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Bridging challenges of clinical decision support systems with a semantic approach. A case study on breast cancer

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ABSTRACT

The integration of Clinical Decision Support Systems (CDSS) in nowadays clinical environments has not been fully achieved yet. Although numerous approaches and technologies have been proposed since 1960, there are still open gaps that need to be bridged. In this work we present advances from the established state of the art, overcoming some of the most notorious reported difficulties in: (i) automating CDSS, (ii) clinical workflow integration, (iii) maintainability and extensibility of the system, (iv) timely advice, (v) evaluation of the costs and effects of clinical decision support, and (vi) the need of architectures that allow the sharing and reusing of CDSS modules and services. In order to do so, we introduce a new clinical task model oriented to clinical workflow integration, which follows a federated approach. Our work makes use of the reported benefits of semantics in order to fully take advantage of the knowledge present in every stage of clinical tasks and the experience acquired by physicians. In order to introduce a feasible extension of classical CDSS, we present a generic architecture that permits a semantic enhancement, namely Semantic CDSS (S-CDSS). A case study of the proposed architecture in the domain of breast cancer is also presented, pointing some highlights of our methodology.

1. Introduction

During the last 50 years numerous technologies for clinical decision support have been proposed worldwide (Blomqvist, 2012; Wright and Sittig, 2008; Holsapple, 2008; Berner, 2007). The benefits given by clinical decision support systems (CDSS) have also been broadly stated: e.g. they provide medical professionals with knowledge at appropriate times and manner. In general CDSS (i) facilitate an efficient and effective decision making about individual patients, (ii) reduce preventable medical errors and (iii) improve the quality of healthcare provided to patients (Berner, 2007; Peleg and Tu, 2006).

Nevertheless, the integration of such systems in daily clinical environments has not been fully achieved yet (Osheroff et al., 2007). Several authors have reported the factors affecting this lack of success (Peleg and Tu, 2006; Sittig et al., 2008; Kawamoto et al., 2005; Osheroff et al., 2007; Das and Eichner, 2010; Friedlin et al., 2007; Holbrook et al., 2003; Garg et al., 2005; Niès et al., 2006; Greenes, 2006; Liu et al., 2006) and have identified and reported the main challenges that current CDSS need to bridge.

1. The first of these challenges is that decision support should be computerized and not paper-based (Kawamoto et al., 2005). Current trends are oriented towards the development of computer-based medical guidelines, as reported by Isern and Moreno (2008). However, actual knowledge representation models for clinical guidelines do not prioritize reasoning as it could be argued that they are mainly focused on alignment and integration of data. These approaches, although signifying a stepping stone towards the inclusion of semantics in CDSS, still lack of the exploitation of the knowledge embedded in the aligned data, and thus, improvements in knowledge representation and reasoning capabilities are still in need.
2. A second aspect being reportedly identified is the fact that clinical workflow integration is recognized as a key aspect for CDSS (Holbrook et al., 2003; Kawamoto et al., 2005; Das and Eichner,

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2010). The importance of workflow integration is evident in the direct impact in the minimization of time consumption during the introduction of patient data and results. In this sense efforts should be done for the integration of CDSS with clinical systems already present in hospitals and medical centers (Holbrook et al., 2003; Das and Eichner, 2010). Additionally, CDSS should be presented as complete solutions that assist clinicians during all different tasks of their daily duties, and not only during specific activities. This fact would promote and normalize the use of clinical decision support.

3. The third challenge states that the design of the system should be developed to allow maintainability and extensibility (Peleg and Tu, 2006). Hence, cost-save solutions are needed to maintain the underlying knowledge model and the criteria for reasoning of the system. For that purpose, there is a need for creating knowledge representations that are sufficiently transparent to be understood directly by domain experts (Greenes, 2006). At the same manner, easy-to-use, and technology-transparent tools for domain experts need to be developed. Ease of use is not only conveyed towards GUI enhancements, but also in allowing medical practitioners to visualize and edit the knowledge models and criteria for the reasoning in a simple, yet powerful way. Apart from that, and following the same learning paradigm as clinicians, the knowledge and criteria embedded in CDSS should evolve with daily experiences (Berner, 2007). Therefore, experience-based approaches are needed.
4. The fourth challenge states that timely advice should be provided in CDSS (Holbrook et al., 2003; Peleg and Tu, 2006). The aforesaid leads to the need of fast reasoning processes, aimed to provide real time, or quasi-real-time, responses from those semantically enhanced clinical decision support systems.
5. The fifth challenge is related to the evaluation of the costs and effects of the CDSS itself (Sim et al., 2001; Peleg and Tu, 2006). Therefore, mechanisms for the quantitative and qualitative evaluation of the performance of the system, as well as of the quality of the knowledge and the models in it should be provided (Liu et al., 2006).
6. The last challenge states that there is a need of creating an architecture oriented at sharing and reusing CDSS modules and services (Sittig et al., 2008).

Our contribution is aimed at overcoming these reported difficulties. To this end, we firstly propose a new clinical task model oriented at the integration of CDSS to the whole clinical workflow. The presented model is both, cyclic and federated.

In our work we propose a generic architecture for Semantic CDSS (S-CDSS), which follows the clinical task model. We have implemented our proposed architecture within the framework of a research project dealing with breast cancer as case study.

We present also an evaluation methodology for our architecture. Such methodology will be applied in the planned evaluation process of the aforesaid research, which will be taking place during 2013.

Our previous work in CDSS architectures is completely aligned with the ideas proposed in this article. Particularly, in Toro et al. (2012) we proposed the development of an architecture aimed to the early detection of Alzheimer's disease (AD). It was able to learn following the same paradigm as physicians, which consists of fine-tuning criteria with the experience acquired during day-today tasks. In that work we proposed a vertical architecture based on five layers (i.e. data, translation, ontology and reasoning, experience, and application) and the use of semantic technologies and experience-based reasoning processes. It was specifically focused on the discovery of new knowledge in the system; which in the case of early detection of AD would be a clear benefit. Nevertheless, it did not approach other current challenges of decision support, such as (i) the integration of CDSS during all different stages of the clinical workflow, (ii) the automation of CDS, or (iii) the evaluation of the quality of the performance and the knowledge on the system. Therefore, we have evolved our previous vertical architecture into a federated approach based on multi agent systems.

This article is arranged as follows: in Section 2 the related work relevant for our approach is presented; in Section 3 our contributions related to the clinical task model and the generic architecture for S-CDSS are proposed; in Section 4 a case study of the architecture for the breast cancer domain is presented; in Section 5 an evaluation methodology for our architecture is presented, and finally, in Section 6 conclusions and future work are summarized.

2. Background concepts

In this section we describe the framework of ideas in which our system is build upon. We first introduce the different tasks of the care process and then we present a short overview of solutions and technologies applied to CDSS covering experience-based, semantic and multi agent-based approaches.

2.1. Clinical tasks and decision support

During daily clinical practice, clinicians perform a series of tasks framed in the care process, which include diagnosis, prognosis, treatment, evolution and prevention.

Diagnosis is the process that identifies the syndrome or the disease of the patient (Bickley and Szilagyi, 2003). As every symptom can refer to multiple causes, physicians need to narrow the possibilities. In order to do so, physicians first gather the clinical history, which consists of asking the patient about (i) relevant details of the symptoms of the disease, (ii) past medical history, (iii) family history, and also (iv) about habits related to work and leisure. Physical explorations (i.e. auscultation, palpation, inspection and olfaction) are then performed by physicians to detect the signs of the disease that patients cannot sense. Finally, complementary explorations such as functional tests, image-based diagnostic tests, endoscopies, biopsies, laboratory tests, and electrocardiography tests, increase or decrease the likelihood of the diagnosis.

Prognosis is the process of generation of a set of forecasts about the pathologic process that affects the patient, such as life expectancy, total or partial functional recovery to treatment and future complications (Banerjee and Watson, 2011; De Castro, 2006; Rozman, 2006).

Treatment implies the understanding the global effects of a diagnosed disease on a patient, which can be physical, psychical, economical and social, for the prescription of the appropriate therapeutic resources, i.e. hygienic, dietetic, pharmacologic, physical, surgical, psychological (Rozman, 2006; De Castro, 2006). An effective communication with patients and their social environment (e.g. family and caregivers), is also an essential part of the treatment.

The evolution of the patients during their disease is controlled by following up the effects of the treatment and the recovery process (De Castro, 2006; Rozman, 2006). Chronic disease management is particularly focused on this stage.

Prevention is the process aimed at avoiding a disease (Gérvas et al., 2008), which can be oriented at immunizations and vaccinations and health education, amongst others (Rozman, 2006).

Decision making plays an essential role during these stages and it is hypothesized that decision support resources aid physicians to carry out them in a more effective and efficient manner (Osheroff et al., 2007).

2.2. Experience-based clinical decision support

Different technologies have been proposed for CDSS since 1960. Power (Power, 2008) summarizes the different approaches of decision support systems (DSS) in general, in five groups: (i) model driven systems, based on simple quantitative models which are defined by limited data and parameters that decision makers need when analyzing a situation (Mathe et al., 2009); (ii) data-driven systems, based on the access and manipulation of huge amounts of data (Rinott et al., 2011); (iii) communications-driven systems, which use network and communications technologies to facilitate decision-relevant collaboration and communication (Fortney et al., 2010); (iv) document-driven systems, which use computer storage and processing technologies to provide document retrieval and analysis (Power, 2008), and finally (v) knowledge-based systems, that contain knowledge about a particular domain, the understanding of problems within that domain, and skill at solving some of these problems (Kalogeropoulos et al., 2003).

Since physicians are already using knowledge and their experience to make decisions, in our work we implicitly show that experience-based systems are yet to be considered as a new category in (Power, 2008), when applied to the clinical domain.

With that challenge in mind, previous works using case-based reasoning have been proposed (Frize and Walker, 2000; Aamodt et al., 2010), but they do not consider the possible evolution of the underlying knowledge model, which occurs indeed in real clinical domains. Machine learning approaches are also present in the literature (Eom et al., 2008), although they require arguably a high cost during system training.

Therefore, for building CDSS we propose in our work the use of experience modeling and reasoning techniques, such as SOEKS and DDNA (Sanin et al., 2007; Sanin and Szczerbicki, 2008). With the use of these technologies CDSS not only integrate in the decision making process of physicians during clinical workflow, but they are also able to learn from the everyday experiences as well as physicians do.

2.3. Semantic and multi-agent based CDSS

Semantic technologies have reportedly been described in the literature as a promising approach to solve knowledge handling and decision support in the medical domain (Gnanambal and Thangaraj, 2010; Lindgren, 2012; Blomqvist, 2012; Hussain et al., 2007; Yu and Jonnalagadda, 2006). In particular, ontologies are very promising, as presented by Mahmud et al. (2011), Farion et al. (2009), Abidi et al. (2007), Subirats and Ceccaroni (2011) and Houshiaryan et al. (2005). They are defined by Gruber (1995) in the computer science domain as the explicit specification of a conceptualization.

For clinical decision support, ontologies can efficiently fulfill the needs for (i) organized and standardized terminologies, (ii) reusability at a structural level and (iii) knowledge representation models for reasoning and inferring of new knowledge (Houshiaryan et al., 2005; Yu and Jonnalagadda, 2006).

In our work we hypothesize that a yet unreportedly need of CDSS is the reutilization of the knowledge gathered among the different clinical stages, as is done by physicians during their different decisions. Nevertheless, we have not found in the literature reported approaches covering this aspect. For instance, Colantonio et al. (2009) present an interoperable and standardized CDSS based on ontologies and a rule-based reasoner tool, intended to integrate the system in the whole clinical workflow. However, the different clinical stages are proposed as separate tasks, and therefore no direct reutilization of knowledge between the stages is supported.

We intend to bridge this aspect with the combination of semantic technologies and Multi -Agent Systems (MAS). The latter are applications in which many autonomous software agents are combined to solve large problems that are beyond the individual capabilities or knowledge of each agent (Isern et al., 2010; Flores-Mendez, 1999). MAS are defined by four main characteristics: (i) each agent has incomplete capabilities to solve a problem; (ii) there is no global system control; (iii) data is decentralized; and, (iv) computation is asynchronous (Sycara, 1998).

Different MAS have been already proposed for medical applications in general, and for clinical decision support in particular (Isern et al., 2010; Paranjape and Sadanand, 2010; Laleci et al., 2008; Shirabad et al., 2012). They are mainly oriented at the reutilization of medical resources distributed in different health centers. The work presented in Shirabad et al. (2012) shares some ideas with our approach. They focus on supporting the entire clinical decision making process with the use of MAS, although no knowledge reutilization is supported between the different stages, as separate decision systems are proposed for each stage. Additionally, no learning mechanisms based on user experience are provided.

3. Proposed model and architecture for a Semantic CDSS

In this section we propose our Semantic CDSS (S-CDSS) that intends to bridge some of the challenges described in Section 1. In our approach we focus on clinical workflow integration, by formalizing clinical tasks as cyclic and federated processes. This model imposes some technological and architectural requirements to the S-CDSS, which allows us to effectively address also the rest of the identified challenges.

3.1. Proposed clinical task model

Decisions made by physicians largely depend on the knowledge available at the moment of decision making. However, conclusions could change by new gathered evidence or even posterior medical results (Rozman, 2006). In other words, decisions made during each stage of clinical tasks, are not final by any means, as exemplified in the cycle in Fig. 1. The cyclic inspiration is found in the work of Ortiz-Fournier and Ramaswamy (2010).

In our work, we partially share the aforesaid view with the ulterior evidence that the different stages do not necessarily need to form part of the cycle and could also act independently. Furthermore, we believe that such models do not take into account the role of the decision maker missing theoretically important inputs.

A decision maker in this context, would potentially handle the knowledge involved in the whole clinical workflow and also learn from every situation, in order to apply the experience acquired in future decisions (Rozman, 2006).

It is this fact that makes an urgent necessity of clinical task models supporting reutilization of knowledge among different stages.

All these characteristics can be achieved only if each stage in the model is both (i) independent, but (ii) at the same time is related to a central entity that controls the generated knowledge for its reutilization.

The aforesaid characteristics are similar to the concept of federation in politics, where a type of sovereign state is characterized by a union of partially self-governing states united by a central government (Xing and Shengjun, 2010).

For the aforementioned reasons, we propose the combination of a cyclic and federated Clinical Task Model (CTM) (Fig. 2). In our model, diagnosis, prognosis, treatment, monitoring and prevention are partially independent stages, which (i) follow a cyclic paradigm and (ii) are united to a central decision maker. The central decision maker consists generally of a multidisciplinary team of clinical

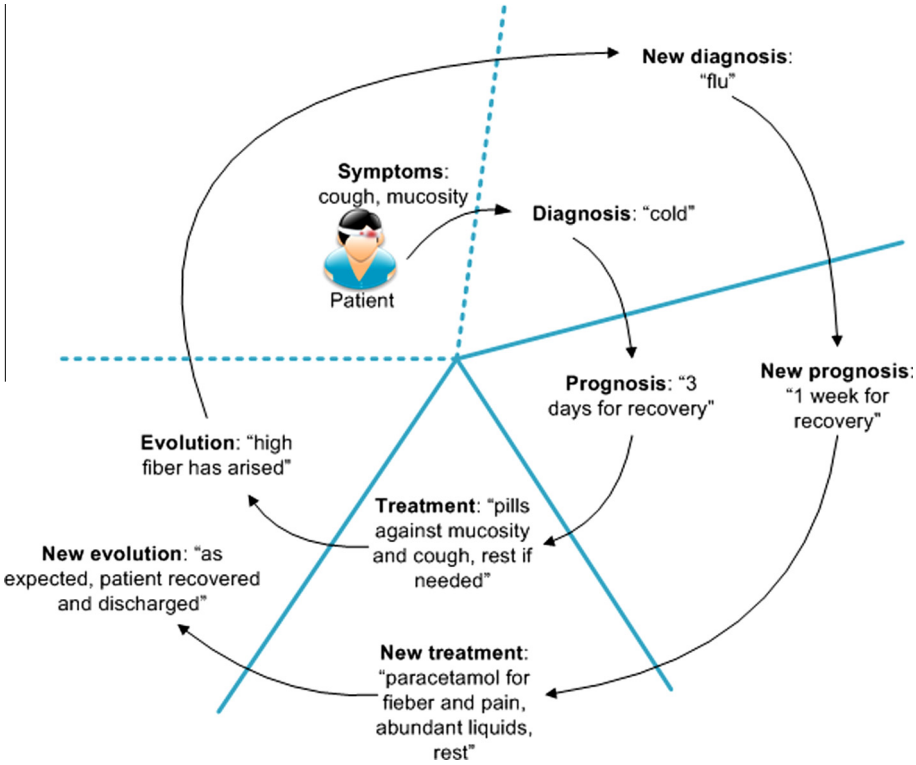

Fig. 1. Example showing clinical decision making process for a patient apparently suffering from cold.

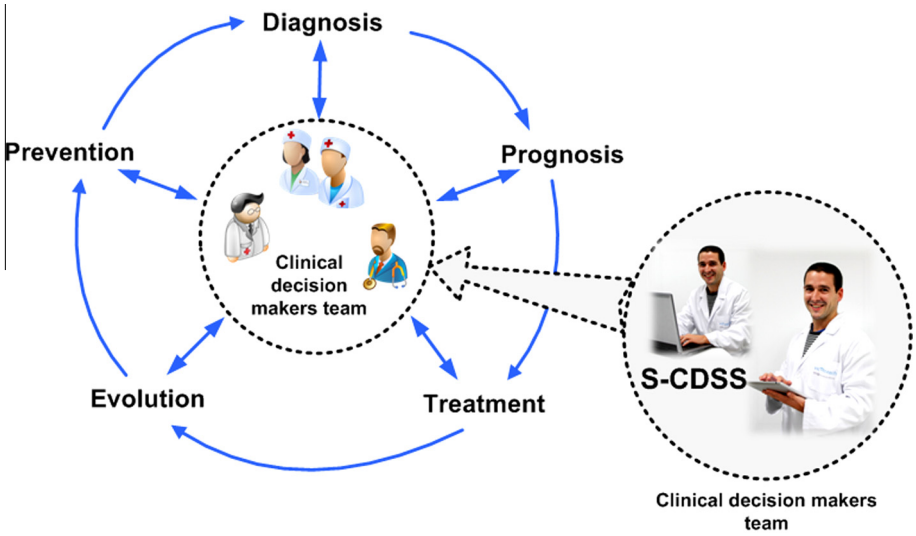

Fig. 2. Proposed clinical task model and its connection to S-CDSS.

professionals that collaborate together to make the different decisions involved during clinical tasks. CDSS will also be located in the center of our CTM together with the decision maker team.

In order to fit in the CTM, the proposed CDSS must provide (a) specialization, to cover the different tasks performed during the stages, (b) control, to handle the knowledge and the performance of the system, and also (c) knowledge reutilization. Both specialization and control capabilities are adequately approached by multi-agent systems (MAS), where each agent can be oriented at specific tasks, also covering inter-agent communication and synchronization. On the other side, knowledge reutilization is supported by the application of semantic technologies. With the combination of those, we propose the concept of Semantic CDSS (S-CDSS).

3.2. Proposed architecture

Fig. 3 depicts an overview of our architecture. At the top, the users of the systems are shown, which could be (i) clinicians or domain expert users, (ii) patients, (iii) patient relatives or caregivers, and (iv) medical institutions, associations or hospitals. They interact with a multi-agent based system, explained in detail in Section 3.3.

Some of the tasks performed by the latter require the access to patient clinical data or the storage of the obtained results. Data are located in the data repository, which consists of (i) a set of databases (DB), such as clinical systems, electronic health record (EHR) repositories, medical image repositories, picture archiving

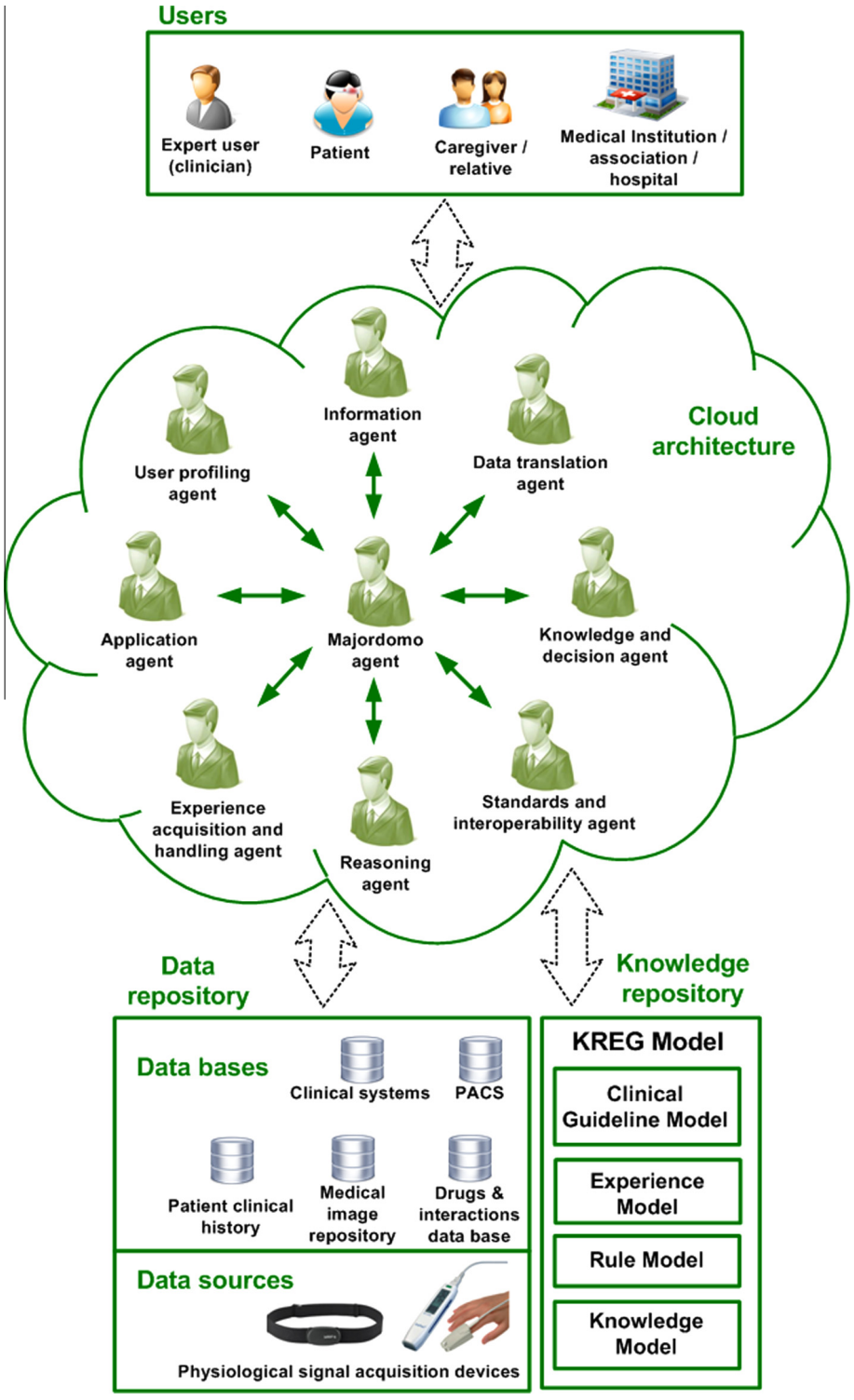

Fig. 3. Proposed architecture for clinical decision support.

and communications systems (PACS), and drugs & interactions DB, and (ii) a set of data sources, like physiological signal acquisition devices (ECG, EEG, respiration rate and effort, spirometry, oximetry, temperature) or other patient monitoring devices. In particular, the different data bases and sources in the repository may be heterogeneous in terms of serialization formats, communication protocols, size, implemented security levels, and location.

The Multiagent system will also perform reasoning tasks, which are based on a knowledge and decision model, stored in the knowledge repository. We call this model the KREG model, as we have divided it into four layers: (i) Knowledge, (ii) Rule, (iii) Experience, and (iv) Clinical Guidelines.

The Knowledge layer contains a set of domain ontologies describing the classes and properties covered by the CDSS. The set of domain ontologies comes from user experience gathering

and some other domain ontologies used in the medical domain, such as ontologies in Bioportal (Whetzel et al., 2011).

The criteria for the reasoning is expressed in terms of rules provided by domain experts and is contained in the Rule layer. Adequate tools will be given to allow expert users edit both ontologies and rules.

Additionally, clinical process models and recommendation criteria coming from clinical guidelines and protocols will be included in the Clinical Guideline layer. Recommendation criteria will be mapped to the rule layer.

Finally, during execution time, for every action performed by a user, the variables, rules, functions and constraints involved in the decisional event are stored in the Experience layer.

3.3. Multiagent architecture

The use of an agents-based paradigm provides the system with the required modularity (Sycara, 1998), and in this way scalability is also intrinsically accomplished by the system. In order to achieve the latter, our system supports the inclusion of new agents, which could be implemented in the future and then incorporated. These new agents could fulfill for instance specific functions belonging to other medical sub-domains, so that their inclusion could broaden the decision support services offered by the architecture and the domains for which it is applied.

Fig. 3 depicts an overview of our architecture. There are nine distinct agents: (i) information agent, (ii) data translation agent, (iii) knowledge and decision agent, (iv) standards and interoperability agent, (v) reasoning agent, (vi) experience acquisition agent, (vii) application agent, (viii) user profiling agent and (ix) majordomo agent.

3.3.1. Information agent

This agent accesses the information stored in the data repository of the architecture. It is in charge of handling (saving, retrieving and editing) data and deals with the corresponding web services and data accessing language and protocols.

3.3.2. Data translation agent

The approach for clinical workflow integration presented in the previous section requires that plain information of the system is semantically enhanced to support richer reasoning processes. In order to do so, the data translation agent performs the mapping of the data structure in the data repository to the KREG Model.

3.3.3. Knowledge and decision agent

The knowledge and decision agent deals with the creation, edition and visualization of the KREG Model, and it is aimed at guaranteeing the maintainability and extensibility of the knowledge in the system. Tools adapted to each of the four layers of the KREG Model are proposed: (i) graphical ontology editors and tools for knowledge extraction from evidence-based medicine (Straus et al., 2011) sources; (ii) tools for rule edition and visualization, as well as for the extraction of the decision criteria embedded in the clinical guideline semantic models; (iii) tools for the visualization and navigation of decisional events in the experience model of the system; and finally (iv) tools for extracting the knowledge from clinical guidelines.

3.3.4. Standards and interoperability agent

The standards and interoperability agent is in charge of aligning the KREG model with standards that will provide the system with interoperability for the communication with other clinical systems and possible CDSS. It will also allow the creation of shareable and understandable clinical decision support services, which open new business models for clinical decision support, e.g. Clinical Decision Support As A Service (CDSaaS). Standards covered by this agent include (i) EHR related standards, such as HL7 (Berson, 2012) and ISO 13606 (Santos et al., 2010), (ii) standardized ontologies, as for instance SNOMED CT (Nyström et al., 2010), ICD-10 (Merabti et al., 2010), UMLS (Merabti et al., 2010), as well as (iii) standards for clinical guideline representation (GLIF) (Patel et al., 1998).

3.3.5. Reasoning agent

The reasoning agent interacts with the KREG Model, a classical semantic reasoning tool and the query engine, in order to obtain inferred responses that will aid clinicians during decision making. In our previous work, we have studied fast querying and reasoning techniques used to provide time efficient performance. We use Reflexive Ontologies (Toro et al., 2008; Artetxe et al., 2013) to provide quasi-real time responses from those knowledge sources. Reflexive Ontologies store the queries that have already been made in a query structure which is a new class added to the original ontology, where individuals are the queries and the corresponding pointers to answers. Thus, every time a new query is made the answer is searched first within this class, and is only computed if it is not present there.

3.3.6. Experience acquisition and handling agent

The experience acquisition and handling agent gathers and stores the experience of clinicians or other users in the system, providing automatic maintenance and updating of the KREG Model. For this purpose, variables, functions, constraints and rules involved in every decisional event are handled.

3.3.7. Application agent

The application agent is in charge of the interaction between the user and the system, that will be held by graphical user interfaces (GUI) oriented at different purposes: (i) decision support, (ii) authoring tools for the edition or visualization of the underlying models, and (iii) patient interface for accessing clinical results, non-clinical results and physiological signals coming from user medical devices. Visual analytic techniques will be presented to facilitate the visualization of patient data, criteria for decision, next steps on the process, and most probable diagnosis or suitable treatments for a specific patient, among others. The main objective of the application agent is to be easy, in order to facilitate the work to clinicians and increase the acceptability of CDSS for their inclusion in the clinical workflow.

3.3.8. User-profiling agent

When a user is logged in, the user-profiling agent characterizes it, using the minimum number of parameters that could characterize user behavior and user attributes. There exist some user characterization modules such as GOMS (Gray et al., 1993) and CommonKADS (Hasan and Isaac, 2011), that present implementation and logic modules for user characterization.

3.3.9. Majordomo agent

The majordomo agent is in charge of the synchronization and control of the agents in the platform. We follow a blackboard approach (Craig, 1995) where agents are explicitly not allowed to talk to each other. For that purpose they must interact through the majordomo. Thereby, security issues are reduced and inconsistencies due to simultaneous communications between different agents are avoided (asynchronism). Whereas the rest of the agents are specialized in different task, the majordomo agent specialization is the control and performance of the rest of the system.

4. Case study: breast cancer

We have implemented this architecture within the research framework of the Spanish project LIFE (Life Consortium, 2012) as case study for the Breast Unit (BU) of the Valencia University General Hospital.

BU are multidisciplinary teams of physicians that work complementarily to treat breast cancer patients. The main characteristic of the BU is that decisions about the healthcare process of patients are made both, individually and collectively. Weekly the most critical cases are analyzed together during a plenary meeting and relevant aspects of their treatment are agreed. Therefore, risky decisions depend on the combination of the knowledge and experiences of different professionals.

In particular, the medical team in the LIFE project is formed by the following services: (i) radiodiagnosis, (ii) nuclear medicine, (iii) radiotherapy, (iv) rehabilitation, (v) anatomical pathology, (vi) general surgery, (vii) medical oncology, and (viii) psychology.

In order to support both, individual- and team-work of the BU, our system must provide integration at the levels of (a) clinical data and results from the different services, (b) domain knowledge and criteria for the decisions involved in each of the services, and (c) the experience acquired during the individual and collective decision making process.

To do so, we have implemented the nine-agent based architecture presented in Section 3. For each agent the following four characteristics have been defined: (i) an id, (ii) the description of the corresponding roles or tasks carried out, (iii) a status, which can be whether idle, running, or stopped, and (iv) an in/out inter-agent communication channel, called the talker.

The talker is used by the majordomo agent for communicating the rest of the agents when to start running and, if needed, which agent to connect. The strategy to decide which agent to launch is given by the functional dependencies established by each task. For instance, for the task of providing recommendations about a treatment to a clinician: (1) the Reasoning agent is launched first in order to obtain the recommended treatments; (2) during the reasoning process, the access to some patient clinical data may be needed (Information agent); (3) then the User profiling agent characterizes the clinician, and (4) the Application agent provides this user a personalized interface with decision support on treatments.

At data level, a mySQL database has been proposed for the unification of the former eight different databases of the hospital (a database per medical service). We call it LifeDB and it contains all information needed by the team of physicians to make decisions. Our industrial partner has been leading this unification, (i) analyzing the current databases, (ii) gathering the requirements and needs of each of the services that should be covered by the new design, and (iii) then aligning such databases.

The data structure of LifeDB is aligned with the KREG model in the knowledge repository. To do so, we have implemented the translation agent, which creates two xml documents in real time every time data is created or modified in LifeDB: (i) one xml document containing the structure of the data and (ii) another containing the query calls to those data in LifeDB. These two xml documents are programmatically loaded to the Knowledge Layer of the KREG model.

In particular, we have implemented the Knowledge Layer with three ontologies, as we argued in our previous work (Sanchez et al., 2011) that SNOMED CT (Nyström et al., 2010), SWAN (Ciccarese et al., 2008) and a domain ontology are sufficient for the modeling of the underlying knowledge of a CDSS. The three ontologies are: (i) SNOMED CT, for clinical description of the patient, the breast cancer and the procedures involved during its diagnosis and treatment; (ii) SWAN, for bibliographic endorsement of criteria for decision making, and (iii) a new domain ontology of breast cancer, containing the results of the specific clinical tests carried out to patients that we name the Life Ontology. A partial view of the Life Ontology is depicted in Fig. 4.

The Rule Layer of the KREG Model consists of an initial set of production rules generated by the medical professionals of the BU. These rules model the different decisions attached to each service. In our implementation, rules follow an IF-THEN-ELSE structure and are both, (i) weighted within an importance hierarchy of rules, and (ii) endorsed by the corresponding bibliographic source. This implementation follows the syntax presented in our previous work (Sanchez et al., 2011), where a rule syntax similar to Rule ML is proposed and serialized following an xml-based paradigm.

The knowledge and decision agent implements tools and techniques oriented to medical domain experts, for the edition and visualization of these production rules and domain ontologies. Graph-based visualization engines have been developed for this purpose.

The application agent is the one in charge of the interaction between the system and the user, which is in our case a medical professional. Therefore, it shows different web-based graphical user interfaces (GUI) for each of the different tools provided to the users: (i) an interface to enable remote access to the gathered patient data and to facilitate the introduction of the clinical results of each service; (ii) an interface for the graph-based visualization,

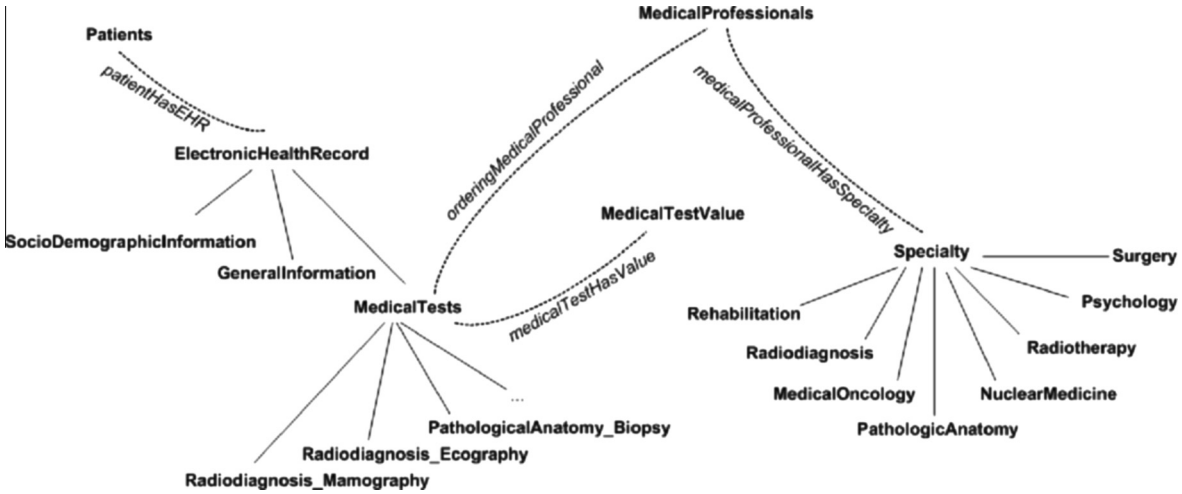

Fig. 4. Overview of the LIFE Ontology.

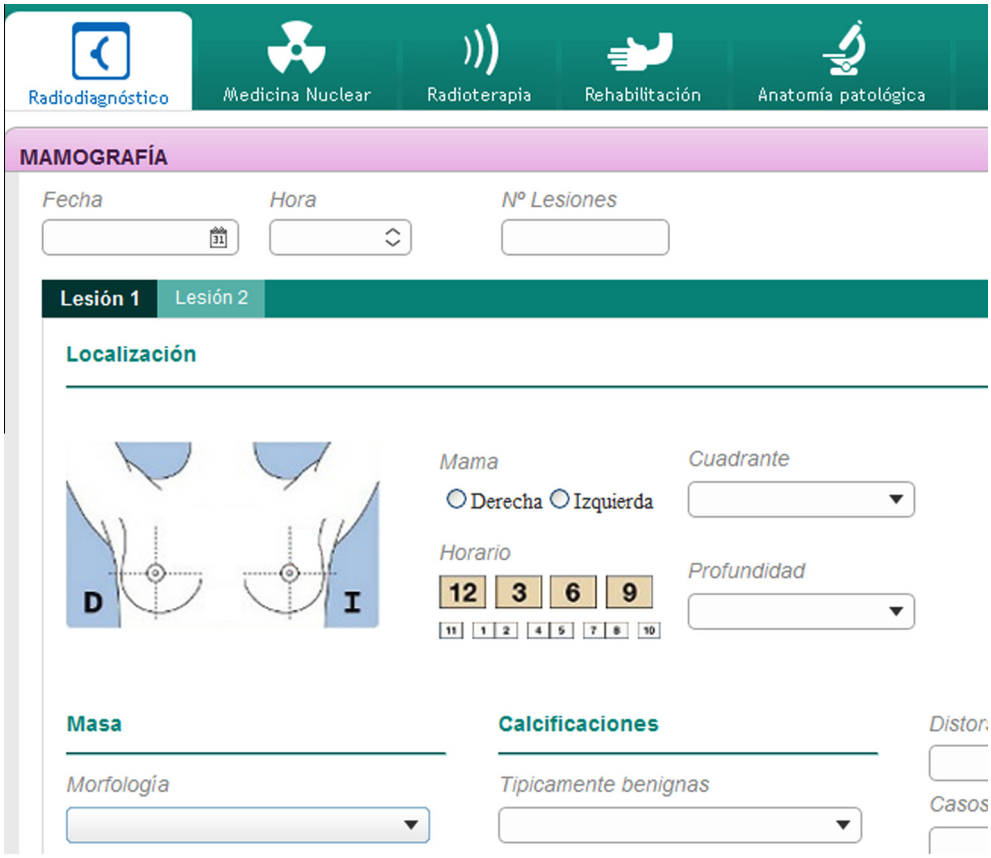

Fig. 5. Example screenshot of the data gathering interface.

edition and mapping of ontologies; (iii) a visual rule editor to ease the generation and the maintainability of rules and decision criteria, and (iv) an interface which reports recommendations supporting the decision as a pie chart, with their attached bibliographic proof. Fig. 5 shows an example screenshot of the data gathering interface.

The reasoning process to infer the corresponding diagnoses, prognoses, treatment plans, monitoring plans and prevention actions is handled by the reasoning agent. In order to provide such mechanisms, we have developed a series of methods programmed using the Protégé OWL API. The semantic reasoning process is based on the Pellet reasoner tool and we have implanted the fast querying technique of Reflexive Ontologies (RO) (Toro et al., 2008; Artetxe et al., 2013) in order to speed up the reasoning time.

In the Experience layer of the KREG model, DDNA and SOEKS technologies have been implemented using their ontology form (Sanin et al., 2007). The experience acquisition agent implements a reasoning process that enables the evolution of the initial set of rules with experience, as was presented in our previous work (Toro et al., 2012). More specifically, for each decisional event, the system stores both, the output of the reasoner and the final decision made by the corresponding physician. Decisions that do not follow the output of the reasoner drive an evolution of the set of rules in the KREG Model.

5. Evaluation methodology

The implementation of our system has been carried out in a real clinical environment and a deep and methodological evaluation of the system will be performed during 15 months starting in June 2013.

Following the work presented by Bürkle et al. (2001), our intended evaluation methodology, consists of four parts: (i) verification, (ii) validation, (iii) evaluation of the human factors, and (iv) evaluation of the clinical effects of the system.

5.1. Verification

Verification is the process of checking whether the development of the system complies with specifications (Bürkle et al., 2001) in terms of provided support for the recommendations. In our case it is trivially done by manual verification.

5.2. Validation

Validation is the process of checking whether the developed design carries out tasks adequately during a real clinical environment (Bürkle et al., 2001). Let $R_t = \{r_1, r_2, \ldots, r_{Kt}\}$ be the set rules of the KREG Model at time t, which contain the criteria for decision making embedded in the S-CDSS. We assume that the knowledge embedded in the system is time-varying, and therefore the set of rules may change in time. More specifically, in (Toro et al., 2012) we described the possible changes as fine-tuning of rules, deprecation or creation of new rules. Each rule is a tuple $r_k = \langle a_k, q_k, w_k, b_k \rangle$, where a_k denote the antecedents of the rule, q_k denote the rule consequent, w_k, is a rule weight, and b_k is the bibliographic endorsement. Let $D = \{d_1, d_2, \ldots, d_D\}$ be the set of different decision domains considered in the S-CDSS. Examples of such decision domains are the diagnosis of a patient, the type of treatment prescribed, and the quantity of drug doses, amongst others. For each decision domain d_i the system outputs a collection of decision tuples $o_i = \{\boldsymbol{dp}_{i,1}, \boldsymbol{dp}_{i,2}, \ldots, \boldsymbol{dp}_{i,C1}\}$. A decision tuple is given by $\boldsymbol{dp}_{ij} = \langle c_{ij}, p_{ij}, R_{ij} \rangle$, where c_{ij}, is a selected decision value, p_{ij}, is the

probability attached to that decision value, and R_{ij} is a set of rules that provide the supporting evidence for the aforementioned value. R_{ij} is formed by the rules $\boldsymbol{r}_k$ whose consequent q_k are equal to the selected decision value c_{ij}, being $R_{ij} = \{\boldsymbol{r}_k | q_k = c_{ij}\}$.

In our validation two different aspects will be checked: (i) similarity between the output of the system and the final decision made by physicians, and (ii) reduction of the error as the experience is acquired by the system.

5.2.1. Similarity between the output of the system and the final decision of physicians

Both, quantitative and qualitative analysis will be carried out in order to validate whether our system infers appropriate results or not.

We define, for the quantitative analysis a **similarity measure** $S(f_i, o_i)$ between (i) the system output decision o_i (collection of decision tuples) inferred for each decisional event d_i and (ii) the final decision f_i made by physicians. At this point, the similarity measure compares the decision value selected by the physician versus the output given by the reasoning tool.

Experimental design: We will collect data corresponding to o_i and f_i of 1000 decisional events, of 10 different decision domains applied to 100 patients. $S(f_i, o_i)$ will be calculated for each decisional event and cases where the normalized similarity value is higher than the 90% will be counted as true positives. As a result of our validation we will report sensitivity of the system, as well as similarity measure distributions by patient and by decision.

The qualitative evaluation will be performed from a short questionnaire filled by the physicians stating their own supporting evidences. This trace of the physician reasoning will be compared with the recommendations of the S-CDSS.

5.2.2. Reduction of the error with the experience

The experience-based evolution process of rules needs to be also validated. For this purpose after 12 months the same patient data will be introduced again in the system. At this time, the system will contain an evolved version of the ruleset, R_{t1}, and thus, inferred outputs could differ from previous ones.

Analyzing the new output for every decisional event allows to measure the **increasing of similarity** with the physician response relative to the initial rule set R_{t0}. From this analysis we will conclude the effectiveness of this agent.

5.3. Human factor evaluation

The human factor evaluation process consists of checking the usefulness of the system, its usability and the satisfaction of the user with the different aspects of the system (Bürkle et al., 2001). Both quantitative and qualitative measures will be obtained.

The qualitative analysis will be focused on a questionnaire where physicians can provide their opinion about usability and utility of the system. The results obtained will be studied for improving the system in a future work.

The quantitative analysis, on the other side, will be based on a log, storing the number of times physicians have voluntarily accessed the decision support module. These statistics will be compared with the answers in the questionnaires in order to conclude which of the reported factors are in fact the most influential ones.

5.4. Evaluation of the clinical effects

Finally, the evaluation of the clinical effects of the system will be carried out comparing statistical outcome quality indicators (i.e. number of diagnosed patients, number of treated patients, number of recovered patients) for (i) the last 12 months before the LIFE system was integrated in the hospital and (ii) the first 12 months of use of it. Possible external changes in between, such as new medical infrastructure acquired by the hospital or changes in available personnel will be taken into account.

6. Conclusions and future work

In this article we have presented a generic software architecture of S-CDSS, oriented to bridging some of the reported challenges of clinical decision support.

Our main contribution consists of a new clinical task model where the different clinical information processing stages (i.e. diagnosis, prognosis, treatment, evolution and prevention) are assumed as a cyclic chain of federated information processing agents. On the basis of this clinical task model, our architecture permits the integration and reutilization of decision support systems along the whole clinical workflow.

Our previous work on CDSS focused on the discovery of new knowledge (implicit). In this article we contribute advances in order to bridge remaining CDSS challenges. We have presented details about the implementation carried out in the breast cancer domain, and about the evaluation methodology that will be used to test the system. Evaluation at the clinical level requires lengthy data gathering processes; in that matter validation results will be available and published in a future work.

In our approach it is not possible to perform a classical validation, where a training data set is used to build the system and a validation data set is used to evaluate it. This is related to the nature of our system of being based on a knowledge model provided by a team of domain experts. Due to the aforesaid reasons the correctness cannot be guaranteed with a classical metric. Our system assumes that the model is correct, and we validate this model comparing decisions recommended by the system with decisions made by end-users (physicians), in order to evaluate discrepancies from a real world decision maker solution.

As future work we will study the full computerized automation of the decision support. We will focus on the acquisition of decision criteria and rules directly from current available knowledge sources, such as clinical guideline repositories and Evidence Based Medicine databases. In particular, we will work on the extraction of the recommendations contained in clinical guidelines. We will model these recommendations as rules, which will feed the Rule Layer of the KREG Model. For this purpose, we will explore natural language processing techniques.

Additionally, we will also work on the application of decision support standards for the modeling of the knowledge and criteria in the system, in order to provide a universal clinical decision support service.

Finally, we aim to explore methodologies and tools for the qualitative and quantitative evaluation of knowledge and experience stored in the system.

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