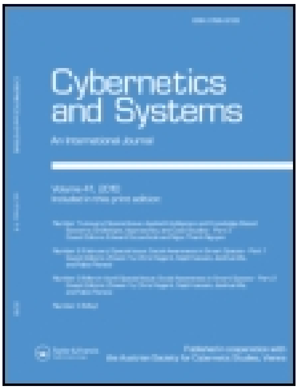

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Using Set of Experience Knowledge Structure to Extend a Rule Set of Clinical Decision Support System for Alzheimer's Disease Diagnosis

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In this article we present an experience-based clinical decision support system (CDSS) for the diagnosis of Alzheimer's disease, which enables the discovery of new knowledge in the system and the generation of new rules that drive reasoning. In order to evolve an initial set of production rules given by medical experts we make use of the Set of Experience Knowledge Structure (SOEKS). An illustrative case of our system is also presented.

KEYWORDS Alzheimer's disease, clinical decision support system, set of experience knowledge structure, user experience

INTRODUCTION

Interest in making clinical decision support systems (CDSSs) for the diagnosis of Alzheimer's disease (AD) is great, because it is the leading cause of dementia in developed countries (Monien et al. 2009). Early diagnosis of

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AD is commonly carried out through analysis of the results of different medical tests, which are multidisciplinary by nature, such as neurological, neuropsychological, and neuroimaging tests (Monien et al. 2009). During this process, a large number of parameters are generated and making a proper diagnosis becomes a knowledge handling problem. In addition, recent advances in early diagnosis of AD date the initial stages even 15 years before the first clinically recognizable symptoms become visible (Monien et al. 2009) and there is still no known cause for AD. Therefore, there is a need for the medical and scientific community to discover which parameters are most relevant and which are not with regard to an early diagnosis.

CDSSs help physicians overcome knowledge handling problems. They are active knowledge resources that use patient clinical data to generate case-specific advice (Liu et al. 2006). During diagnosis processes, CDSSs analyze data from those medical tests and present results to physicians so they can make decisions more easily and efficiently and obtain a proper diagnosis.

In this article we present a CDSS that (i) supports physicians during diagnosis of AD and (ii) offers tools needed to fulfill the aforementioned need to discover relevant parameters for this diagnosis. In fact, this CDSS is based on the experience acquired or learned from the user, and it enables the discovery of new knowledge in the system and the generation of new rules that drive reasoning.

This CDSS is an evolution of the system proposed by Sanchez et al. (2011) that consists of a knowledge-based approach based on semantic technologies for knowledge representation and a set of static production rules provided by domain experts. This static rule set drives the reasoning process that leads to a diagnosis; in other words, it is the criteria for the diagnosis.

According to the aforementioned need to find the relevant criteria for diagnosis of AD, the system presented in this article discovers new knowledge from this set of rules. In this way, new rules are generated based on experience.

There are several approaches that can be used to endow the proposed system with the ability of adapting and discovering rules when special conditions are encountered, such as fuzzy logic or neuronal networks, among others. We propose the use of the set of experience knowledge structure (SOEKS) and decisional DNA (DDNA; Sanin and Szczerbicki 2005, 2008, 2009) in their Web Ontology Language (OWL) form (Sanin et al. 2007) as a novel way of attaining this behavior. These elements will allow the system to capture previous experiences and discover new knowledge using bio-inspired techniques and the reasoning capabilities offered by ontologies.

This article is arranged as follows: in the next section we present some background concepts about CDSS, semantic technologies, and SOEKS, which will be referenced throughout the article. Following, we present the experience-based CDSS. Then, we present the application of SOEKS and the process of the evolution of the rules or generation of new ones with it.

Next, we introduce a case study that uses the aforementioned experience-based CDSS for the evolution of the initial rule set. Finally, we discuss our conclusions and future work.

BACKGROUND CONCEPTS

In this section we present a short overview of the relevant concepts that are discussed in the following sections.

Clinical Decision Support Systems

Classical CDSS share some common limitations that have not been entirely overcome yet (Wright and Sittig 2008). Firstly, the representation of knowledge is static, limiting the type of knowledge that can be represented. Additionally, CDSS definition is specified only through explicit information enumeration (i.e., case-based systems) and, thus, arguably no discovery of new knowledge is directly supported (Sanchez et al. 2011). Secondly, knowledge sources are often heterogeneous and disperse, which increases the complexity of CDSS. Third, criteria for diagnosis are by nature highly changeable due to the high frequency of new findings and advances and should be updated often. Hence, the maintainability of the system could be a critical problem. Lastly, terminological interoperability is also an important matter that classical approaches in CDSS do not solve appropriately (Wright and Sittig 2008). Two different CDSSs may not understand each other, even if their domain and purpose is the same, because they can adopt different terminologies or, in extreme cases, due to the inertia related to monolithic and legacy system architectures.

In the literature, several architectures for CDSS have been presented (Michalowski et al. 2005; Hussain et al. 2007). According to Wright and Sittig (2008), the evolution of architectures for CDSS has followed four phases: standalone CDSS, CDSS integrated to clinical systems, standards-based systems, and service models. The main challenges addressed by these architectures deal with (a) the integration of CDSS into clinical workflows and systems and (b) the transference of successful interventions from one system to another (Wright and Sittig 2008).

Semantic Technologies Applied to Clinical Decision Support Systems

Knowledge engineering (KE) techniques can efficiently deal with the aforementioned problems such as terminological interoperability, system maintainability, and source heterogeneity and disparity. More precisely, semantic technologies have 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 2011).

In particular, ontologies are very promising. Gruber defined ontologies in the computer science domain as the explicit specification of a conceptualization (Gruber 1995). Ontologies can fulfill the needs for organized and standardized terminologies and reusability efficiently at a structural level (Houshiaryan et al. 2005). They also deliver interesting benefits when used for reasoning and inferring new knowledge (Yu and Jonnalagadda 2006); for instance, the fast query systems presented by Toro et al. (2008).

Among the most widely used ontologies within the medical domain are the Semantic Web Application in Neuromedicine (SWAN; Ciccarese et al. 2008) and the Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT; Nyström et al. 2010).

Set of Experience Knowledge Structure and Decisional DNA

Knowledge has been an important asset for individuals, organizations, and society throughout the ages. Decision makers, in general, base their current decisions on lessons learned from previous similar situations (Sanin and Szczerbicki 2005); however, much of the experience held by individuals is not properly capitalized on due to inappropriate knowledge representation or administration. This leads to decision reprocessing, inadequate response times, and lack of flexibility to adapt when new environmental conditions are found.

In order to represent and reuse experience in an adequate form, Sanin and Szczerbicki (2005, 2008) proposed the concepts of the SOEKS and DDNA. SOEKS is a knowledge representation designed to store formal decision events in an explicit way and is based on four basic elements that are considered to be crucial in decision-making actions. These elements are variables (V), functions (F), constraints (C), and rules (R).

Variables are used to represent knowledge in an attribute-value form, following the traditional approach for knowledge representation. Given that the set of F, C, and R of SOEKS are different ways of relating knowledge variables, it is safe to say that the latter are the central component of the entire knowledge structure. Functions describe associations between a dependent variable and a set of input variables; therefore, SOEKS uses functions as a way to establish links among variables and to construct multi-objective goals (i.e., multiple functions). Similarly, constraints are functions that act as a way to limit possibilities, restrict the set of possible solutions, and control the performance of the system with respect to its goals. Finally, rules are used to represent inferences and correlate actions with the conditions under which they should be executed. Rules are relationships that operate in the universe of variables and express the connection between a condition and a consequence in the form if–then–else.

SOEKS is the basis for the creation of DDNA, which is a structure capable of capturing decisional fingerprints of an individual or organization. The name *decisional DNA* is an allegory to human DNA because of its structure and the ability that if offers to store experience within itself. Let us illustrate this metaphor: the four elements that comprise a SOEKS can be compared to the four basic nucleotides of human DNA, and they are also connected in a way that resembles a human gene. A gene guides hereditary responses in living organisms, and analogously a SOEKS guides responses in decision-making processes. A group of SOEKS of the same "type" (i.e., knowledge category) comprise a decisional chromosome, which stores decisional "strategies" for a specific category. Therefore, having several SOEKS chromosomes is equivalent to having a complete DDNA strand of an organization containing different inference strategies. SOEKS and DDNA have been successfully applied in industrial environments, specifically for maintenance purposes, in conjunction with augmented reality (AR) techniques (Toro et al. 2007), and in the fields of finances and energy research (Sanin et al. 2009).

EXPERIENCE-BASED CLINICAL DECISION SUPPORT SYSTEM FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE

In this section, we propose an experience-based CDSS for the diagnosis of AD. The experience of the physician using our system is stored in it and with this experience the system is able to (i) make explicit the implicit knowledge contained in the system and (ii) generate new criteria to drive reasoning.

The proposed system is the evolution of a previous work presented by Sanchez et al. (2011) in which a knowledge-based CDSS for the diagnosis of AD was presented. The system was based on ontologies for knowledge representation and a semantic reasoning process that inferred diagnoses for patients. The semantic reasoning was driven by a static set of production rules provided by AD experts. The previous system has been extended with the application of SOEKS to provide it with the ability to evolve the rule set and discover new rules.

The architecture of the CDSS presented consists of five layers (Figure 1): a data layer, a translation layer, an ontology and reasoning layer, an experience layer, and an application layer.

Heterogeneous and spatially disperse databases (DBs) store the data that feed the experience-based CDSS presented in this article. These DBs, which can be provided and maintained by different organizations, are all accessible to our system and they form the data layer of the architecture. The translation layer performs an alignment between data in the DB of the data layer to knowledge that is stored in the ontology and reasoning layer; each DB is related to a translation module in the translation layer. In this way, DB do not need to be aligned in between or intercommunicate directly; they remain

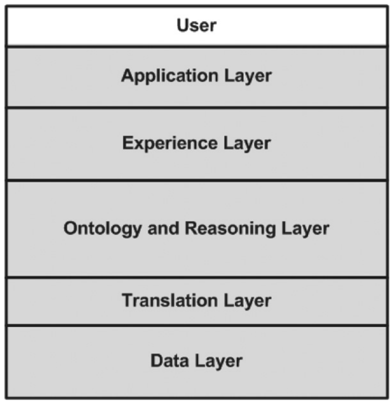

FIGURE 1 Proposed architecture for the CDSS.

decentralized. The ontology and reasoning layer contains the knowledge of the system and performs reasoning processes for clinical decision support. Figure 2 shows the structure of the ontology and reasoning layer.

Ontologies were chosen as the knowledge containers of the system. In particular, three different ontologies model this domain of diagnosis of AD: the Mind ontology (Sanchez et al. 2011) and the supporting ontologies SWAN (Ciccarese et al. 2008) and SNOMED CT (Nyström et al. 2010). Firstly, SWAN links and endorses the criteria of the system with the hypotheses and publications that are being held by the medical and scientific community, and the contents of our system can be validated and verified to be current and updated. Secondly, SNOMED CT is used for standardization purposes. Lastly, the Mind ontology contains the tests carried out on patients diagnosed with probable AD, such as neuropsychological, neurological, radiological,

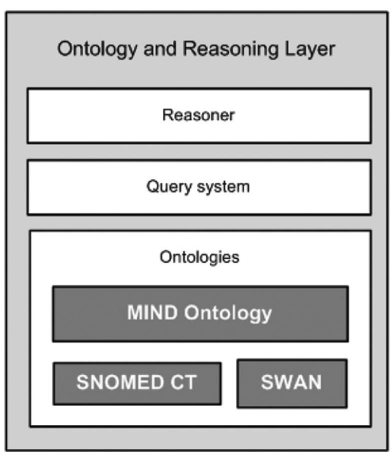

FIGURE 2 Proposed structure of the ontology and reasoning layer.

metabolomical, and genetic tests. It is mapped to both SWAN and SNOMED CT.

The intrinsic semantics embedded in the ontologies can lead to the discovery of new knowledge, such as diagnoses from implicit knowledge or new connections in the model when queried and inferred using production rules and description logic (DL) reasoners. Our domain experts have generated a set of production rules that drive the semantic reasoning (Sanchez et al. 2011). They follow an if–then–else structure and the syntax is inspired in RuleML recommendation with minor changes given basically for usability reasons. Each rule has been endorsed by the corresponding bibliographic source (by means of the mapping to SWAN) and has also been weighted depending on its importance within the rule hierarchy. This importance was set by the criteria of our domain experts. Figure 3 depicts a production rule example.

The experience layer above is based on SOEKS and DDNA. It stores the experience of the user (the methodology and criteria used for the diagnosis process) in forms that represent the formal decision events in an explicit way. This experience is then applied, and new knowledge and new rules that drive the diagnosis are discovered by the system. In this way, not only are diagnoses suggested to physicians but new or modified rules to achieve those diagnoses are also supplied. In the next section the evolution process of the rule set with the use of SOEKS and DDNA is explained in detail.

Finally, the application layer deals with the interaction between the user and the system. A graphical user interface (GUI) gathers the inputs given by users and presents the results to physicians to provide support for decision making. Figure 4 depicts the diagnosis inferred by the system and presented to physicians.


```
[redacted]xml version="1.0" encoding="ISO-8859-1"[redacted]
<RuleSet>
    <LoadRule>
        <RuleID>HUVR_1</RuleID>
        <Rule>if (( CLASS InformacionClinicaNeurologica with the PROPERTY InformacionClinicaNeurologica_E
        <weight>1</weight>
        <AccordingTo>
            <classes>
                <class>JournalArticle</class>
            </classes>
            <contributionAuthors>
                <contributionAuthor>Rafael Blesa</contributionAuthor>
                <contributionAuthor>Montse Pujol</contributionAuthor>
                <contributionAuthor>Miguel Aguilar</contributionAuthor>
                <contributionAuthor>Pilar Santacruz</contributionAuthor>
                <contributionAuthor>Imma Bertran-Serra</contributionAuthor>
                <contributionAuthor>Gonzalo Hernández</contributionAuthor>
                <contributionAuthor>José M. Sol</contributionAuthor>
                <contributionAuthor>Jordi Peña-Casanova</contributionAuthor>
            </contributionAuthors>
            <doi>10.1016/S0028-3932(01)00055-0</doi>
            <title>Clinical validity of the 'mini-mental state' for Spanish speaking communities</title>
```

FIGURE 3 Production rule example.

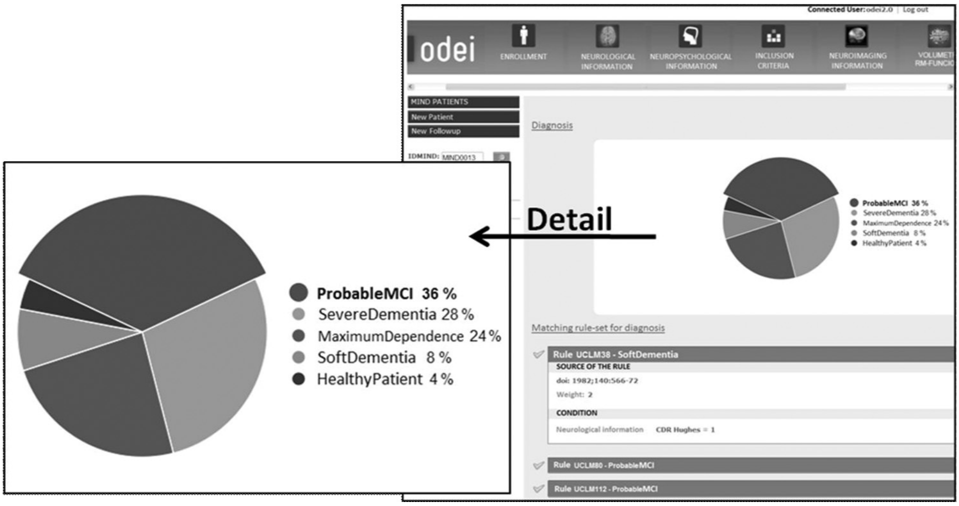

FIGURE 4 Suggested diagnosis from the system (partial view).

EVOLVING THE SET OF RULES USING SOEKS

As a type of decision maker, medical experts base their current decisions on lessons learned from previous similar situations, which in the context of Alzheimer's diagnosis are represented by studies performed on several groups of patients in different contexts. In spite of the wide range of scenarios considered by medical studies, the rules and conditions that are derived from them may prove to be insufficient, too general, or simply not relevant in scenarios with very particular characteristics. This situation clearly illustrates the need for an automated solution capable of determining adaptability in the set of rules of the diagnosis system, with the purpose of increasing the accuracy and effectiveness of the diagnoses made by medical experts. We propose the use of DDNA and SOEKS in their OWL form (Sanin et al. 2007) as a novel way of attaining this behavior.

The proposed integration takes existing decisions made by experts stored in the system and feeds them into SOEKS/DDNA ontology. Each decision is translated into its corresponding SOEKS equivalent, and then the system is able to infer new rules in three categories:

- Fine-tuned rules: a combination of existing rules to generate a new one.
- Deprecated rules: rules that are deemed not to be relevant anymore based on previous experiences.
- Original rules: rules discovered by the system that were not apparent to the experts.

In order to successfully accomplish the extension described previously, some considerations have to be taken into account. First of all, rules in the ontology and reasoning layer are defined by experts; in other words, they are heuristics representing the experience of several medical practitioners, which means that they are decisions. Secondly, for the knowledge stored in the ontologies of the system, several restrictions on the possible values that the variables can take have been defined but mathematical functions that relate the different variables in an independent/dependent form have not.

For the aforementioned considerations, the different SOEKS that are created based on this existing decisions (i.e., heuristics) are considered a special type of SOEKS. A SOEKS resulting from the parsing process will not have any functions or rules; instead, each heuristic represents an experience, which is comprised at this stage of variables and constraints. This approach reflects the decision-making process performed by the medical staff in a more precise way, based on rules derived from scientific studies, where each rule is a decision drawn upon experience.

CASE STUDY

The implementation of the proposed experience-based CDSS is being developed as part of the Spanish MIND project (http://www.portalmind.es), which follows a multidisciplinary approach for the early detection of AD. Clinical trials have been performed on more than 350 patients in three hospitals in Valencia, Spain, with the intention of gathering information about the early diagnosis of MCI patients evolving to AD. The CDSS described in this article is a technological tool that supports the work of physicians during the clinical trials. This section describes the current implementation of the system, which uses the Protégé OWL Application Programming Interface (API) as the mechanism to create and manipulate OWL-DL ontologies. In addition, an outline of the future implementation of the SOEKS/DDNA integration and rule discovery process is presented; however, the details of the inference procedure required to execute such a process are outside the scope of this article.

Initially, the system requires data from the different trials performed on the patients. Such data are gathered via a Web-based system called ODEI. When new data are loaded, the Mind ontology is instantiated using the information provided by users through ODEI's user interface. Then, a semantic reasoning process based on the initial set of production rules is executed with the objective of inferring diagnoses. An evaluation of the inferred diagnoses and decisions on the appropriate course of action are made by the physicians; their final decisions are loaded to the SOEKS/DDNA ontology.

As described in the previous section, a translation and inference process between the SOEKS/DDNA ontology is required. However, performing such translation process on a one-on-one basis every time a record is inserted is not practical; it is time consuming with a large number of concurrent users and may lead to inaccurate results when the system is "learning" (i.e., has little or no experiences in its initial state). This last issue is due to the fact that an accurate inference requires the evaluation of similar elements or situations; therefore, numerous experiences are preferred in order to execute the automated inference process.

Consequently, a microbatch approach is proposed, similar to those used in data warehouses, that allows processing a reasonable amount of data without the heavy workload of large batch processes or the inherent infrastructure complexity required for real-time or near real-time processing. Additionally, processing small batches of knowledge allows the system to deliver better inference results even when the system is still learning. According to these ideas, the batch process to load the SOEKS/DDNA ontology has two main steps: (1) translate knowledge between ontologies and (2) execute the inference process. As mentioned previously, the details regarding step 2 are outside the scope of this article.

The translation process will use a parser in charge of reading the knowledge from the Mind ontology, extracting the details of all OWL classes, individuals, and attributes and inserting them into the SOEKS/DDNA ontology using the SOEKS API. This API is a Java-based library that provides the means to create, manipulate, and import/export SOEKS in XML or OWL formats; the API was developed by the Knowledge Engineering Research Team (KERT) from the University of Newcastle, Australia.[1] The parser will comprise three main submodules: one to extract classes, one for variables, and one to extract constraints. Each module will create an image in memory of the SOEKS that is being processed, which is written to the SOEKS/DDNA ontology once the extraction is finished. To illustrate the functionality of the modules, we use an example production rule. It is assumed that the variables and restrictions in the following example are already stored in the Mind ontology:

```
IF((CLASS NeuropsychologicalInformation WITH THE PROPERTY
NeuropsychologicalInformation_FAQPfeffer GREATER THAN 5)) AND (CLASS
NeuropsychologicalInformation WITH THE PROPERTY NeuropsychologicalInformation_GDS SMALLER
THAN 6) THEN (( CLASS Diagnosis WITH THE PROPERTY Diagnosis_ReasonedDiagnosis EQUALS TO
ProbableAlzheimer ) AND (CLASS Diagnosis WITH THE PROPERTY Diagnosis_ReasonedRisk EQUALS
TO Low))
```

In the first place, the class module reads every class in the Mind ontology and translates them into individual SOEKS. In the example, we have

[1]Visit http://www.newcastle.edu.au/school/engineering/research/KERT/ for more information.

the classes NeurophsycologicalInformation and Diagnosis; as a result, two SOEKS instances (i.e., two experiences) are created as follows:

```
SOEKS NeurophsycologicalInformation =new SOEKS();
Category cat=new Category();
cat.setArea("Neuro Psychological Information");
NeurophsycologicalInformation.setCategory(cat);

SOEKS Diagnosis =new SOEKS();
cat.setArea("Diagnosis");
Diagnosis.setCategory(cat);
```

Each of these experiences has different variables. For the NeurophsycologicalInformation class, the variables are FAQPfeffer and GDS, and for the Diagnosis class, the variables are ReasonedDiagnosis and ReasonedRisk; therefore, the variable module will create two variables as shown below:

```
Variable FAQPfeffer =new Variable("FAQPfeffer",
                                    Variable.VARIABLE_TYPE_NUMERICAL,

                                     causeValue,effectValue,unitType,true);

Variable GDS =new Variable("GDS ",
                                      Variable.VARIABLE_TYPE_NUMERICAL,

                                     causeValue,effectValue,unitType,true);
Variable ReasonedDiagnosis =new Variable("ReasonedDiagnosis",

                                     Variable.VARIABLE_TYPE_CATEGORICAL,

                                     causeValue,effectValue,unitType,true);
Variable ReasonedRisk =new Variable("ReasonedRisk",

                                     Variable.VARIABLE_TYPE_CATEGORICAL,

                                     causeValue,effectValue,unitType,true);
```

The previous code fragment illustrates the process of creating SOEKS variables in memory. Each variable is assigned a name, a type (numerical or categorical), cause-and-effect values, the unit of measurement, and a flag to indicate if it is internal or external. The cause-and-effect values represent the variable in its current and desired states, respectively; the unit of measurement of the variable being processed is defined by the experts; and the internal/external flag indicates whether the variable can be controlled by the decision maker or not.

Once the SOEKS and its variables are created, the constraints module will read the OWL properties and constraints for every variable and construct the constraints elements in memory. For example, according to the production rule, FAQPfeffer is greater than 5; therefore, a constraint based on this knowledge should look like this:

```
Constraint FAQ_Constraint=new Constraint();
               FAQ_Constraint.value(5);
               FAQ_Constraint.symbol(">");
               FAQ_Constraint.variable(FAQPfeffer);
```

This process is repeated for every constraint and variable in the system. The last step before inserting the experience into the SOEKS/DDNA ontology is to link all of the elements of each SOEKS together. To do this, we will create a set of variables and a set of constraints that will be added the individual experiences. The following code fragment illustrates the process with the NeuropsychologicalInformation SOEKS.

```
VariableSet varSet=new VariableSet();
varSet.add(FAQPfeffer);
varSet.add(GDS);
NeurophsycologicalInformation.setSetOfVariables(varSet);

ConstraintSet consSet=new ConstraintSet();
consSet.add(FAQ_Constraint);
NeurophsycologicalInformation.setSetOfConstraints(consSet);
```

Finally, the translation process will write the SOEKS to an OWL-DL ontology. This is done by simply calling the soeksToOWL( ) method provided by the SOEKS API. After all of the experiences in the batch are translated using the ideas described before, the inference process is executed to discover new rules according to the categories described in the previous section. Then, assuming the existence of more knowledge in the system, under specific conditions and after validation against other experiences, the inference process might be able to determine that the values obtained from the Folstein test and the probabilities of suffering from AD are related. As a result, the original rule discovered by the system could be as follows (assuming the existence of other experiences in the system):

```
IF ((CLASS NeuropsychologicalInformation WITH THE PROPERTY
NeuropsychologicalInformation_MMSEfolstein SMALLER THAN 16 )
THEN ( CLASS Diagnosis WITH THE PROPERTY Diagnosis_ReasonedDiagnosis EQUALS TO
ProbableAlzheimer)
```

As a result of the extension of the system with the experience layer using SOEKS and DDNA the system is able to discover new knowledge and rules using bio-inspired techniques and the reasoning capabilities offered by ontologies. By using these methods, the system acts as an advisor for physicians and supports their decisions.

CONCLUSIONS AND FUTURE WORK

In this article we presented an experience-based CDSS for the diagnosis of AD that enables the discovery of new knowledge and new rules in the system. The process that leads to this discovery has also been presented and discussed, as well as a case study of the system.

This system supports physicians during diagnosis processes, but it is also a research tool that could help them determine the most relevant parameters for the diagnosis of AD and its cause.

The system proposed in this article is arguably very promising, because it does not rely only on the criteria given by the domain experts providing the rule set but also relies on the experience of the domain experts that are using the system. With this experience, some of the rules may be modified or some other may be generated in order to have a more accurate rule set.

SOEKS has been shown to be a valid technology for the discovery of new rules. As future work we are working on the extension of the SOEKS to not only discover new rules but to make decisions based on previous ones. We will also work on the measurement of the quality of the captured and generated experience.

The use of SOEKS and DDNA in this project is a contribution in the field of decision support systems that takes existing elements from rule-based and expert systems to create an intelligent experience-based system.

The CDSS presented in this article could also be extended to cover other areas in the domain of AD, such as drug discovery, as well as extended to other purposes, such as treatment or patient monitoring. It could also be applied to other domains—for example, cancer or sclerosis—where the discovery of new knowledge, and especially new rules, plays a fundamental role.

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