEHR, HL7 CDA, HL7 VMR and HL7 RIM VMRs can be found [22,25,54,152]. The same occurs when expressing metadata for KM where HL7 KA, GLIF or openEHR GDL propose different formats[47,53,69]. At the moment different vendors and health organizations use different standards, therefore it does not seem realistic to design technologies dependent on one standard to overcome the limitations previously explained. To realize the vision of LHS knowledge implemented as shareable CDSS they need to be developed as collaborative efforts [13,153]. This leads to the need of specifying CDS systems in a way that can be automatically understood regardless of the standards used, interlinking of many terminologies to infer when two concepts are the same and mapping local terminologies to standard terminologies etc. For CDSS to be effectively and safely executed across different EHRs they need to be not only human-understandable but also machine computable [34]. Sharing CDS in wide health networks would limit the availability of direct support by implementers; therefore the development of new approaches to describe the services without ambiguity, in a machine-interpretable manner and independently from the details of each implementation standard becomes crucial.

One may argue that these challenges could be overcome adopting common standards by all health institutions and developers. However, if only one standard is imposed at a national level, this will jeopardize the ability to access CDSS that are previously specified in another standard and will create a burden to implementers that prefer other implementation options. Furthermore, even if all organizations in a country were using the same standard, the implementation would have the limitations inherent to syntactic technologies already explained. A sensible way to approach the challenges presented is to build on existing standards extending them with a semantic layer. This way previous developments do not need to be readapted and impositions regarding one single standard or terminology can be avoided.

5.1.2. Requirements for a semantic computing framework in CDS

The semantic web allows us to express knowledge at a conceptual level regardless of the syntactic implementation [37]. It can define an unambiguous agnostic conceptual view of CDSS supporting rich semantics allowing the automatization of some terminology mapping, search and analysis tasks. But in order to generate such specification not only the existing medical terminologies are needed. If we attend to the different approaches to specify CDSS [41] it is possible to appreciate that some allow to express functionality, others allow to specify data interfaces (VMR) and other KM metadata. A semantic model that aims for specifying CDS services that can be shared and consumed in a wide health network needs to be able to specify all those types of semantics. Additionally, the model to produce such specifications cannot be defined by a single organism, but needs to be universally available and widely shared and maintained. Otherwise the cost of maintenance would be too high for only one institution[13]. This leads to two requirements for generating CDS services semantic specifications: a) the first requirements is a methodology for the semantic description of CDS services that unambiguously identifies the concepts interlinked in their specification of data, functionality and KM; b) the second requirement is to count on a universally accessible knowledge base that allows to produce such semantic specifications independently on any underlying standard and enables to interlink the concepts and terminologies used in the CDS specification with other knowledge models.

The first requirement (a) is covered by the paradigm of SWS that provides a framework to extend Web services with ontological specifications, thus overcoming the limitations of their syntactic nature[112,154]. The second requirement (b) can only be covered by published interlinked ontologies universally available. Conveniently since 2009 the Linking Open Data project has driven the development of the Web of Data [155]. The Web of Data is formed by a massive set of published interlinked ontologies that include information about life sciences, geography and governments among many others.

5.2. Methods

5.2.1. Semantic Web Services the perfect symbiosis

Sharing CDS functionalities regards a problem of software components reuse. The semantic Web research has approached that problem proposing the paradigm of SWS. SWS were defined as extensions of Web services to provide unambiguous machine-understandable descriptions of the service properties and interfaces [156]. These descriptions are coded, as semantic annotations to allow SWS performing tasks that otherwise would require human intervention. Examples of such tasks are the automatic discovery, orchestration and composition of a set of Web services in order to accomplish a certain goal limiting human intervention merely to the precise specification of the outcomes desired.

The rich semantics that describe SWS are the corner stone to determine which activities can be automated and to define service properties without ambiguity. That specification is not only useful to automate tasks but to allow invokers deciding whether a service is appropriate to perform some processing and what the appropriate way of invoking that service is. There are two main approaches to define service semantics top-down and bottom-up [112].

Top-down approaches start by modeling the semantic dimensions of the service with a rich conceptual model and afterwards they ground it to the syntactic level. The most prominent models that follow a top-down approach are OWL-S [157] and Web Service Modeling Ontology (WSMO) [158]. OWL-S main components are service, service profile, service model and service grounding [159]. Service is the main component that links to the other entities. The profile specifies the purpose of the service. The service model specifies how the service works (functionality) and how to interoperate with it. Grounding defines how to access the implementation of the service from the semantic level. WSMO main components are ontologies, goals, mediators and web services [151,159]. Ontologies provide the concepts and semantics to describe all WSMO components. Goals describe the task and objective that the service will accomplish. Web Services define the properties of the service such as functionality and deployment properties. Mediators act as connectors to match heterogeneous models.

Rich ontology models that follow a top-down approach assume that the service semantics (data, functional and non-functional descriptions) are modeled before grounding them to the syntactic level (WSDL, Swagger, XML etc.) where the service internal logic is executed [160]. However, this is rarely the case since typically organizations implement first the communication technologies of the service as a SOAP or RESTful Web service and deploy it. Afterwards, it may be necessary to enhance the service with semantic annotations to overcome some of the limitations of the syntactic layer and the organization may add some semantic annotations to the existing implementation. This annotation process is complex, therefore for implementers it is convenient to add the minimum semantic descriptions to satisfy the implementation demands and enhance them when needed following a bottom-up approach. Bottom–up approaches depart from syntactic specifications of the service in an IDL (e.g. WSDL, WADL, Swagger etc.) and define methods to hook the IDL specification to semantic descriptions of the service. Several models are available to implement bottom-up approach: SAWSDL is used for SOAP services[161]; whereas MicroWSMO [162] and SA-Rest [163] are used for RESTful services.

With the broad adoption of REST architectures the concepts developed to support bottom-up approaches needed to evolve in order to enable the annotation of RESTful services. Kopecký et al. [164] proposed the hRESTS microformat to enable the annotation of html documents describing RESTful Web services. Their approach exploits the html documents that describe services for developers by adding labels that allow for describing the service for machines as it is done in WSDL files. In order to hook semantic descriptions they defined an extension of hRESTS called MicroWSMO.

Both SAWSDL and MicroWSMO define hooks to point to a reference ontology[6] but they leave open which model is referenced to define the semantics of the service. The W3C standard SAWSDL does not define any particular ontology to define the service and it is up to the implementer to choose which model will be used to attach semantics [160]. Aware of the difficulties presented by original top-down models Vitvar et al. [160] defined WSMO-lite as a light weigh ontology to incrementally build SWS on top of SAWSDL or MicroWSMO. WSMO-lite adopted the model of WSMO but simplified it leaving aside complex aspects such as explicit behavioral semantics (internal service logic). Furthermore it relied in RDF syntax, thus adopting a W3C standard but at the same time allowing the choice of more expressive languages such as OWL, RIF or WSML.

The different models to define SWS use different names and concepts to identify each type of properties of the service. Nevertheless, regardless the name that each model uses, there are four main types of semantics common to all of them [112]:

- Data/information model semantics: define the data models of the input and output messages of the service
- Functional semantics: define the functionality of the service
- Execution semantics: define exceptional behaviors such as restrictions on the executions of the service or runtime exceptions
- Non-functional semantics: define the properties of the service not defined by the former types. E.g. KM or governance information such as issuer, date of publication, version of the service etc.

[6] In the SWS literature the reference ontology that is used to atach semantics to a Web service description is in most cases referred as Reference Model. Here that term has been avoided since it is important not to confuse it with the reference models that are used to define CIMs (openEHR RM, HL7 RIM etc.).

The specification of all those semantic dimensions aims to enable the development of mechanisms that allow publishing the service to make it available for clients; the discovery of the service by the clients, and the analysis of the service by clients to be able to interoperate at a semantic level with them [156].

The original vision of intelligent services that automatically combine their functionalities to provide a requested outcome is not yet realized, in fact the adoption of SWS has been very limited [112]. Some reasons for this are the complexity involved in Web services annotation, the incompatibility of services definition models, the lack of publicly available ontologies to annotate services, the need of additional machinery as reasoners, and the complexity in transforming models to invoke them [112,165]. For example, models such as WSMO or OWL-S allowed specifying accurate complex semantics but the level of complexity involved in their definitions required highly skilled professionals to define them. Some of these limitations can now be overcome thanks to the advent of the Web of Data that provides many widely available ontologies expressed in W3C standard formats.

5.2.2. Linked Data and the Web of Data

Linked data are a set of principles derived from Semantic Web research to enable the publication of data on the Web in machine-interpretable standard formats of the World Wide Web Consortium (W3C) [165–167]. Besides, data published following Linked Data premises is also identified with the term Linked Data [167]. Linked data is based on four principles: (1) every resource exposed should be identified by a URI; (2) HTTP URIs should be used so people can look up for resources; (3) the resource, when accessed, should offer machine computable information using standards such as RDF(S); (4) links to other URIs to discover related information should be offered [112]. The gradual incorporation of these principles and techniques is exposing the information contained in documents as interconnected computable data that can be navigated, discovered and reused using universal standard languages. This has driven the transformation of the Web of Documents into the so called Web of Data [154]. The Web of Data can be envisioned as a global growing repository in the form of navigable graphs that contain computable semantic descriptions of each object [154]. The most prominent developments in extending the Web with the Web of Data have been carried out by the Linked Open Data (LOD) Project [155] and its central dataset DBpedia [168]. DBpedia makes available information in RDF about persons, places, locations species, diseases etc. and allows executing highly expressive queries over it. The Web of Data is encouraging organizations to publish their data at a scale without precedents. With DBpedia as core, the Web of Data has grown exponentially incorporating data sets from diverse categories such as geography, drugs or government. Particularly relevant are the ontologies for life sciences. The collection of Linked Data published on the Web is known as the Linked Open Data cloud (LOD cloud). In its report of 2014 the LOD cloud contained 1014 datasets [169], of which only the core (DBpedia) contains at the moment 412,887,618 triples [170]. Currently it doubles its size every 10 months [167]. The Web of Data has demonstrated how the investment in light-weight semantic annotations brings benefits to organizations. This has led to the creation of an extensive global knowledge base which parts are sometimes widely exposed and other times behind enterprises firewalls [167].

5.2.3. Linked Services: the symbiosis between Semantic Web Services and Linked Data

The advent of the Linked Data and the possibility of exploiting its knowledge models in combination with light weight models to gradually evolve implementations into SWS brought renewed passions to SWS research. The knowledge contained in the LOD cloud can be referenced from services annotations using it as a common knowledge base and releasing developers from modeling tasks of complex domains.

Linked Data has opened the door to produce applications that use its massive body of knowledge to navigate across services providing a processing layer to the Web of Data. Based on that, Pedrinaci et al. proposed to evolve the paradigm of SWS into Linked Services [112]. Linked Services are based on the principles for publishing service annotations (RDF(S) vocabularies) in the Web of Data and creating services that process Linked Data [112]. These services can easily be queried and invoked based on the semantics that they expose following Linked Data principles.

The following principles summarize the conclusions of research for the development of models to expose services to the Web of Data [165]:

- Semantics are needed to allow the automatization of tasks during the Web service life cycle. Examples of these tasks are ontology matching, determining how a service can be invoked or discovering services using intelligent queries etc.

- Finding an appropriate trade-off between expressivity and computation power is paramount; therefore lightweight ontologies must be prioritized against complex models. This is needed for allowing semantic models to be processed by most applications and facilitate the semantic definition tasks to developers. Previous sections have presented how heavy semantic models with very advanced capabilities needed to evolve into simpler models (e.g. WSMO-lite) that could be managed by most triple stores without needing specific reasoners to process them.
- The annotation of services must be as simple as possible. One of the reasons for SWS to be downplayed in the past was the difficulty in their adoption since specific knowledge on SWS frameworks was needed. In order to allow most developers to adopt them, models need to be as explicit and simple as possible. Developers are often familiar with systems based on extensional logic (e.g. relational or object oriented models) but are less familiar with intensional definitions (e.g. description logics used for the definition of axioms in ontologies). Then, models need to limit the use of heavy semantics definitions only to those scenarios where they cannot be specified by means of less expressive but simpler languages (RDF(S)).
- SWS should build upon existing standards (e.g. WSDL, RDF and SPARQL). SWS should not be based in new emerging paradigms, but build on established technological standards. W3C standards are the ones used by nearly all enterprise developments and the semantic model must allow extending definitions such as WSDL, REST, XML etc.
- Linked Data principles represent the best practice for publishing data on the Web [171]. Linked Data guarantees that if an ontology is published following its principles, it will be possible to discover it with queries that explore the URLs describing semantically the relations with other ontologies.
- Links between available data sets are needed for the scalability of the knowledge bases. The only way to ensure that third parties can understand a new model is to define it in terms of already accepted and publically available ontologies. Therefore any new development needs to be linked to existing models. For example, linking them to the LOD graph.

The ability of Linked Services to add a processing layer over semantically annotated data can be useful to offer semantically interoperable descriptions of CDS services which interfaces can be queried and explored.

5.2.3.1. Minimal Service Model

The research in Linked Services was realized in the EU project SOA4All which defined methods and provided the technological framework to integrate linked data and light weight semantics for services definitions. In order to publish services in the Web of Data a standard model that allows their discovery and their connection with linked data models is needed. This role is covered by the Minimal Service Model (MSM), a light weight RDF(S) ontology for services specification based on WSMO-Lite [165]. MSM is a model that captures the maximum common denominator among the existing conceptual models for SWS specification. This way MSM intends to be model agnostic and simple to facilitate the annotation and rely on Linked Data to attach meaning to the service components. MSM supports the specification of functional, non-functional, data and execution semantics.

***5.2.3.2.** iServe*

iServe is a service warehouse that together with MSM realizes the principles of Linked Services [172,173]. iServe allows for the publication, discovery and exploration of SWS. It allows importing services specified in different IDLs (at syntactic level) transforming them into MSM. iServe exposes service definitions as Linked Data, thus providing machine-interpretable definitions of services. iServe runs on top of a triple store or reasoned but provides a web API to abstract the user from the complexities in managing and querying semantic models. Users can perform discovery based in URLs that identify a particular concept that represents the data, functional or non-functional semantics of a service. For example, one may provide the URL that identifies a SNOMED-CT concept of heart disease and the system will retrieve systems for the management of atrial fibrillation by applying subsumptive reasoning over the relation of heart disease and atrial fibrillation.

5.2.4. It is not all about semantics

One may argue that with the powerful expressiveness of semantic web technologies the full definition of a CDS service (including clinical models such as archetypes), should be done at a semantic level. Expressing archetypes with semantic web languages may enable reasoning over them. CIMs in general and archetypes in particular carry their own implicit micro-ontology [56] that can be detached and expressed as a conceptual model with Semantic Web technologies [67,113]. In addition, CIMs also specify very expressive data constraints over the RM entities to model clinical information that reasoners cannot process in an effective way. For example, a component of the Archetype Definition Language (ADL) specification is the constrain ADL (cADL) language to define openEHR archetypes[174]. Some constraints commonly used in cADL for archetypes definition allow expressing negations, specific cardinalities for concepts relationships or restrictions over some of the instances that may populate a collection at runtime. Although OWL in its Full and DL version allows that level of expressivity, the model results in a computation that is not tractable (i.e. it will no finish in polynomial time). To overcome this problem there are several flavors of OWL depending on the modeling needs that restrict some of the mentioned constructs for the sake of tractability. That is the case of the OWL EL, which is the OWL flavor used by most biomedical ontologies. OWL EL sets restrictions over the use of constructs for specific cardinalities, enumerations that involve more than one individual or negations among others. Therefore archetypes data constraints cannot be fully expressed in OWL flavors that guarantee tractability [117], thus introducing important barriers for large enterprise developments.

Besides computation limitations, there is also a practical reason for not taking that approach to only rely on semantic web technologies. The reason is that the maturity of enterprise software architectures managing complex issues related to transactions, high availability, concurrency, robustness etc. The semantic web has been available during 20 years with limited adoption by industry whereas enterprise models such as RDBMS have been covering the high demands of critical infrastructures for 40 years in many scenarios [175].

A sensible approach is to mix the advantages of both syntactic and semantic architectures. This can be done by the considering the semantic model as a layer over other application layers that provides mechanism for complex knowledge expression and analysis but not as a substitute of other necessary technologies and models that provide benefits for efficient, robust and scalable information management.

5.3. Results

As described before, current standards for representing CDS artifacts and services have limitations as a consequence of the syntactic nature of the technologies used in their implementation. In fact, even the use of standard CIMs and terminologies has not resolved this due to a lack of unambiguous semantics in clinical models specification [14]. In this chapter, I propose to deal with these limitations by evolving CDS SOA implementations into Linked Services. This chapter presents a summary of the results from the paper *Publication, Discovery and Interoperability of Clinical decision Support Systems: a Linked Data Approach [67].* The paper presents a machine-understandable and standard-agnostic semantic model that allows the publication of CDS services as Linked Data, their discovery inside health networks using expressive queries, and their analysis browsing ontological descriptions.

Previously, it was explained how in order to define services at a semantic level the specification of three types of semantics are need: data semantics for expressing the data consumed and produced by the service, functional semantics for expressing the functionality of the service, and non-functional semantics for expressing other properties such as KM. The following sections show a summary of the results from the paper [67] for building a semantic model that encompasses these three types of semantics. The semantic model proposed builds on openEHR archetypes to drive the definition of data semantics. For specifying functional semantics, it proposes a common taxonomy of functionalities based on previously published taxonomies and SNOMED-CT. For specifying KM properties (non-functional semantics) the model identifies the common core of properties among existing standards, and provides the standard ontologies available to specify them in a linked data fashion.

5.3.1. Data Semantics

The specification of data semantics involves the projection of archetypes as machine-understandable models that allow for reasoning. Provided that a clinical model may be used in several CDS service implementations, it is important that they are decoupled from the service message specification that MSM provides as a separate Clinical Models Ontology (CMO). At the same time, the domain ontologies used to bind clinical meaning to the CMO need to be maintained separately so they are independent from the clinical models using them. Therefore, three layers can be defined for the specification of data semantics: a) the MSM specification for input and output messages of each service; b) the CMO common to all services defined based on standard ontologies; c) the standard domain ontologies used to attach semantics to the CMO. This separation in layers avoids replicating ontology binding tasks by sharing the CMO across all clinical models, separate models maintenance and perform separate reasoning when needed [67,176].

Figure 11 shows the syntactic and semantic levels for the *er du syk* service. The syntactic level shows an excerpt of the WSDL that specifies the operations of the service and the XML Schema created from an openEHR template for representing the data structure of the input message. The semantic level is divided into 3 layers for the specification of service messages specification, clinical models and domain ontologies.

The service message model shows how MSM defines the structure of the message for each service and breaks it into smaller items (message parts). Each part can be then linked to the clinical model layer to attach semantics to them. Figure 12 shows how the CMO is defined taking SNOMED-CT as main domain ontology and using other domain ontologies when needed. An excerpt of the CMO is displayed in Figure 12. The figure shows how the clinical models Symptom and LaboratoryTestRequest are defined using an RDF(S) structure that represents the concept by referencing SNOMED-CT concepts. Gray ellipses represent SNOMED-CT classes and stripped ellipses represent other ontologies in the LOD cloud or literals. Linked Data principles allow referencing every concept of any model with a valid URL, therefore any of the ontologies in the different layers can be referenced in the LOD cloud (if they are previously published) or a private network. That guarantees that anyone with access to them can search by the KM properties, functionality or input/output semantics and follow the msm:isGroundedIn link to know how to invoke the service.

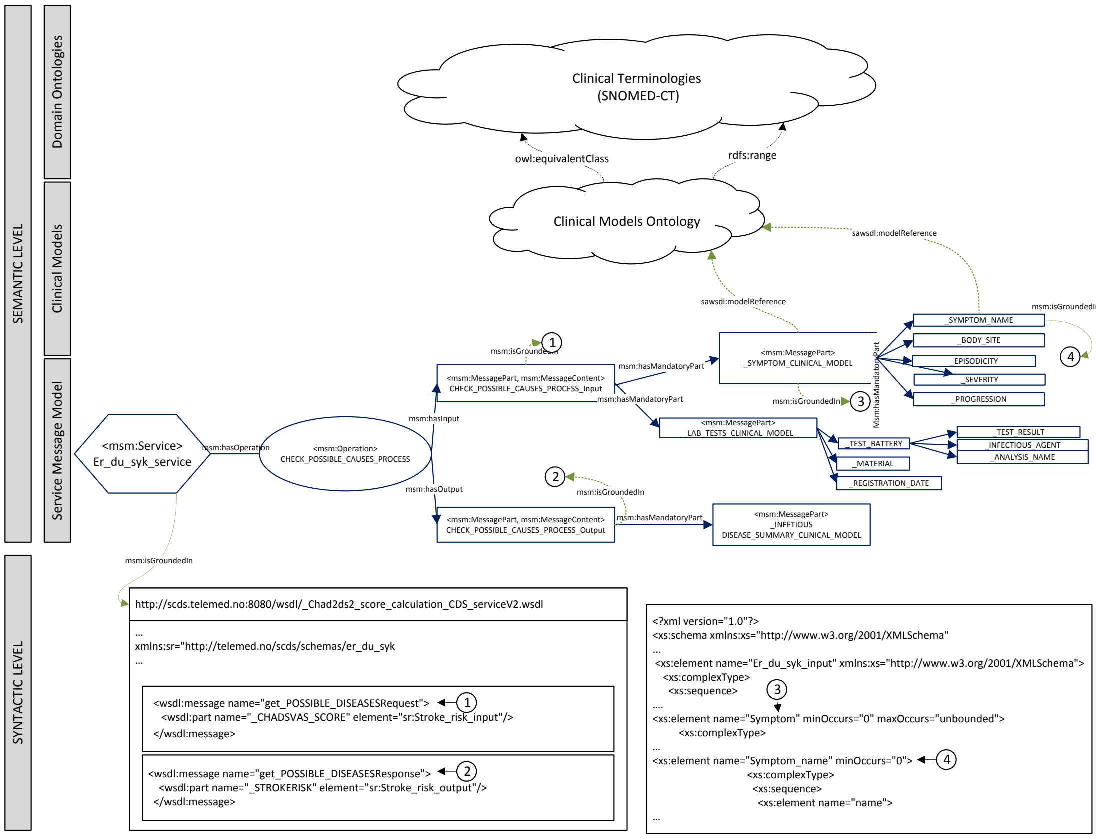

Figure 11. Syntactic and semantic levels.

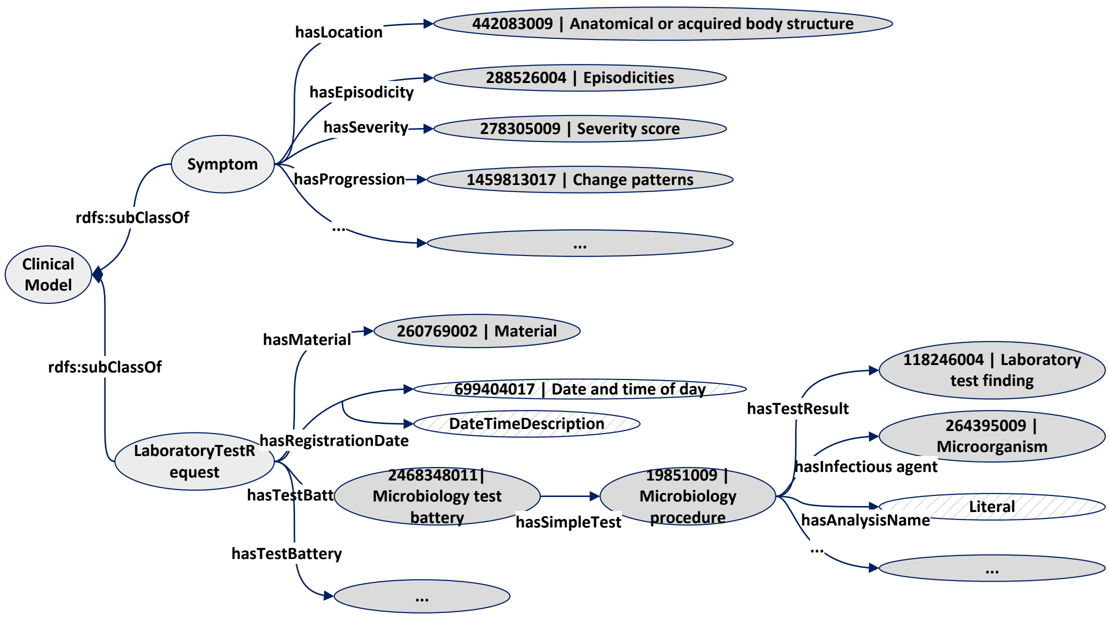

Figure 12. Excerpt of the Clinical Models Ontology.

5.3.2. Functional Semantics

In order to express the functionality of CDS services one needs to specify the clinical target task and the clinical domain of application. This allows specifying functionalities such as *CDS service for chronic disease management focused on diabetes*. This makes necessary to follow a schema similar to the one proposed by Fox et al. for specifying clinical goals: Goal=<Verb:Object> [107]. In the case of CDS services, the functionality specification needs to follow the schema Functionality=<Clinical Target task: clinical focus>.

The semantic model should allow for defining CDS functionalities in a broad way so anyone can search and explore any service independently of the standard used in its development. This requires building an ontology of any functionality that any developer has found (e.g. chronic disease management, prevention, diagnosis etc.) and, at the same time, link it to the clinical domain where the functionality is applicable (e.g. diabetes mellitus). Moreover, that ontology must act as a lingua franca that is common to most CDS developers. The broadest terminology to specify clinical concepts is SNOMED-CT. SNOMED-CT allows expressing the clinical focus for that concept by using the *hasFocus* attribute of its compositional grammar. However, SNOMED-CT lacks of concepts to specify CDS target tasks. Only the general concept *Decision Making Support* is available.

Figure 13 displays the semantic model implementation to allow the specification of functional semantics. In first place, the clinical target task needs to be specified. Gray ellipses represent the clinical target task taxonomy developed by merging the CDS functionalities taxonomies found in the literature [177–183]. By merging the different classifications available, the taxonomy aims to guarantee the maximum coverage of all possible functionalities. In second place, the clinical focus needs to be expressed for each target task. Therefore, once the clinical target task ontology is available, it is possible to use the clinical concepts that can be associated to *Decision Making Support* to extend each of the concepts in the taxonomy (gray ellipses) with the clinical domain of application*.* The valid concepts that can be post-coordinated in SNOMED-CT for *Decision Making Support* are the concepts in the *Procedure* and *Clinical Finding* hierarchies. Following the SNOMED-CT schema, the semantic model proposed can use the *Clinical Finding* and *Procedure* hierarchies to extend each of the target tasks (gray ellipses) with the possible clinical focus proposed by SNOMED-CT for *Decision Support*. That results in a poly-hierarchy that can both specify the target task in the available literature and the clinical focus allowed by SNOMED-CT. Figure 14 shows the annotation of the *er du syk* service specifying that it is a service with functionality for *Prevention_and_screening_focused_on_disorder_of_the_gastrointestinal_tract* and *Prevention_and_screening_focused_on_disorder_of_the_respiratory_system*. The annotations are coded as URLs referencing the functional taxonomy from the service specification. The development of the poly-hierarchy in RDF(S) provides an unambiguous specification of the system functionality. Intelligent queries over it can be executed to search and explore services. For example, one may ask to retrieve all systems for Prevention_and_screening and retrieve *er du syk* by subsumption reasoning.

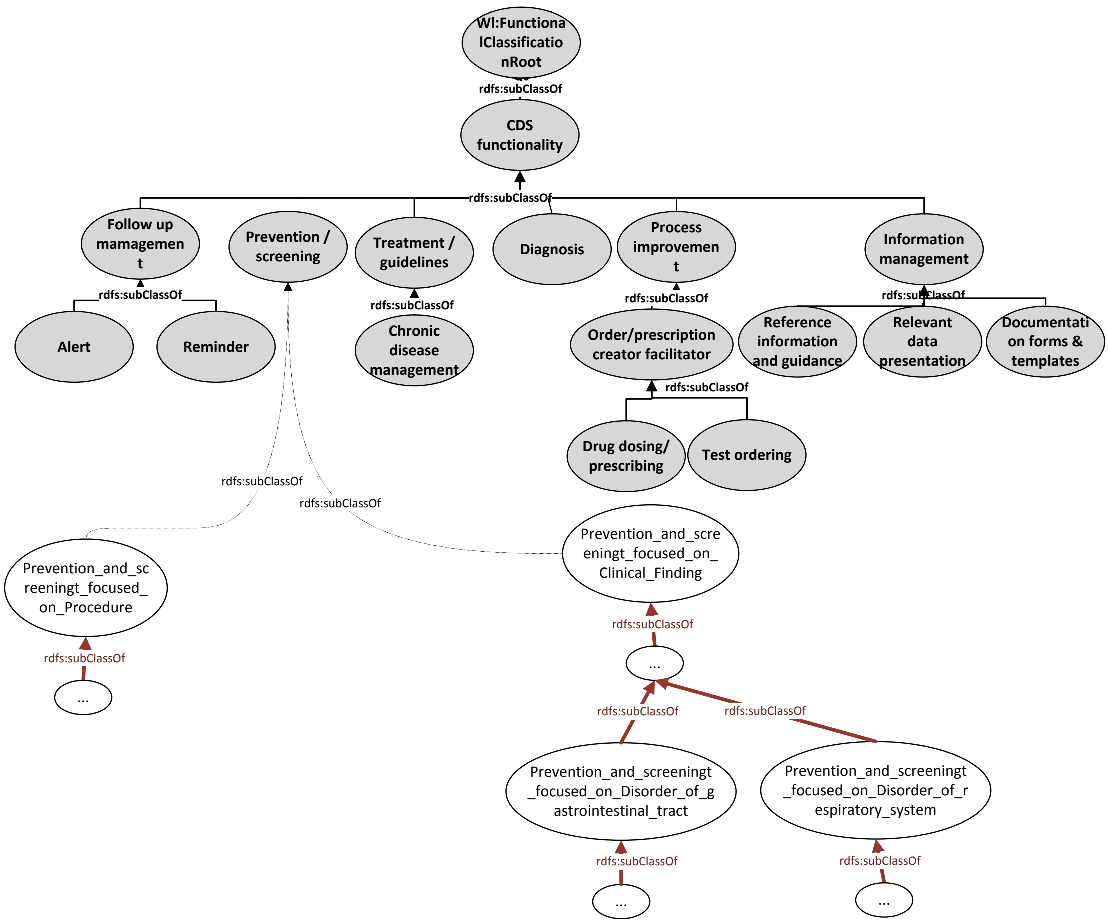

Figure 13. Functional classification taxonomy extended with clinical focus.

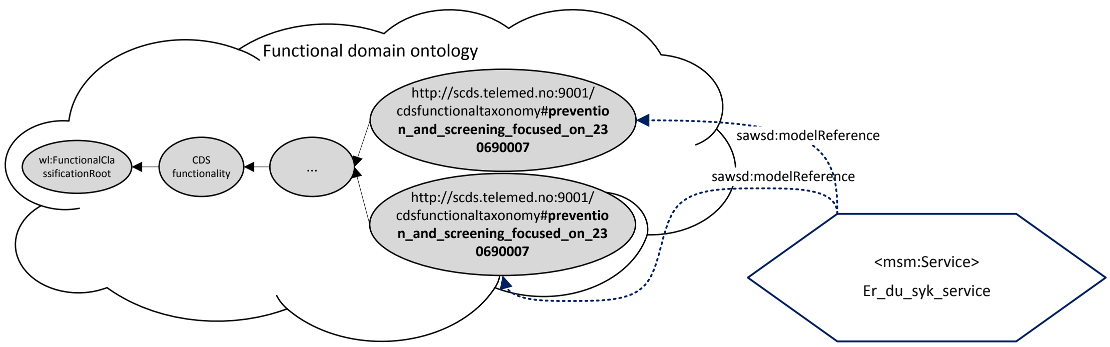

Figure 14. Functional annotation of the service Er du syk.

5.3.3. Non-functional Semantics

Many CDS specification standards provide a set of properties for KM of CDS artifacts. In most cases they define properties such as name, literature that supports the artifact definition, institution that issued the artifact etc. These properties are known as non-functional properties in the SWS jargon. Table 3 shows the KM properties in Arden, SAGE and HL7 DSS IG in the first three columns. The last column displays the semantic model properties selected to represent the maximum common denominator among the other three models. Non-common properties among standards are marked with hyphen and are not mapped to the semantic model. The properties from the semantic model have been selected from public ontologies published in the LOD cloud for metadata specification such as the Dublin core or schema.org. Figure 15 shows the *er du syk service* annotated with the KM properties defined. The annotations, following linked data principles, use ontologies properties expressed as URLs to link the value for each property. The example shows how the service has been annotated with a semantic relation dcterms:bibliographicCitation to express the literature that supports the decision algorithm implementation. scham:provider allows to specify the institution issuing the system. dcterms:hasVersion allows to define a version description and title with two further semantic relations.

Arden Syntax	**SAGE**	**HL7 DSS IG**	**Standard ontology equivalents used in the semantic model**
Title	Description	Explanation	rdfs:comment
MLM Name	Label		rdfs:label
Arden syntax version			-
Version	Revision plan Release Version		dcterms:hasversion
Institution	Issuing organization	Steward Organization	schema:provider
Author		Author list	dc:creator
Specialist			-
Date		Creation date Last Review date	dcterms:datesubmitted, dcterms:dateaccepted
Validation			-
Purpose		Purpose	*(implemented as functional semantics)*
Explanation			dc:description
Key words		FreeTextKeywordList CodedValueKeywordList	dcterms:subject
Citations			dcterms:bibliographiccitation
Links	Endorsements		rdfs:seealso
Type	Category		dcterms:type
Data			-
Priority			-
Evoke	Usage context Enrolment criteria		wl:condition
Logic			dcterms:conformsto
Action			-
Urgency			-
	Knowledge development		-

	External review		-
	Recommendation		-

Table 3. Non-functional properties for KM in Arden, SAGE, HL7 DSS and in the semantic model (last column)[67]

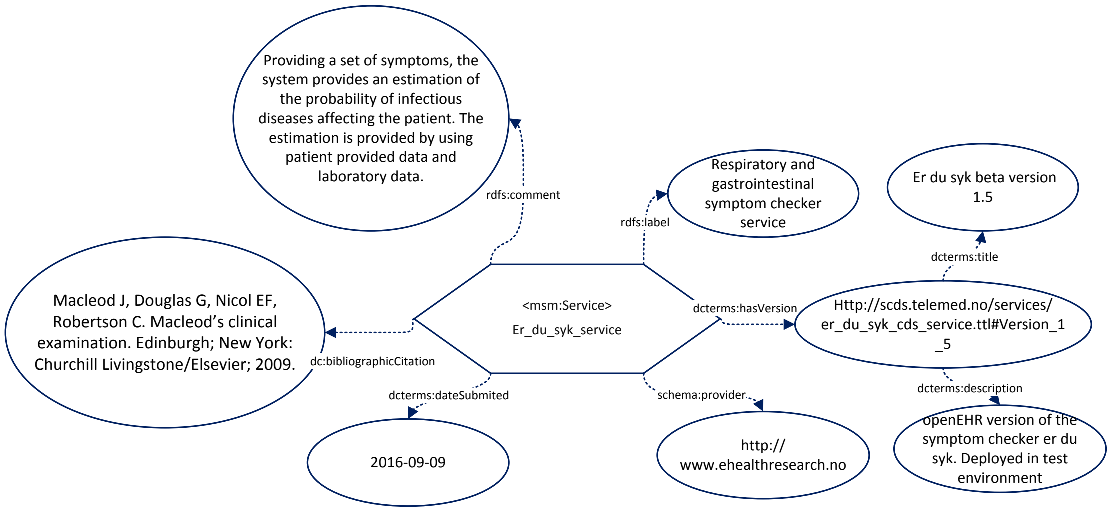

Figure 15. Service annotated with non-functional semantics for knowledge management.

5.4. Discussion

The semantic model developed follows the recommendation principles of SWS development explained in section 0. They are modeled as RDF(S) models compliant with linked data principles that prioritize scalability and viability, thus ensuring processing by most triple stores and reasoners. This has a counterpart in the expressivity that the models provide. For example, rather than expressing the functionality as an OWL axiom to link the clinical target task and the clinical focus relying on a reasoned to classify a functional annotation; all possible combinations of clinical target task and clinical focus were made explicit in an RDF(S) poly-hierarchy. This disallows the use of the SNOMED-CT concept model to process post-coordination. However, relying on intensional semantics based on description logics would disallow the processing of the ontology by RDF(S) triple stores [184] which are the preferred choice in Web of Data. Then, aiming to guarantee that most implementations can process the semantic model generated, light-weight semantic models in RDF(S) have been prioritized.

Another aspect of discussion is whether the distribution in different layers is the most appropriate. The separation in layers avoids replicating ontology binding that is the most time consuming task. Additionally, maintenance of ontologies can be a very tedious task [32]. With the separation of semantic layers each model can evolve at different speeds and be managed by different organizations. For example, the service message layer would be managed by application developers, the CMO can be managed by some clinical domain experts and information architects and the maintenance of ontologies is performed by different organizations such as the Dublin core, IHTSDO or schema.org.

Most of the effort in building the semantic specification of a system is related to data semantics specification. Conveniently, national CKMs and international CKMs have recently published a validated set of clinical models. The approach presented is designed to build upon those developments taking them as the basis that guides the semantic model definition.

The specification of semantic models as Linked Data leads to the definition of a Linked Knowledge Base (LKB). The LKB provides a conceptual representation of all CDS properties regardless the standard used in its implementation expressed in a lingua franca widely available formed by all the ontologies in the LOD cloud. Figure 16 illustrates how the semantic models of different CDS services are interlinked by a LKB where their functionality, data interfaces and KM properties are expressed. For example, the figure shows how the Atrial Fibrillation CDS KM properties and data interfaces are specified in the RDF(S) graph that forms the LKB. The fact that all CDS services use w3C standard formats to represent the services at an implementation level can be exploited to define links to the semantic layer. For example, whether openEHR archetypes or HL7 templates are used to represent the CIMs that the service messages contain, when the system is implemented, these data structures are represented as XML schemas that can be annotated to reference the semantic layer. Also, regardless of the logic specification, the operations, messages etc. are described in an IDL such as WSDL or Swagger. Therefore any of these implementations can be referenced as URLs from MSM to perform the grounding. This provides linkage among different models opening the door to infer equivalences among terminologies and properties used in different organizations. Having a common interlinked LKB encompassing diverse CDS implementations is key in facilitating the search, analysis and interoperability of CDS services[14].

Concrete examples of the functionality that a Semantic model provides are:

Publication of CDS services in health networks. Linked data principles are a set of best practices to publish knowledge models that can be applied either openly in the WWW or behind enterprise firewalls [167]. Therefore the semantic model proposed can be used to expose CDS services developments in health networks allowing the organizations inside that network to find and analyze them.

Intelligent queries based in the analysis of semantic relations. For example, query for all those systems developed by the Norwegian Centre for e-Health Research would analyze the non-functional properties of services and retrieve *er du syk*. One may query by systems for prevention and screening and the functional hierarchy would be crawled retrieving *er du syk*. Another type of query is by data semantics, for example, querying those systems which output is a list of possible diagnoses and retrieve *er du syk*.

Unambiguous descriptions of system interfaces. Describing input and output messages as interlinked clinical models and terminologies allow establishing automatically when a concept is equivalent of another, a subtype or a super type. This is of paramount importance for establishing semantic interoperability among clients and invokers of CDS services which is reported as a mayor challenge [14].

The discovery of systems published in health networks and the semantic interoperability among them allows sharing the functionality of knowledge implementations. That opens the door to collaborate in the development of new knowledge artifacts to rapidly assimilate new evidence in the form of CDS implementations.

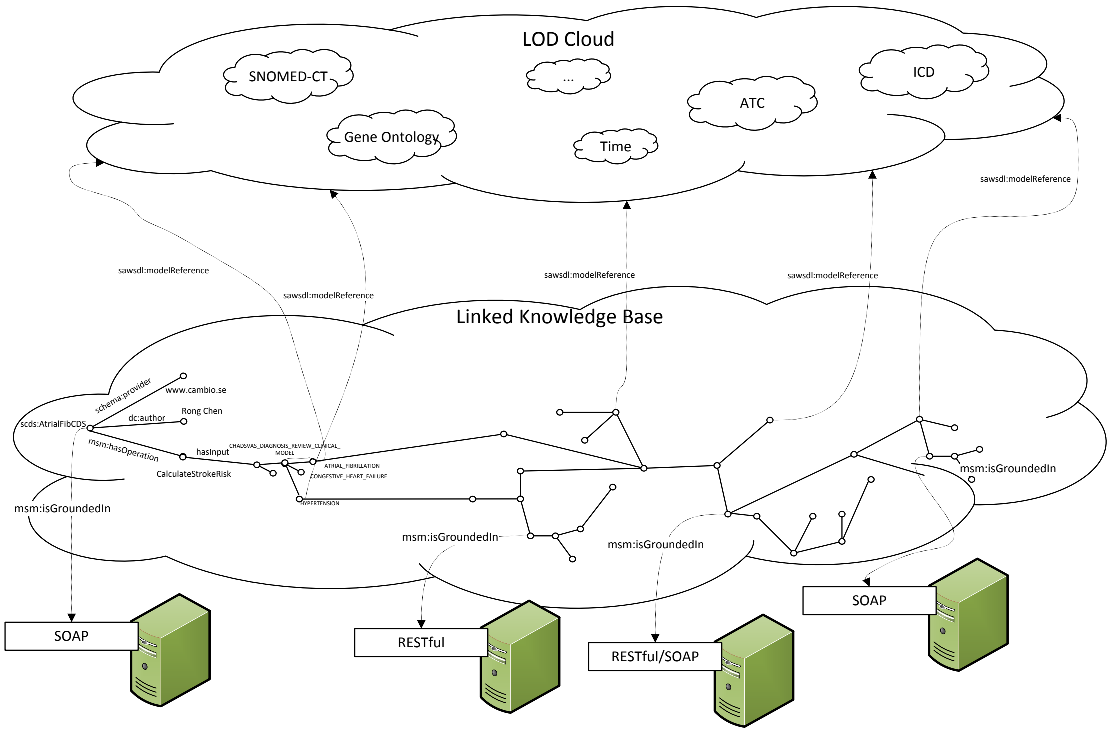

Figure 16. Semantic model integrating CDS services

Linked Services in combination with biomedical domain ontologies allow developing semantic descriptions of CDSS interfaces and properties. When such ontologies are available in the LOD cloud, they conform a universally available standard agnostic KB that allows for integrating heterogeneous CDS systems and enables reasoning over CDS ontological specifications. That reasoning can be used to discover CDSS in large health networks and analyze how to interact with them alleviating technical interoperability challenges.

6. Human-Computer Perception Model

Summary: Previous chapters have presented the proposed data perception model and the semantic model. This chapter tackles the problem of patient provided information. This chapter explains the methodology designed to evaluate the user interface of er du syk in a cost-effective manner combining remote testing with think-aloud techniques. The contents of the chapter are based on the results of PAPER 3.

6.1. Background

Previous chapters have explained the challenges in data perception. Data perception concerns access, integration, transformation and abstraction data from heterogeneous data sources so it becomes available to decision models. The sources of data may be very diverse encompassing EHRs, LIS, PHRs etc. The data perception model and semantic model presented make use of openEHR and ontologies such as SNOMED-CT to allow for recording contextualized clinical data. But there are also challenges beyond these technical dimensions. In chapter 1 I explained how the LHS introduces the patient as an active actor in the decision making process. Therefore, data used in CDS is very likely to be provided by patients and recorded following the standards and terminologies mentioned. When patients provide their data to a CDSS without the mediation of a clinician two situations may occur. The first situation occurs when objective measurements are involved. Objective measurements concern "data perceivable by persons other than the affected individual" [185]. When the clinician does not mediate in the communication, objective measurements are usually automatically recorded by displays or they are read and recorded by the patient without interpretation. Therefore, when they are self-reported, these measurements often require a low cognitive effort to be interpreted and reported. Examples of objective measurements are glucose measurements, blood pressure monitoring etc. [76]. In such cases data is read, stored and it can be integrated and abstracted with the data perception mechanisms presented. In these situations the context that transforms data into information can be automatically attached by checking the party (who recorded the data), the time of the measurement, the units, the time of the day etc. All these variables are objective observations that may require some interpretation if they are not recorded automatically. However that interpretation requires low cognitive effort.

The second situation occurs when subjective measurements are involved. Subjective measurements are those that need to be perceived by the affected individual because they are not completely perceivable by examiners or sensors [186]. In the previous example the observations correspond to data that does not need a significant cognitive effort to be interpreted by the patient. However, subjective measurements such as symptoms, signs, feelings, mood etc. require an interpretation by the patient to understand what information the system is requesting and contextualize it. This may not be a straightforward process since the complexity of such concepts may be very high for some patients. For example, in the case of *er du syk,* the backend contains clinical information entities modeled with archetypes and SNOMED-CT [123]. In order to record a symptom, many attributes need to be specified. Examples are the onset type (sudden, rapid, gradual), time patterns (periodic, continuous etc.), location of the symptom, cessation etc. To report his health information, the patient needs to reason about the semiology of his health status. This involves the understanding of medical concepts (e.g. sputum), symptom time patterns, progression etc. Additionally, users are not a homogenous group. They have different ages, socio cultural levels and health literacy levels. In fact, only 30% to 60% can be considered literate[187]. Therefore the ability for understanding and correctly report subjective health measures may vary from one subject to another.

These are aspects that will impact the quality of the data recorded and, by extension, the quality of the advice that the decision model will provide.

The challenge when the patient dimension is introduced in the CDS perceptual model is not technical anymore, but a problem of HCI. If the patient does not understand what the system is asking for, the quality of data provided will be low. This will cause the decision model to provide poor advise. That is a problem that will affect any CDS intervention that gathers subjective data directly from the patient. Symptom checkers such as *er du syk* are one of the applications that will be the most affected by these problems. A user that accesses a symptom checker faces the challenge of interpreting the information that the GUI is asking for. The success in that interpretation will determine how well that user communicates his health status to the system. Which, in turn will impact the quality of the advice provided by the system. A fact that will influence the success of the human interaction between the CDSS and the patient is the complexity of the information requested.

Symptom checkers are in their first generation [119], nowadays most of them usually request a basic set of data from the patient and provide advise based on static algorithms about the diseases that may affect them. However, the next generation of those systems is expected to exploit information from several sources such as epidemiology in order to improve their performance [119]. That is the case of *er du syk.* In addition, *er du syk* relies on archetypes and ontologies to define its knowledge base [123]. If these models are used, the completeness of the information stored as archetypes can improve the decision algorithm. However, this makes data recording more complex to users provided that every symptom contains a large amount of contextual data. In such a complex environment, it is not reasonable to evaluate a GUI based on a set of heuristics [188] and expect that it will be successful in guiding users through the information recording process. Not even the thorough evaluation of the interface by experts with methods such as cognitive walk through will be able to asses where HCI challenges are likely to appear due to the heterogeneity among users. In essence, everybody with an internet connection may use a symptom checker like *er du syk*, therefore potential users will have different ages, educational background, socioeconomic status and, most importantly, health literacy levels.

Evaluate the GUI with end users becomes necessary to detect and understand HCI barriers. However techniques involving end users are also the most expensive [189]. That is the case of think-aloud, the most spread technique when one needs to understand the cognitive process of users when they use a system [189]. Performing a test of a complex GUI with think aloud would have a huge cost. The complexity of the interface and the heterogeneity of users would lead to a very large sample for covering the evaluation of the GUI. For example, in *er du syk,* the symptom archetype contains 14 sections (some with subsections), and the respiratory module has 9 symptoms. This leads to 126 possible areas to test. Then, how can one determine if the patient perception mechanisms (GUI) are good enough to deploy a CDSS? Is there any technique that can test this kind of interfaces providing insights of end users experiences and, at the same time, keep evaluation costs under control?

Many studies in usability have combined different types of usability techniques such as expert based, heuristics, think-aloud with end users etc. to cover different test scenarios [70,118,190,191]. However, little is known on how to deal with complex variable scenarios such as the described for *er du syk*. In order to endow the perceptual model with means to build a reliable GUI I propose a usability testing technique that can deal with the complexity of interfaces to record patient subjective measures in a cost-effective manner.

6.2. Methods

The technique proposed encompasses two phases. The first one is a Technology Acceptance Model (TAM) based study performed online with a large sample size. By keeping the test online, it is possible to count on a large heterogeneous sample of users and, at the same time, minimize the cost. The outcome of testing in the first phase is the areas where users have reported barriers for technology acceptance. The second phase is an execution of the think-aloud protocol with a reduced sample. This phase aims to concentrate think-aloud testing in those areas that were detected as problematic in the first phase. The two phases aim to allow testing with a large variety of users but concentrate the most expensive method (think-aloud) only in parts with reduced technology acceptance to diagnose the causes.

6.2.1. Technology Acceptance Model

The TAM is a model proposed by Davis et al. [192] that aims to capture a measure of the ease of use and the usefulness perception. TAM relies on a set of questions where half are oriented to measure the ease of use and the other half is oriented to measure the usefulness perception.

6.2.2. Think Aloud

In order to understand the process of cognition, techniques that take into account the user cognitive process are needed. The think-aloud procedure is the most extended technique to understand the cognitive process of users when using a system [193]. In think aloud users are presented a use case to execute. During the execution they are asked to verbalize their interactions (what they think, what frustrates them, what they like/dislike, what causes confusion etc.). Verbalizations are usually transcribed and analyzed qualitatively, thus providing the necessary input to diagnose why a usability problem is present. Think-aloud is considered to detect one third of the problems that heuristic evaluation identifies [194]. However, it allows to detect more severe problems and understand their cause; whereas expert-based methods do not [194]. The main drawback of think aloud is its high cost and that it only reveals usability problems perceived by users.

6.2.3. Phase 1: Problem Detection

The first phase aims to maximize the sample size of users to grant an appropriate coverage. In order to keep the cost of testing under control, the test should be performed remotely. This way recruitment and evaluation can be done relying on autonomous users that do not need to visit the usability laboratory. In the case of *er du syk* that was the approach followed. Advertisements were posted though Facebook Ads campaigns and at the university website. In the advertisements posted, they were instructed to visit the web of *er du syk* and record some demographic data and a set of symptoms of their choice. At the end of the recording process, a questionnaire to evaluate technology acceptance was presented. The questionnaire was formed by the subset of questions adapted from the TAM ease of use set. In addition, a question to detect problems related to the lack of familiarity with medical concepts was added (Q1). Table 4 contains the set of questions that conformed the evaluation questionnaire. Originally the study aimed for a sample of 100 users. However, after removing duplicates by checking the IPs of submission, a total of 53 submissions had completed the questionnaire.

Table 4. TAM-based questionnaire.

Variable	Type	Possible values
Q1. I think that the vocabulary that expresses the information in the symptom recording was familiar to me	Quantitative	1 to 10
Q2. I think that the symptom recording at "Are you ill?" is easy to use	Quantitative	1 to 10
Q3. I think "Are you ill?" is a useful tool to record my symptoms and health status	Quantitative	1 to 10
Q4. "Are you ill?" system worked as I expected for a symptom recording system	Quantitative	1 to 10
Q5. Overall, I am satisfied with the ease of recording the details of my symptoms and health status	Quantitative	1 to 10
Q6. Overall, I am satisfied with the amount of time I used	Quantitative	1 to 10

to record my symptoms and health status		
Q7. Overall, I am satisfied with using the symptom recording at the "Are you ill?"	Quantitative	1 to 10

TAM questionnaire results represent a measure of the technology acceptance. Using that results, it is possible to determine which areas have a significant impact on the technology acceptance by regressing the areas of the GUI that each user completed and the result to the TAM questionnaire submitted by each user. One may consider using, for example, a linear regression model to establish that significance. However, a closer look to the problem reveals that this cannot be done in a straightforward manner. The dependent variable (technology acceptance) is divided into 7 variables that are the responses to the questionnaire. Therefore, to find the significance of each GUI variable to the TAM response it is required to apply multivariate techniques. An appropriate technique is the Principal Components Analysis (PCA). PCA will help to summarize that response in a minimum set of Principal Components (PCs). Once these components are found, the regression of the variables that represent GUI sections will be possible. At the end of the analysis, the regressions will determine what are the variables (sections of the GUI) with significance over the technology acceptance. Therefore these areas are the ones that need to be further analyzed to understand why they are significant with end users in phase 2.

6.2.4. Phase 2: Problem Diagnosis

Phase 1 has reduced the application areas to evaluate to only a few significant ones. This allows applying think-aloud in an optimal way in Phase 2. In order to execute think aloud a new recruitment needs to be performed. In the case of *er du syk,* recruitment was done though the university website. Five vignettes containing the symptoms corresponding to the significant areas were designed with the help of a GP so they could represent common diseases that cause such symptoms. Think-aloud was executed with a total of 15 individuals. The procedure was stopped when the findings in the interviews were repeating. The experience with *er du syk* showed that think aloud is not an easy procedure and needs preparation and training of both the interviewers and the interviewees. The experience with *er du syk* determined that the following stages need to be followed for optimal results in think aloud:

1. Introduction to the system functionality and objective.

2. Explanation of what think-aloud is. First a video showing how to perform think aloud was displayed; and second, the participants practiced using a flight reservation website (unknown to them) until they performed properly.
3. Execution of think-aloud over the system with a vignette. While the participant performed the think aloud, two interviewers wrote the moments of hesitation, doubts and comments about the system.
4. Retrospective interview to analyze the problems noted by the two interviewers during the procedure.

Think aloud sessions need to be videotaped and transcribed verbatim in order to be analyzed quantitatively. In *er du syk* the Framework method [195,196] was used for qualitative analysis with support of NVivo11 software. Figure 17 shows the steps followed in each of the phases.

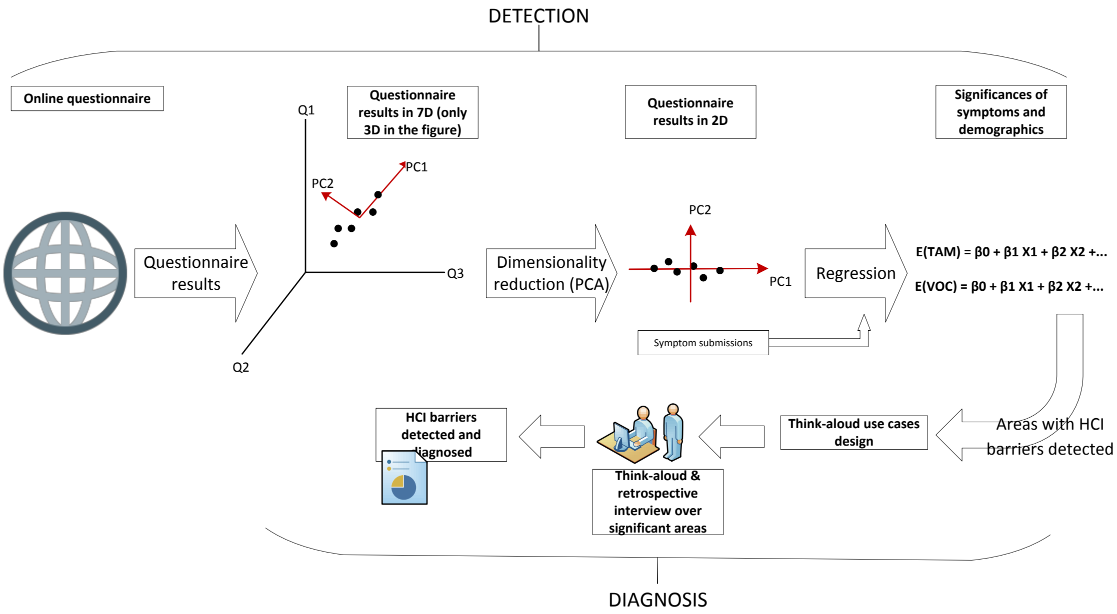

Figure 17. Detection and diagnose phases.

6.3. Results

This section presents the results of applying the methodology presented in order to detect and diagnose human computer interaction barriers in *er du syk*.

6.3.1. Phase I: Problem detection

Applying PCA the 7 responses of TAM were reduced to only two. One summarized the technology acceptance and the other the familiarity of vocabulary. Figure 18 shows the biplot with each of the 53 observation (numbered dots) projected in the 2 dimensional space formed by the components. We have moved from 7 dimensions, one per variable, to only 2 that summarize the variability in the response. The red vectors represent the gradients that provide an illustration on the direction of variation of each variable (qi). The smaller the angle between vectors is, the more correlated their variables are. The set [q2, q3, q4, q5, q6, q7] corresponds to the responses to questions from TAM and q1 corresponds the familiarity of vocabulary. It is possible to appreciate how q2 to q7 are more correlated with each other than q1. The direction of q2 to q7 is better identified with dimension 1 that corresponds to PC1. Q1 is better identified with the vertical dimension that corresponds to PC2. This interpretation was confirmed with the correlation coefficients of each PC with each variable (PAPER 3).

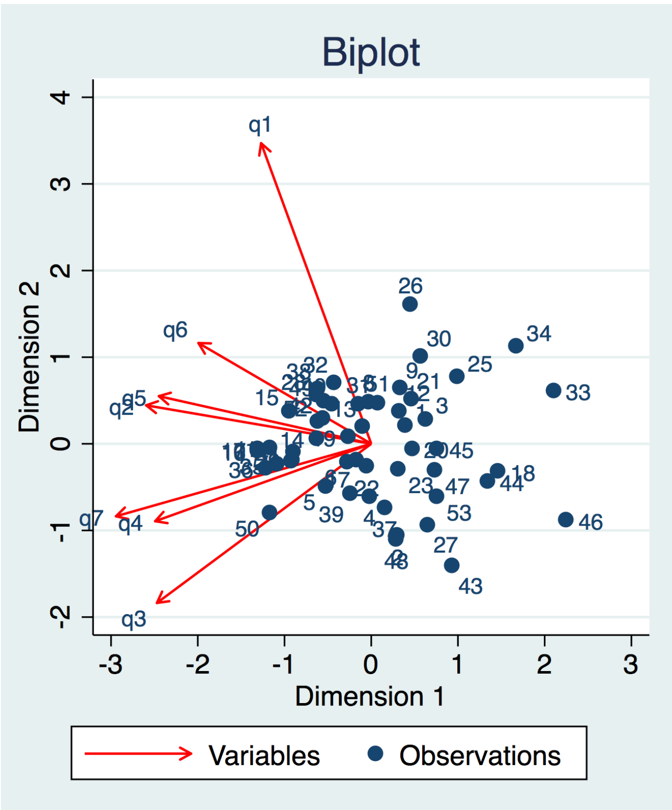

Figure 18. Biplot of Qi values projected on the selected principal components.

The coordinates of each observation in each dimension are called scores in PCA. Scores ,in this case, define two variables with 2 clear meanings: a) the technology acceptance; and b) the familiarity of vocabulary. At this moment, it is possible to regress the variables that represent the sections of the GUI with each of the scores. This will determine which of these sections have a significant effect over the technology acceptance (TAM model) or the familiarity of vocabulary (VOC model). Table 5 and Table 6 show the variables with positive and negative contributions to the TAM and VOC models. All the variables are binomial (0/1) except age that is categorical and identifies each of the age groups that the application records. Green color represents variables that were not significant at 95% (p-value<0.05) but are close to being significant. An insufficient sample may decrease the significance of some variables. In this case the target amount of 100 users was not reached, therefore variables with borderline significances were also included in use cases . The full details of the analysis can be checked in PAPER 3.

TAM model	
VARIABLE	CONTRIBUTION TO TAM
WHEEZING	NEGATIVE
COUGH	POSITIVE
FEVER	POSITIVE

Table 5.Variables with significant contribution over TAM (PC1).

VOC model	
VARIABLE	CONTRIBUTION TO TAM
ILL_PERSON	NEGATIVE
AGE	POSITIVE
WHEEZING	NEGATIVE

Table 6. Variables with significant contribution over VOC (PC2).

A set of vignettes containing the variables that appear in the models presented before were created.

6.3.2. Phase II: Problem diagnosis

Phase 2 consisted in executing a think-aloud procedure with the set of vignettes that represent health conditions containing the variables that contributed to the technology acceptance or familiarity of vocabulary. Participants were recruited from the university website. After transcribing all interviews verbatim, they were analyzed with the framework method. Proceeding inductively the index of problems displayed in Table 7 was built.

Table 7. Framework index.

Name	Sources	References
Design issues	0	0
Missing functionality or option	4	16
Lacking option for describing symptom	12	87
Whole symptom missing	2	6
Navigation problem	7	31
Bugs	2	13
Lack of coherency between options	9	40
Feedback	4	30
Interpretation issues	1	2
Time pattern interpretation	12	70
Vagueness in scales	1	2
Differentiation of time scale	8	49
Difference among intensity levels	7	23
Difference among quantity levels	5	19
Lack of clarity when requesting information	15	150
General user opinions	14	107
Too tedious	5	38
Improvement proposal	11	82
Context influencing the user experience	7	20
Usefulness perception	10	35
Data security concerns	1	4

The qualitative analysis diagnosed the causes for both positive and negative contributions to the technology acceptance and familiarity of vocabulary.

6.3.2.1. Negative contributors to TAM and VOC

The variable with negative contributions for both TAM and VOC was WHEEZING. Main problems were related to the bad localization of the archetype. Archetypes according to the openEHR methodology are maximum data sets that need to be constrained limiting the number of attributes for each use case. In *er du syk*, some attributes of symptoms were not constrained. For example, the symptom wheezing contained sections that were not relevant for them and caused confusion. Examples are timing pattern or the onset/cessation character. For VOC another variable with negative contribution was ILL_PERSON. This means that when the user had some condition at the time of recording his evaluation related to VOC was more negative. However, it was nor possible to diagnose that variable since ill patients would be needed for that.

6.3.2.2. Positive contributors to TAM and VOC

FEVER had positive contribution for TAM due to a perfect localization. The symptom archetype elements were restricted to the values for the temperature, and site of measurement. The case of the positive contribution of COUGH to both TAM and VOC was again related to localization. Nearly all the components in the symptom archetype are relevant for cough. Therefore it was evaluated positively. Think aloud, besides explaining the problems also revealed other problems affecting to the technology acceptance not detected in the first phase. For example, sputum introduced problems related to lack of references to quantify volume and color. The positive contribution of AGE to VOC was related to a lack of attention to detail. Think-aloud revealed that senior users had less attention to detail going through complex navigation areas in a superficial way without trying to understand the text. This caused them not to detect vocabulary problems in such areas evaluating better the applications despite using it in the wrong way. Young users tended to perform a more thorough analysis of sections and detected more usability barriers.

6.3.2.3. Other issues

Think aloud provided insights into other issues as well. It was determined that users need better feedback and guidance across sections so they know what information relates to each section unambiguously and when they have finished a section. Otherwise the amount of detail makes them loose perspective on what they are doing. Users also pointed out that the amount of detail made them feel anxious. They recommended informing about how much information they need to record before finish a section. Other issues were related to lack of options and functionalities needed to record the precipitating factor and some extra symptoms that they considered relevant.

Users were compressive with the amount of detail of the system, but they recommended reducing it. Users also pointed to the need of providing more examples in order to be able to quantify volumes, understand time patterns etc. For example, sputum could be quantified with examples such as “half a tea spoon”. Finally, think-aloud allowed us to appreciate the general user opinion about the CDS initiative. All users except one were positive and considered the system useful to avoid unnecessary GP visits.

6.4. Discussion

This chapter has presented a methodology to evaluate GUIs used as human perception models. The methodology provides an evaluation framework to determine patients HCI barriers in CDS user interfaces. This way it can be determined if it is safe to deploy or not a CDSS. Other studies have approached usability in CDSS by combining different evaluation techniques [70,71,118,190,191]. These techniques have approached usability testing successfully in their scenarios. However usability testing in scenarios with large heterogeneity among users and complex interfaces may set important costs restrictions is a rather unexplored area. The methodology presented aims to guarantee high coverage relying in remote testing which results are summarized by means of statistical methods in order to determine what are the areas with significant contributions to TAM. Once they have been determined, think aloud can be concentrated in those areas to diagnose the causes.

The application of the methodology to *er du syk* unveiled many important issues to consider. During design stage, it was attempted to build a simple design and provide guidance with navigation bars. However, users pointed to the need of simplifying some sections and provide even clearer navigation. Users like reassurance when they finish a section. They like to know exactly where they are and determine how much time left they need to devote to get a result. Additionally, when many symptoms need to be recorded, users prefer to start by the symptom they are more concern about and leave those that they are less worried about for the end. It is appropriate to ask users directly stating questions rather than set titles as simple statements. Users like to have examples nearly for every section to be sure they understood the information requested. Users also demonstrated to be comprehensive with challenges faced by health services and are willing to help optimizing their use.

Regarding Phase I, several variables in the models were not significant and the R^2 was low. Low R^2 are common psychology related models. Nevertheless, other studies should consider increasing the sample size in PHASE 1 to provide clearer significances of variables and model. After all, executing advertisements campaigns and posting Ads is a relatively cheap measure. Although models were successfully used to detect areas with low technology acceptance, they are not robust enough. For example, among all the response provided by all users there were 4 missing values (see PAPER 3). After a discussion it was decided to imputate them as the average of the column. Although imputations is many times questioned, it was considered that dropping all the observation (7 answers) for one missing answer would drive to more loss of information than imputating the missing one. If these observations are left out, the TAM model does not vary. However, in VOC model, the significance of ill_person becomes not significant, and the significance of wheezing and age increase. This does not influence the results of the methodology or the *er du syk* evaluation since all these variables have been double-checked with think-aloud as gold standard (except really ill). However, this means that VOC model is brittle and a significantly higher sample would be needed to have more robust conclusions in Phase I. In other scenarios where think aloud cases need to be restricted to operate at minimum costs (leaving borderline significances out), evaluators should consider increasing the sample in phase I. Otherwise significant sections could be left unexplored in think-aloud.

Regarding Phase II the sample size was considered more that appropriate. From user 6 onwards it was not possible to extract new information, and the issues detected were often repeated. Think-aloud was used to understand the reasons of the barriers detected in Phase I and it was used as a gold standard to confirm borderline significances. Phase II unveiled reasons for problems such as the interpretations of time patterns, the need of localization of many symptoms, and the need of considering reducing the level of detail. With regards to the later, further studies are needed to determine what information can be omitted without affecting the accuracy of the advice.

The successful perception of data provided by patients depends on their appropriate understanding of the concepts requested by the system. Therefore, HCI barriers need to be carefully assessed. When archetypes-based GUIs are designed to capture complete data sets and applications such as symptom checkers are involved, testing may be too expensive. The combination of remote testing with think-aloud can result in a cost-effective technique. In a first phase, remote testing can help to operate over large samples determining which areas have a large concentration of barriers. In a second phase, think-aloud can be restricted to areas with significant contributions to the technology acceptance minimizing costs. This way an appropriate coverage is guaranteed and, at the same time, the causes for HCI barriers can be diagnosed.

7. Conclusions and Future Work

Summary: Previous chapters have presented the different developments during the thesis to implement a semantic and a perceptual model for CDS in the Learning Healthcare System. This chapter summarizes the contributions made and presents the final conclusions.

7.1. Summary of accomplishments

The LHS introduces both challenges and opportunities for CDS research. In this thesis I have proposed several models and methods to overcome some of these challenges. On the one hand, the proposed perceptual model covers: a) data integration and abstraction in openEHR environments; b) the evaluation of GUI for patient-CDSS interaction. On the other hand, the semantic model tackles the problem of defining CDS properties as machine-understandable models using Linked Data principles to enable their semantic search, publication and analysis. Table 8 presents the alignment of the requirements presented in chapter 1, the research gaps presented in chapter 2 and the contributions presented in chapters 4, 5 and 6.

Table 8. Alignment of the gaps and contributions presented in this dissertation.

Requirement	Research gap	Contribution
R1- Requirement for data perception	**GAP1:** CDSS require architectures that: a) integrate openEHR with more powerful horizontal operators for distributed access; and b) provide technology independent abstraction mechanisms.	**Contribution 1:** In chapter 4 this dissertation proposed a methodology that combines Data Warehousing techniques with openEHR developments allowing access to heterogeneous sources and technology independent abstraction by means of AQL.
R2- Requirement for semantic description	**GAP2:** Current CDS specification standards and technologies do not provide the level of expressivity required to share CDS functionality across institutions.	**Contribution 2:** In chapter 5 this dissertation described a method to extend CDS services with machine-interpretable semantic annotations that use the LOD cloud as common knowledge base. This allows the automatic analysis of their properties to understand how to interoperate with them.

R3-Requirement for human-computer perception	**GAP3:** CDSS GUIs used to capture patient data must be free of human-computer interaction barriers to safely deploy consumer-oriented CDSS.	**Contribution 3:** In chapter 6 this dissertation presented a methodology to evaluate and detect HCI barriers between patients and CDSS.

7.2. Thesis contributions

Data perception model

The methodology presented for data perception provides several advantages:

- The proposed architecture combines several existing developments to exploit the advantages of each of them. SNOW is used as an horizontal operator to grant access to distributed sources, LinkEHR is used to transform the integrated view provided by SNOW into openEHR compliant extracts and the openEHR persistence platform Think!EHR is used to perform queries over standard datasets providing abstractions for CDS. This way, CDS data integration and abstraction can be performed along with the advantages provided by data warehousing and clinical information standards.

- Another contribution is the use of AQL to define data abstractions using standard queries. This allows defining queries directly over standard data schemas, independently of the underlying technology of persistence. In this way, even if the persistence technology evolves, there is no need to change the abstraction queries.

- The last contribution is to provide insights into how models for CDS should be managed by interacting with CKM editors. In order to allow users to understand the data perception process the models that drive it need to be widely accessible and well governed.

Semantic model

The proposed semantic model contributes to CDSS by using the Linked Services paradigm to specify their functionality, data interfaces and KM properties. In specific, it proposes:

- A set of properties to describe CDSS KM metadata.
- An ontology of CDS functionalities that defines: a) a generic taxonomy of functionalities developed by merging pre-existing studies (e.g. CDS for prevention and screening); b) an extension of each functionality based on SMOMED-CT to specify the clinical domain of application (e.g. focused on stroke prevention).
- A method to guide the specification of the clinical semantics implicit in archetypes as machine-understandable models.

The main advantage of the proposed semantic model is that it does not restrict the use of ontologies to a fixed set of biomedical ontologies. Rather it exploits the paradigm of Linked Services and the LOD cloud as a universal machine-understandable Knowledge Base. Therefore, by means of linked data principles, it allows to link CDS specifications using any ontology in the Web of Data as a LKB that can evolve and be maintained independently of the CDSS implementation. This opens the door to use, not only biomedical ontologies, but ontologies for time, space, data provenance etc. LKBs allow for performing semantic discovery of CDSS, analyzing them and overcoming interoperability challenges related to ambiguity in CDSS´ interfaces descriptions.

Human perception model

The proposed human-perception Model contributes in several aspects to patient-CDSS communication:

- This thesis proposed a method to evaluate archetype based GUIs to detect HCI barriers that could lead to negative outcomes of the CDSS. The proposed method uses remote testing to detect areas with significant contributions to technology acceptance using large samples. Later, think-aloud is restricted to significant areas with a low sample size. The method allows dealing with end-user evaluation in a cost-effective manner.

7.3. Generalizability of results and limitations

The methodologies and results presented in this dissertation focus on providing data perception, semantic and human-computer perception models to enable CDS in the LHS. The developments presented build on pre-existing models and technologies such as terminologies, EHR architectures, SWS and usability testing methods. The methods are generic, therefore they can be applied to other scenarios, but some limitations need to be overcome in future works.

Data perception model

Regarding the data perception model, the infrastructure proposed for its implementation was tested in the *er du syk* project by integrating, standardizing and abstracting data from the microbiology services of Troms and Finnmark regions. The data processed corresponded to a population of circa 230,000 patients. The architecture can be directly applied to other openEHR deployments by changing the set of archetypes that model the information and connecting SNOW data export modules to other sources. In fact, all the technologies involved have been extensively used in other scenarios demonstrating their scalability [27,134,197,198]. Nevertheless, these technologies and standards were originally designed for EHR information representation and communication, whereas in this dissertation they are used for data perception in CDS. This imposes some requirements to the technologies and standards that were not considered when such standards were developed. The first limitation was explained in Chapter 4 and it is related to the expressivity of AQL. AQL was not originally developed for data abstraction but for querying EHR extracts [98,99]. Therefore, the set of operations provided for data aggregation are limited [98]. Although the specifications and developments are evolving and may introduce some important features in the future, current limitations may require using languages such as GDL in some scenarios. Another limitation is the way of dealing with privacy preserving requirements. At the moment, when privacy requirements are high in data sources, only aggregated data is extracted (e.g. number of positive pertussis tests in Alta) and the archetype needs to be adapted to contain aggregations. This leads to a model less reusable across use cases since not all the EHR schema is available to perform queries. This means that the more abstract the baseline schema is, the less it is possible to adapt it to different scenarios with queries. In order to allow executing any query over a fine-grained EHR schema, if only the extraction of aggregations is allowed, the distributed execution of AQL queries would be needed. Although in my research group this challenges are being explored, the methods and technologies still depend on a broad adoption of openEHR [199,200]. If the adoption of openEHR progresses, eventually, the majority of HIS could be queried using AQL in a distributed manner, thus guaranteeing privacy. Another limitation related to the data perception architecture proposed is the lack of transactional control over ETL operations. In order to overcome it, not only a global transaction framework is needed, but also the extract passed from one stage to the next one should treat information as versioned objects by means of the openEHR Extract Model. Finally, at the end of chapter 4, I briefly introduced the need of adapting published openEHR archetypes for some CDS scenarios. I discussed how the work presented was coordinated with CKM editors and provided insights on the best way of approaching such issue. However, modification patterns and guidelines on how to proceed when published archetypes are modified are needed.

Semantic model

With regards to the semantic model proposed, it presents a generic framework to allow for specifying, not only CDSS clinical semantics, but also any type of semantics (e.g. functional, data and non-functional). Provided that it relies on the LOD cloud as generic Knowledge Base, any CDS specification can be interlinked with others leading to a common LKB. This makes the CDS semantic specification independent of the underlying standard used in the CDS implementation. The semantic model was applied to define *er du syk* semantics and 7 GDL-based CDSS for stroke prevention deployed by Cambio Healthcare Systems [67]. Although the systems are openEHR-based, the solution can be generalized straightforward by simply referencing other implementations from the semantic layer. For example, the same set of ontologies could be used to define data semantics for HL7-based CDSS by referencing HL7 data models. The technologies used in its implementation have already been used in other domains than healthcare integrating heterogeneous systems [165]. A possible limitation of the approach presented may appear when models that rely on more expressive semantics need to be managed. The model presented mostly relies in light-weight semantics (RDF(S) and limited use of OWL) and therefore may not allow to exploit all the expressivity of ontologies such as SNOMED-CT. However, previous experiences in semantic web applications development [112,160] have shown that, in many cases, it is convenient to sacrifice expressivity to make implementation easier and avoid restricting the reasoners that can be used, thus powering scalability. After all, when a scenario needs advanced expressivity, the model can be hosted in a reasoner capable to process it and reference it with a proper URL from the CDS semantic model without interfering the deployment.

Another limitation is related to a topic not covered in this thesis. CDSS in general, and Clinical Interpretable Guidelines in particular, when are adopted by a new institution often need to be adapted to the internal policies and rules. This process is known as local adaption [15]. Tackling local adaption at a semantic level with the methods proposed would require expressing internal guidelines logic as Linked Data models. This would have benefits as automatic comparison of guidelines to determine if they are suitable to be adopted by a new institution. However, that is a complex problem that remains out of the scope of this dissertation.

Human-Computer perception model

With regards to the human-computer perception model this dissertation proposed a methodology to evaluate GUIs to record subjective patient health information. *Er du syk* exploited archetype repositories such as the Norwegian national CKM to build the models that drive the development of the CDS interface[123]. The HCI evaluation method presented aims to deal with the complexity of consumer-oriented CDSS GUIs. These systems need large samples of users for testing as a result of their complexity and users heterogeneity. The methods proposed can be generalized not only to openEHR developments but to any HCI evaluation scenarios.

In the application of the methodology to *er du syk* several limitations were detected. The GUI is designed based on a symptom archetype that represents a nationally agreed maximum data set. The first attempt was to generalize as much as possible the symptom registration using such schema for most symptoms. However, that resulted in symptoms that asked users for attributes that were not related to them. Therefore a proper localization and adaption of the archetype to each symptom is needed as the openEHR methodology mandates. The methodology was successful in identifying many barriers. However, phase I, where remote testing is performed, needs to be done iteratively until the models that detect significant contributions to the technology acceptance stop improving.

7.4. Concluding remarks

Enabling CDS in the LHS includes all the challenges that have been present during decades in the development of CDSS and adds even more complex ones derived from the inclusion of new actors and values. I have presented a set of models to lay the basic pillars to build complex CDS interventions upon. In order to achieve this, it is necessary that initiatives such as the ones started in Norway [59,122] and the US [201] finish the wide deployment of health information standards such as openEHR. This is needed to allow the decision model to access data from several data sources. Other challenges require the formalization of CDS systems properties and establishing organizational bodies [18]. The semantic model proposed provides a supporting framework that can be extended with ontologies from the LOD cloud to define processes, provenance or further contextual information. In fact, good contextualization is needed to determine when a particular CDS is adequate for a set of health data.

The models presented are far from being a silver bullet to exploit any type of data in CDS. Nevertheless, they represent the minimum set of models to build upon. Developments such as the IoT, the Web of Data, cognitive computing etc. open the door to exploit many information flows to provide better health as envisioned by Sheth [42].

There are many exciting technical advances ahead. Nevertheless, in my opinion the most difficult challenges to overcome are the human ones. For example, a common repository and governance body of CDS is needed at a national or international level [13,18]. Greenes names such organization Oversight Body[18]. Such governance could be done in a distributed way relying on the LKBs presented. But it would require the alignment of many CDS initiatives such as openclinical.net, openCDS etc. Resources would be needed to maintain such alignment and the governance body [13]. A possible way to orientate it may be to think in funding schemas for the governance body similar to the ones of initiatives like IHTSDO that distributes SNOMED-CT. But for governments to invest in such initiative, the benefits would need to be very clear. It is the responsibility of CDS researchers and vendors to work towards a better integration at a global scale that shows the benefits of CDS investment. A second human challenge, crucial for the LHS, is the involvement of patients in CDS interventions. We still know very little about how to guide them in using consumer-oriented CDSS. Although the methods proposed can evaluate HCI barriers, more knowledge is needed to determine how to use CDSS for making users more health literate and helping them to make a better use of healthcare resources. Furthermore, we need more knowledge on users profiles to detect when the use of CDSS for self-care is not adequate, and a clinician needs to intervene.

Finally, all these technical and human interventions need to be performed within a framework that provides a clear vision on where CDS need to head in the LHS. That is only possible with the contribution of social science researchers that need to establish the direction of work and synthesize the views of all the actors involved [1].

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Included Research Papers

PAPER I

Marco-Ruiz L, Moner D, Maldonado JA, Kolstrup N, Bellika JG. Archetype-based data warehouse environment to enable the reuse of electronic health record data. International Journal of Medical Informatics 2015;84:702–14. doi:10.1016/j.ijmedinf.2015.05.016.

PAPER II

Marco-Ruiz L, Pedrinaci C, Maldonado JA, Panziera L, Chen R, Bellika JG. Publication, discovery and interoperability of Clinical Decision Support Systems: A Linked Data approach. Journal of Biomedical Informatics 2016;62:243–64. doi:10.1016/j.jbi.2016.07.011.

PAPER III

Marco-Ruiz L., Bønes E., de la Asunción E., Gabarrón E., Avilés-Solis J.C., Lee E., Traver V., Sato K, Bellika J.G. Combining Multivariate Statistics and Think Aloud to Asses Human-Computer interaction barriers in Symptom Checkers. (Submitted to the Journal of Biomedical Informatics)

PAPER IV

Marco-Ruiz L, Maldonado JA, Traver V, Karlsen R, Bellika JG. Meta-architecture for the interoperability and knowledge management of archetype-based clinical decision support systems. 2014 IEEE-EMBS International Conference on Biomedical and Health Informatics (BHI), 2014, p. 517–21. doi:10.1109/BHI.2014.6864416.

PAPER V

Marco Ruiz L, Maldonado JA, Karlsen R, Bellika JG. Multidisciplinary Modelling of Symptoms and Signs with Archetypes and SNOMEDCT for Clinical Decision Support. Stud Health Technol Inform., Madrid: IOS press; 2015.

PAPER VI

Marco-Ruiz L, Budrionis A, Yigzaw KYY, Bellika JG. Interoperability Mechanisms of Clinical Decision Support Systems: A Systematic Review. Proceedings from The 14th Scandinavian Conference on Health Informatics 2016, Gothenburg, Sweden, April 6-7 2016, Linköping University Electronic Press; 2016, p. 13–21.