Mémoire: A Framework for Semantic Interoperability of Case Based Reasoning Systems in Biology and Medicine

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Abstract. Mémoire is a framework for sharing and distributing case bases and case based reasoning (CBR) systems in biology and medicine. This paper first introduces the semantic Web approach to build a better Web where search engines, knowledge sources and servers, applications and services can live, work, and learn in cooperation. This semantic approach is particularly well suited for biomedical domains because significant ontologies have been developed there, and constitute a sound basis for the standardization effort required for the
semantic Web. Case based reasoning systems in biomedicine have also benefited from these biomedical ontologies and models. This article demonstrates on three such systems how a semantics infused approach in CBR gives better, more accurate results in CBR. It is from this previous work on a semantic approach in CBR in biomedicine that the Mémoire framework has evolved. Mémoire proposes a unified OWL-based representation language for cases and case based ontologies in biomedicine, and a set of tools for building case based reasoning systems compliant with its language. Mémoire is extensible and can be adapted to different types of biomedical application domains, tasks, and environments. Mémoire will permit to bridge the gap between the multiple case based reasoning systems dedicated to a single domain, and make available to agents and Web services on the Web the case based competency of the CBR systems adopting its interchange language. The approach could be extended to other application domains of CBR.
1 Introduction

The semantic Web is a particularly active area of research in artificial intelligence. Its creators have defined the semantic Web as "an extension of the current Web in which information is given well-defined meaning, better enabling computers and people to work in cooperation." [2]. They describe the semantic Web as a framework for spreading and distributing information/data, information/data structures, and information/data about articulation between ontologies. Here, we hypothesize that a similar approach would enable the distribution of cases, case structures, and information/data about articulation between the ontologies comprising these cases. As a matter of fact, the semantic Web is an endeavor to introduce semantics and semantic interpretation in Web documents and data, beyond current syntactic approaches. Similarly, taking as examples several case based reasoning (CBR) systems in biology and medicine, we show that a semantic approach is required to understand and reuse cases well, and that in order to build shared, distributed case bases, the approach of the semantic Web is a good model to apply to the task of building large, synergistic case bases in medicine and biology. This paper introduces the Mémoire project, as a framework for sharing case bases and distributed case based reasoning systems in biology and medicine.

In the second section, we will introduce the reader to the semantic Web. The third section summarizes the semantic Web current application in biology and medicine. The fourth section explains how biomedical case based reasoning makes use of semantics, by analyzing three CBR systems in this domain. The fifth section presents the Mémoire project, which is essentially a framework for sharing case bases in biology and medicine. The sixth section sets forth and evaluation of Mémoire. It is followed by a discussion and the conclusion.

2 Semantic Web

The goal of the semantic Web spans beyond pure information retrieval purposes: “The Semantic Web is a vision: the idea of having data on the Web defined and linked in a way that it can be used by machines not just for display purposes, but for automation, integration and
reuse of data across various applications” [8]. It is to reuse information and data available on
the Web with all the word reuse can encompass. This implies reasoning from information and
data on the Web, such as cases. CBR systems in the future will be able to answer to agents’
searches for tailored, specific information as its methodology excels in this domain.

The semantic Web currently has three main components, or layers (see Fig. 1):

1. **Information/data in HTML or better XML format.** XML is a common language
to represent Web content, and using it facilitates integration of documents from dif-
f erent sources, in particular via XSLT transformation language. Nevertheless, the
meaning of the different tags across applications is not provided in XML, so that an-
other layer needs to provide that semantic mapping.

2. **Information/data structures in a semantic Web format such as RDF.** Resource
Description Framework (RDF) [16] provides this mapping between different XML
or database schemas. Information in RDF can be simply merged from different Web
sources and queried as though they came from a single source. RDF permits to de-
scribe not only the data, but rules to interpret the data.

3. **Information/data about articulation between ontologies.** Extensions of RDF such
as RDF-schema, or Web ontology language, such as DAML [9] and OWL [15], per-
mit to represent ontologies of terms (thesauri) and concepts in hierarchies expressing
how these terms relate to one another.
DAML and the "Semantic Web".

**Fig. 1.** DAML and the Semantic Web, showing its three layers: XML, RDF, and DAML. DAML is a semantic markup language for Web resources, and can represent propositional logic, predicate calculus, and first order logic, in order to make ontologies accessible through its interchange level language to Web agents, applications, and services.

The semantic Web framework enables so-called Web services, applications, and agents to get information/data from different sources, interpret and integrate them seamlessly. Thus the goal is to foster the development of intelligent applications that can handle and reason from distributed data and information on the Web. A Web service is a server application available to users on the Web, often being other Web services, to accept a query in a semantic Web language, and to return results in the same language. Examples of Web services to integrate for company A might be [13]: Purchasing parts from a vendor company B; Shipping from a large freight company C; and Providing space availability from the different plants in company A. Integrating these three Web services together will permit to answer a question such as a salesman in company A placing an order, and the orchestration of the other services providing the solution as the supply chain at work [13], and a complete delivery plan to the right plants of company A.
The ultimate ambition of the Semantic Web as a framework enabling software agents to interrogate, interoperate, and dynamically discover information and knowledge resources requires the explicit representation of the semantics associated to these resources. Examples of semantics are explanations about what this resource information/data/knowledge is about, and what it is for [11]. Specific languages and technologies have been developed for that purpose of representing and reasoning at a semantic level, such as first RDF [16], then DAML+OIL [9], and now OWL [15]. A Unique Resource Identifier (URI) identifies each concept/resource on the Web.

DAML (see Fig.1 and Table 1) and other XML/RDF-type systems such as a draft standard of the Joint Intelligence Virtual Architecture (JIVA) and topic maps promise to keep a record and capture semantic information better than is currently possible using Natural Language Processing (NLP) systems. DAML language has risen as a dominant ontology language for capturing distributed domain knowledge. DAML+OIL has been officially submitted to the World Wide Web Consortium (W3C) in 2001, accepted as a standard in 2002 under the name OWL, then as recommendation for Web Ontology Language on February 10th, 2004.

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Many efforts in different communities, mostly in connection with artificial intelligence, have chosen DAML and OWL to represent their ontologies and semantic networks, for example in medicine in biology.
3 Semantic Web in Biology and Medicine

As worldwide efforts to construct the semantic Web attest, building semantic systems is a very ambitious task. This article focuses on a semantic Web-like approach to case bases and case based reasoning in biology and medicine, because biomedicine is already a consequent application domain, and one of the hardest ones.

An advantage of this domain is that it is well studied and formalized from a semantic viewpoint, as is presented in this section, such that it is the most advanced ontologies engineering niche available today. To the point that it is not acceptable in this domain to ignore past and present efforts in standardization, as is acceptable in most other application domains. Indeed biomedical informatics is now a well-established academic discipline, better equipped than most others to transition into the semantic Web.

![Emerging Reference Models](image)

Fig. 2. Emerging reference terminologies in biomedicine (adapted from [20]).
The advantage of biomedicine is that it has fostered and achieved the development of standard terminologies in many subfields which are available for systems to build on (see Fig. 2) [20]:

- **Terminology servers**, such as National Cancer Institute’s Enterprise Vocabulary Server (EVS), or National Library of Medicine’s Unified Medical Language System Knowledge Source Server (UMLSKS).
- **Systematized Nomenclature of Medicine – Clinical Terms (SNOMED-CT)** from the College of American Pathologists (CAP), describing 984,000 accepted terms to express clinical concepts, such as diseases, symptoms, procedures, sites, medications, and organisms.
- **Current Procedural Terminology (CPT)** from the American Medical Association (AMA) for procedure codes.
- **Genes, proteins, diseases** from NCI modeling 250 genes associated with cancer.
- **Government Computer Based Patient Record (GCPR) Medications** reference terminology defining for each drug its chemical structure class, mechanism of action, and therapeutic use.
- **Mouse Models of Human Cancer Consortium (MMHCC)** from the National Cancer Institute (NCI) describing detailed diagnostic and imaging terminologies for eight cancer organ sites in mice, as a model for same sites in humans.
- **Gene Ontology** is an effort by the GO Consortium, regrouping many biotechnology research centers, to produce a controlled vocabulary to represent and describe genes that can be applied to all organisms even as knowledge of gene and protein roles in cells is accumulating and changing.
- **Open Biomedical Ontologies (OBO)** regroups well-structured controlled vocabularies for shared use across different biological and medical domains and covers both human and animal domains, and some imaging terms.

A common characteristic of these projects is that they use a Description-Logic based representation [20]. Other reference terminologies are being developed for vertebrate anatomy,
such as the University of Washington (UW) Digital Anatomy Project, and human physiology, such as Oak Ridge National Laboratory (ORNL) Virtual Human Project.

Thus the effort of developing an ontology for biomedicine is well underway, and there are even efforts for the sharing of terminologies across subdomains. For example, HL7 [14] is a proposed standard for exchanging semantic messages in healthcare, and builds on the terminologies presented above. Another effort is the Unified Medical Language System (UMLS) [21] of the National Library of Medicine (NLM) that comprises a metathesaurus for bridging the gap between different terminologies, describing medical concepts with a unique identifier, similar to the semantic Web URI, their synonyms in different classifications and common usage, and a semantic network organizing these concepts through 54 relationships.

Fig. 3. A portion of the UMLS semantic network [21].

The semantic Web, and particularly OWL, being very recent accomplishments, the integration of these biomedical ontologies in the semantic Web is still to be performed, by adopting OWL as a representation language, or writing OWL mappings of UMLS, HL7, and others. A few applications have demonstrated the value of the semantic Web approach in biology and medicine. Two notable examples are the use of the semantic Web for querying multiple bioinformatics data sources [7], and for connecting several distributed ontologies [19]. Many pro-
jects are underway to showcase how these ontologies can improve in particular biomedical information search, and cooperation of distributed systems.

Case based reasoning systems in biology and medicine can also take advantage of these ontologies like in no other application domain. If CBR is often presented as a method for fast knowledge base engineering since theoretically it can be simply built from a set of data – called cases - experience in this domain has shown that better results are obtained by a mixed approach where CBR is supported by some kind of ontology. We can call it a semantic approach in CBR.

Mr. MARTIN:

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<th>CLINICAL</th>
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<td>gender : male</td>
<td>pulse : 80</td>
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<td>resistance-AHT : present</td>
<td>vascular-murmur : present</td>
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<td>age : 50</td>
<td>peripheral-pulse : present</td>
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<tr>
<td>observance-problem : absent</td>
<td>creatininemia : 99</td>
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<tr>
<td>asthenia : present</td>
<td>kaliemia : 2.8</td>
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<tr>
<td>smoking : present</td>
<td>natremia : 145</td>
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<tr>
<td>anti-AHT-treatment : present</td>
<td>bicarbonatemia : 31.0</td>
</tr>
<tr>
<td>sport : absent</td>
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Fig. 4. ALEXIA’s case representation (partial).

4 Semantics and Case Based Reasoning in Biology and Medicine

Case based reasoning systems in medicine generally do not adopt a pure syntactic approach. Although it is in principle possible to conceive CBR systems as simply reusing some preexisting data, most researchers have acknowledged that the task is more complex. Most have complained of the fact that generally the data in existing databases do not comprise all the knowledge required for achieving excellent case-based clinical support. Many have even reported that generally electronic patient records simply do not store the details required for case based reasoning, and that the cases need to be created from other sources – which is a long process. Therefore adding ontologies to CBR is neither uncommon, nor to be considered as a disloy-
alty to CBR, as “pure” CBR researchers may be tempted to argue. On the contrary, we discuss and show in this section that ontologies are used in varied ways to make accurate and useful CBR possible. Among the different ways of adding ontologies to CBR, one can list the levels of case representation, case interpretation, also called abstraction, and case reuse or adaptation. The CBR systems presented in this section illustrate these different levels of ontological support for CBR. These systems do not comprise only patient cases. They resort to domain models at several steps of their reasoning process. These domain models are ontologies of a sub domain of medicine and/or biology. This section describes three such case based reasoning systems in biomedicine, focusing on their case representation, ontologies, and discussing their results. These systems have been successive implementations of the same concept of case based reasoning system in biomedicine, and thus can be seen each as an improvement from the previous one.

Fig. 5. ALEXIA’s causal physiopathological model.
4.1 ALEXIA

Presentation. ALEXIA [3] is a case based problem solver. As usual case based systems, it uses an indexed memory of previously solved cases to propose a solving strategy for a new problem. However, since the application domain is the determination of a patient’s hypertension etiology, the classical memory indexation architecture has been enriched with a meta-indexation level to estimate the most probable diagnosis by saturation of a causal physiopathological model (Fig. 5). Moreover, the dependency relations expressed through the causal model provide a functional point of view that does objectify the selection of the best analogue.

Case representation. ALEXIA represents its cases along three dimensions: intake, clinical, and biological (Fig. 4). In addition, memorized cases store theoretical model instantiations, which are the values induced by the qualitative physiopathological model, and experimental model instantiations, which are the values measured for the same deep nodes by lab tests, when available. The determination of the exact levels of hormones at different body sites is invasive, therefore it is generally not performed, and theoretical values are most frequently available.

Ontology. ALEXIA’s ontology is a set of classes and rules associated with the classes in frames represented in an object-oriented kernel – called K language [6]. It comprises 20 nodes representing the main hormones regulating arterial tension (Fig. 5), 20 signs and symptoms, 111 observations, 31 further tests, and 26 edges. Examples are: renin (a hormone, and also a node), arterial tension (a sign), weight (an observation), renal scanner (a further test), and renin $\rightarrow$ angiotensin I (an edge).

Results. ALEXIA was tested on 18 new cases selected by the clinician as a good test sample because it contained both ‘easy’ cases, and ‘difficult’ ones. The ‘difficult’ cases were the ones that failed either a Bayesian network, or an expert system, both tested on the same dataset. The original memory stored only 8 solved cases, equitably representing the three main etiologies: Conn adenoma (CONN), renal artery stenosis (RAS), and pheochromocytoma (PHEO),
as well as the etiology by default: essential Arterial Hypertension (AHT). ALEXIA solved satisfactorily all 18 cases, with a single iteration of its reasoning process, even for essential AHT. The exceptionally good results of the system were attributed to the combination of the knowledge-based approach of its qualitative physiopathological model, and the numeric approach of its case based reasoning. Tests involving the case base alone without the physiopathological model provided much lower accuracy for the diagnosis classification, and thus for the further tests strategy. Both an expert system and a Bayesian network developed on the same database gave lower results on the diagnosis classification task – lower than 95%. Moreover, the authors of ALEXIA were not given access to the complete dataset, but only to a subset of 36 cases out of several hundreds.

**Fig. 6.** Representation of a contextual patient’s state in a patient’s case.

### 4.2 MNAOMIA

**Presentation.** MNAOMIA is a case based reasoning system providing assistance to clinical staff in psychiatry eating disorders for diagnosis, treatment, and research hypothesis recommendation [4]. It is thus a form of decision support system. Thus it is a system capable of
adapting to different cognitive tasks, both analytical, such as diagnosis, and synthetic, such as research hypothesis recommendation. The memory model of the system comprises both an experimental and a theoretical memory, expressed in a unified knowledge representation language, and organization. The components of the memory are cases and concepts, in the experimental part, and prototypes and models, in the theoretical part. The reasoning supported by this memory model takes advantage of all the components, whether experimental or theoretical. For example to assist an analytical task such as diagnosis both prototypes and cases are reused. To assist a synthetic task such as clinical research concepts and trends learnt by the system – we can say “synthesized” by the system – are reused. Therefore, one of the main theses of this project is to show that there is a match between the type of task performed by the system, and the memory structure reused. Because of the multitask competence of the system, the reasoning process is strongly constrained by some specialized models in theoretical memory, called the points of view.

Table 2. Description of the patients for diagnosis evaluation.

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<tr>
<th>Patients</th>
<th>Number</th>
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<tr>
<td>Anorexia Nervosa</td>
<td>41</td>
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<tr>
<td>Bulimia Nervosa</td>
<td>30</td>
</tr>
<tr>
<td>Anorexia Bulimia</td>
<td>40</td>
</tr>
<tr>
<td>Other Eating Disorders</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>115</strong></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>13</td>
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<tr>
<td>Pathological Personality</td>
<td>43</td>
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<tr>
<td>Depression</td>
<td>3</td>
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Case representation. MNAOMIA represents its cases along several dimensions, namely general, behavioral, somatic, psychic, and biological (see Fig. 6). A case description contains 2287 attributes among which most come from self-administered or psychiatrist-administered tests. The most consequent of these questionnaires is the food questionnaire filled by the patients, which counts 696 foods. These questionnaires being readministered several times during patients’ hospital stay, which can last up to 6 months, the data stored in a case increase
over time. Since this disease requires a long-term follow-up and clinical support, patients continue being monitored after discharge from the hospital, and thus the data increase with regulation reevaluations.

**Ontology.** MNAOMIA’s ontology contains diagnostic category prototypes, as described in psychiatry nomenclature, normal subject prototype, and average subject prototype, a domain model about foods, and prototypical treatment plans. Other models are the points of view. Since the system can adapt to several cognitive tasks, its memory structures the information through several points of view, such as biological symptomatology point of view, or cognitive task point of view. In a domain such as psychiatry, researchers have noted that there is currently no global model available explaining the relationships between findings, diseases, and treatments. Only partial mappings have been found. When working on the DSM classification of mental disorders, psychiatrists have pondered how to best describe the diagnostic categories. They have determined [18] that prototypical models - which state whether a person belongs to a category by evaluating his/her proximity to an ideal prototype - are the best suited for psychiatry. They regret that there is no physiopathological, not biological model to describe mental disorders [18]. Some psychiatrists hope that a genetic model may bring to the classification of mental disorders, and their associated treatments, a deeper, more coherent, and precise model. This remains to be proven. Meanwhile, a representation of diagnostic categories through prototypes, representing the most typical patient in this category, is the most adequate [18]. CBR is then a method of choice to establish a diagnosis by assessing the proximity of a new case with diagnostic prototypes and cases in the case memory.

**Results.** MNAOMIA’s performance was evaluated on diagnosis evaluation task. Results are given here for the diagnosis at patients’ admission. The accuracy of the diagnosis has been compared with that of the clinical staff after several weeks of hospital care. Table 2 describes the patients’ population, and Figure 7 shows the results for the first 60 cases processed. The diagnosis accuracy is about 80% for the first 30 cases, and about 95% from the 30th case to the 115th. It is compared with the results of the same diagnosis process performed only with the data of the food questionnaires of the patients, for which no prototype is available. The results after the 30th case are about the same (93% accuracy), but are very different for the
first 30 cases. The advantage of the prototypes in theoretical memory is here obvious at least at the beginning of the reasoning process. These results show that in this domain also, although being much less formalization prone than hypertension, an ontology modeling the domain through prototypes and models, even partial, is indeed advantageous for case based reasoning. Although a number of 30 is not very large, we must consider that this evaluation deals only with a subset of diagnostic categories. We only considered 7 of the Axis I mental disorders of DSM-III R [1], while the number of possible diagnoses along the two axes is much larger. In particular, we considered only the main diagnostic categories, and not the sub-diagnostic categories. Since these can co-occur in a patient, the complexity of solving the complete diagnosis task would require more patient cases than was available at this hospital, in spite of the fact that this is the leading treatment center for eating disorders in France. Therefore the contribution of prototypes in this system is irreplaceable.

Fig. 7. Accuracy of diagnosis (each ascending line between two X-axis points is a diagnosis success, and each descending line a failure) comparing accuracy without resorting to prototypes, and with resorting to prototypes, in addition to case reuse.

4.3 CARE PARTNER

Presentation. CARE-PARTNER is a computerized decision-support system on the World-Wide Web (WWW) [5]. It is applied to the long-term follow-up (LTFU) of patients having
undergone a stem-cell transplant (SCT) at the Fred Hutchinson Cancer Research Center (FHCRC) in Seattle, after their return in their home community. Home care providers use CARE-PARTNER to place contacts with LTFU on the Internet, and receive from the system decision-support advice in a timely manner for transplant patients follow-up. An essential characteristic of CARE-PARTNER is that it proposes to implement evidence-based medical practice by applying clinical guidelines developed by FHCRC for the care of their patients.

Fig. 8. Example of a LiverChronicGVHD clinical pathway.

Case representation. CARE PARTNER cases are represented in an electronic medical patient record, along several dimensions, namely flowsheet, problems, contacts, demographics,
pre transplant, day 80 workup, Graft Versus Host Disease (GVHD), medications, labs, reports, protocols, and risks.

**Table 3.** CARE-PARTNER evaluation for inter-rater agreement and summary ratings for two raters over three patients.

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<tr>
<th></th>
<th>Applicable Cases</th>
<th></th>
<th>Concordant Cases</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent Agreement Rating</td>
<td>Kappa coefficient of agreement</td>
<td>Number</td>
</tr>
<tr>
<td>Labs</td>
<td>57</td>
<td>94.7</td>
<td>.71</td>
<td>54</td>
</tr>
<tr>
<td>Procedures</td>
<td>70</td>
<td>95.7</td>
<td>.83</td>
<td>67</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>79</td>
<td>86.1</td>
<td>.74</td>
<td>68</td>
</tr>
<tr>
<td>Treatment</td>
<td>77</td>
<td>92.2</td>
<td>.81</td>
<td>71</td>
</tr>
<tr>
<td>Pathways</td>
<td>53</td>
<td>88.6</td>
<td>.71</td>
<td>47</td>
</tr>
<tr>
<td>Overall Appreciation</td>
<td>178</td>
<td>91.6</td>
<td>.77</td>
<td>163</td>
</tr>
</tbody>
</table>
### Table 4. Improvement in CARE-PARTNER computerized decision support over time.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Fails to meet standards</th>
<th>Adequate</th>
<th>Meets all standards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labs</td>
<td>1</td>
<td>14.3%</td>
<td>14.3%</td>
<td>71.4%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.0%</td>
<td>0.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.0%</td>
<td>0.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Procedures</td>
<td>1</td>
<td>35.7%</td>
<td>7.1%</td>
<td>57.1%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>5.6%</td>
<td>0.0%</td>
<td>94.4%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0.0%</td>
<td>2.9%</td>
<td>97.1%</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>1</td>
<td>30.0%</td>
<td>25.0%</td>
<td>45.0%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12.5%</td>
<td>12.5%</td>
<td>75.0%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>8.3%</td>
<td>4.2%</td>
<td>87.5%</td>
</tr>
<tr>
<td>Pathways</td>
<td>1</td>
<td>10.5%</td>
<td>0.0%</td>
<td>89.5%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>6.7%</td>
<td>6.7%</td>
<td>86.7%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>7.7%</td>
<td>23.1%</td>
<td>69.2%</td>
</tr>
<tr>
<td>Overall Appreciation</td>
<td>1</td>
<td>6.4%</td>
<td>27.7%</td>
<td>66.0%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>11.1%</td>
<td>2.2%</td>
<td>86.7%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.4%</td>
<td>8.5%</td>
<td>90.1%</td>
</tr>
</tbody>
</table>

**Ontology.** CARE-PARTNER resorts to a multimodal reasoning framework for the cooperation of case-based reasoning (CBR) and rule-based reasoning. The system’s memory here also comprises both patient cases, in the experimental memory, and a theoretical memory, or ontology. The ontology of the system contains the description of 1109 diseases, 452 signs and symptoms, 1152 labs, 547 procedures, 2684 medications, and 460 sites expressed in SNOMED classification. Notable in this system are 91 prototypes, mainly associated with diagnostic categories, such as liver chronic GCHD (Fig. 8) – a complication of transplantation - and called clinical pathways. The ontology is particularly used during the interpretation of input data, to transform them into qualitative values. Moreover, prototypical cases are reused during differential diagnosis when they are preferably used over cases when an equivalent number of attributes are matched. This matching and ranking process is described in detail in [5]. The theoretical part of the memory also contains clinical practice guidelines representing as rules and frames, and mobilized by rule-based reasoning.
Results. A sample evaluation of CARE-PARTNER decision-support performance has been performed by team statisticians, and is provided in Table 3. On 163 different clinical situations or cases, corresponding to contacts between the system and a clinician about three patients, the system was rated 82.2% as *Meets all standards*, and 12.3% as *Adequate*, for a total of 94.5% of results judged clinically acceptable by the medical experts. Table 3 also shows that the advice provided by the system covers most of the clinicians’ tasks: labs and procedure results interpretation, diagnosis assessment plan, treatment plan, and pathways information retrieval. Pathways represent prototypical cases retrieved by the system, and correspond to diagnostic categories (see Fig. 8 for an example). Important in this system is the evolution of the competency of the system over time, reaching 98.6% *Meets all standards/Adequate* for patient 3 for all his 54 contacts (see Table 4). This improvement in accuracy is completely attributable to case based reasoning.

4.4 Semantics in Biomedical CBR

All these systems show the importance of biomedical ontologies for interpretation of the data and throughout the reasoning process, thus showcasing the importance of a semantic approach in biomedical CBR applications. They also demonstrate the variety of knowledge to represent, mainly models, such as qualitative models, and prototypes to represent typical signs and symptoms, diagnostic evaluation plans, and treatment plans, associated with domain dependent diagnostic categories. Without these deep domain ontologies, these systems would not have been able to perform acceptable clinical assistance, and this finding is coherent with the improvement in the quality of care measured as a result of better, evidence-based formalization of medicine, fostering the development of the biomedical ontologies listed in section 3.

It is notable that these three systems cover application areas with different ontological characteristics. ALEXIA was developed in the hypertension domain, where a physiopathological model was available in the literature. MNAOMIA was developed in the eating disorders domain in psychiatry, where a significant description of prototypical cases was available in the literature, but no model. CARE-PARTNER was developed in the stem cell post-transplantation domain, where neither prototypical cases nor models were available. The
prototypical cases had to be developed from experts’ knowledge and clinical experience. Clinical practice guidelines provided some framework for clinical expertise, although not at a level of detail sufficient to make them operational without additional knowledge. In spite of this, CARE-PARTNER’s ontology was the most thorough because it relied on existing ontologies such as the UMLS, which includes SNOMED standardized terminology to represent findings, diseases, medications, sites, and organisms. Figure 8 shows that for instance clinical pathways were built using a standard terminology so that the clinical pathway editor component can be reused in any domain of medicine. This is a main advantage of working with standards, as the Mémoire framework will further illustrate.

5 Mémoire Framework

Mémoire is a framework for sharing and distributing case bases and the ontologies associated with them in their memory.

5.1 Motivation

Case based reasoning systems in medicine have so far been developed as standalone systems. With that regard, they have kept away from the efforts to share and connect biomedical information and knowledge bases. One of the main reasons is that cases are patient identifiable data. Legislation about patient data requires institutional agreement to access, use, and transmit such data, making it difficult to consider transmitting these case bases between institutions, except in the context of consortiums of institutions, of which many examples exist such as the VA, or for large-scale clinical trials. Non patient identifiable data are restricted just the same, because institutions are protective of their data as their assets for research and funding purposes. Nevertheless, single institutions may want to connect distributed CBR systems developed in their institution, for example connecting the three CBR systems presented above, where a patient may combine diseases from hypertension domain, eating disorders, and require stem cell transplantation, and a biomedical literature retrieval system through a terminology server. Also, it will be advantageous to develop CBR systems as Web services in the future, to receive patient input data from the Internet, securely, to process them against several
CBR systems, combine with non-CBR systems, and give back a consolidated result from several sources. In this scenario, patients data would not have to be shared among institutions, but only the system recommendations would be shared. Patients may want to query themselves these services, for alternate recommendations. Another reason would be to exchange CBR systems ontologies, as models and prototypes. Since prototypes are often processed as regular cases, then the problem of exchanging them will have to be solved in the same way as for real patient cases. In addition, advance in information assurance, such as trust agents, will even enable secure sharing of patient specific data [10, 19]. Considerable effort is also underway to make compatible electronic medical records, to allow patients to be transferred between hospitals with their record. A notable effort in this domain is the Government Computer Based Patient Record (GCPR).

5.2 Mémoire Representation Language

For all these reasons, the Mémoire project proposes a framework for the exchange of biomedical cases and related ontologies in the semantic Web, based on OWL ontology language. The choice of OWL, since it has been adopted as a recommendation by W3C, will provide a language format allowing for easy WWW integration, and is recognized as a standard for connected applications on the WWW. Mémoire framework should also satisfy the following requirements [12]:

1. The language should allow for easy extensibility since knowledge can be added iteratively.
2. The language should be applicable to several biomedical domains.
3. The language should support distributed, physically remote, maintenance of ontologies and cases.
4. The language should allow for the representation of complex, non-hierarchical knowledge structures.
5. The language should allow for distinguishing generic (IS-A) from partitive (PART-OF) relations.
<rdf:RDF
xmlns:owl = "http://www.w3.org/2002/07/owl#"
xmlns:rdf = "http://www.w3.org/1999/02/22-rdf-syntax-ns#"
xmlns:rdfs= "http://www.w3.org/2000/01/rdf-schema#"
xmlns:mem= "http://biomed.insttech.washington.edu/memoire#">

<owl:Ontology rdf:about="">
    <rdfs:comment>
        Case Based Reasoning in Biology and Medicine Ontology
    </rdfs:comment>
</owl:Ontology>

<owl:Class rdf:ID="Prototype">
    <rdfs:subClassOf rdf:resource="#Class" />
</owl:Class>

<owl:Class rdf:ID="Case">
    <owl:subClassOf mem:resource="#Prototype" />
    <owl:disjointWith rdf:resource="#Concept" />
</owl:Class>

<owl:Class rdf:ID="Model">
    <rdfs:subClassOf rdf:resource="#Class" />
</owl:Class>

<owl:Class rdf:ID="Concept">
    <rdfs:subClassOf mem:resource="#Class" />
    <owl:disjointWith rdf:resource="#Case" />
</owl:Class>

<owl:Class rdf:ID="Guideline">
    <rdfs:subClassOf mem:resource="#Class" />
    <owl:disjointWith rdf:resource="#Concept" />
</owl:Class>

<owl:Class rdf:ID="PrototypicalCase">
    <owl:equivalentClass rdf:resource="#mem;Prototype" />
</owl:Class>
</rdf:RDF>
Fig. 9. Partial Directed Labeled Graph representation of biomedical CBR domain.

OWL is a language providing a syntax and formal semantics that extend RDF, thus one way of writing an ontology in OWL is to code it in RDF/RDFS framework, which is what Mémoire has chosen to do because it is a generic representation language taking the intrinsic structuring capabilities of XML. In addition, OWL provides for three levels of semantic representation: OWL Lite, OWL DL, and OWL Full. OWL DL is both more expressive than Lite, and more strict than Full, such that it can be interpreted non-ambiguously.

OWL syntax defines the following elements:

- **Namespaces** indicate the vocabularies used, with their URIs, for example `mem` in Fig. 9 is defined inside an opening `rdf:RDF` tag.

- **Ontologies** in `owl:Ontology` tags support the annotations associated with ontologies, such as comments, version control, and inclusion of other ontologies.

- **Data aggregation and privacy** is enabled by the presence of relationships such as `owl:sameAs` or `owl:equivalentClass` that permit to automatically infer properties from one element as they relate to another one, or to extend a previously defined element, thus satisfying our criteria (1) and (3) (see an example on Fig. 9).

- **Classes, properties, instances of classes, relationships between classes and instances** permit to define such classes as `Case`, `Prototype` for our prototypical cases, `Model`, `Concept`, and `Guideline` for our CBR in Biology and Medicine domain. These classes are subclasses of `owl:Class`, except for class `Case` which is a subclass of `Prototype`. Some domain specific classes, such as `mem:Food` are already defined in owl as an ontology of foods is provide in the owl domain, so that many domain specific objects are readily available, such as `owl:Pasta`, `owl:Dessert`, and so forth. Still, Mémoire has defined most of the classes from the ontologies of ALEXIA, MNAOMIA, and CARE PARTNER defined above. Cases are represented as instances of `owl:Case`. We can special-
ize this class in the future to accommodate different case representations, although we have defined a case structure, using the part-of relationship, for different domains (owl:inverseOf rdf:resource="#isPartOf"). OWL has been found suitable to answer the requirements (2), (4), and (5) listed above.

Recently, on May 21st, 2004, a proposal to add RuleML [17] as a sublanguage for representing rules in a first-order language, in a format that is compatible with most AI inference engines, such as Jess for instance. In fact, this combination of OWL (DL or Lite) and RuleML, called SWRL, is compatible with such AI methods as Prolog, production rules (OPS5 and its descendants such as Jess), event-condition-action rules, and SQL (where views, queries, and facts are all rules). The Semantic Web Rule Language (SWRL) combines the OWL DL and OWL Lite sublanguages of the OWL Web Ontology Language with the Unary/Binary Datalog RuleML [17] sublanguages of the Rule Markup Language. This new addition will bridge the gap of explicit rule support, required in such systems as CARE-PARTNER that make use of clinical guidelines. This recent proposed fusion is the natural outcome of the fact that DAML already possessed RuleML to represent propositional logic rules, and since OWL builds from DAML, it can certainly reuse this representation. This is why we have coded rules with RuleML in Mémoire. Several proposals have been set forth for OWL first order logic rules, and we will adapt our chosen representation to these once one becomes a standard. Mémoire can reuse OWL ontologies already defined in biology and medicine, in particular an ontology of change [20], since medical and biological classifications change constantly, or easily translate those that were defined in DAML.

OWL semantics defines in addition:

- **Axioms** are used to associate class and property identifiers with specifications being either partial or complete, or additional specifications such as restrictions. For instance, it is possible to define a class as a set of instances, which is interesting for CBR. These additional specifications are particularly pertinent in biomedical domains where ontologies provide standards about classes and their properties. Examples of property axioms are: Symmetric, Transitive, Functional, Inverse-Functional, which were added for a biomedical application before OWL [12].
- **Facts** are used to represent instantiations of class, for instance real patient cases from the `mem:Case` class.
Mémoire makes available to biomedical researchers and application developers a set of tools to facilitate building a case based reasoning system in medicine, while also adopting a standard representation that will allow their system to be accessible from semantic Web compliant agents, servers, and services.

Mémoire main components comprise both tools to build and update the memory, shown on the right in Fig. 10, and reasoning tools, shown on the left in Fig. 10. The main components are the following:

- An ontology editor illustrated in Fig. 11, which enables the user to specify diseases, functions, plans, procedures, and sites that the application domain requires. An important feature of this ontology editor, in comparison with a ge-
neric one, is that it lets the user reuse previous ontologies, including SNOMED, and UMLS. It can be defined as an ontology editor specialized in biology and medicine.

- **A prototype editor** to enter into the system prototypical cases, and their variations such as prototypes and clinical pathways (see Fig. 8), like in CARE-PARTNER [5]. Although it is not recommended to use this editor to represent clinical guidelines in the system, it is possible to do so. A clinical guidelines interpreter will be an extension of the system for a future release.

- **A model editor** to enter into the systems domain models such as ALEXIA’s pathophysiological model (see Fig. 5).

![MEMOIRE ONTOLOGY EDITOR](image_url)

**Fig. 11.** Mémoire Ontology Editor enables the user to select subsets of SNOMED or other UMLS compliant terminologies to use them to define the domain ontology.
• A case editor to enter into the system the structure of a case, with several dimensions – expressed with OWL’s part-of relationship – and the list of attributes present in a case.

• A case based reasoner capable of reasoning from cases and prototypes. It is optimized to be able to reason fast from both large case bases and high-dimensional cases, like the ones encountered in bioinformatics.

• A rule inference engine capable of reasoning from first-order rules in RuleML format, and from models built with these.

• A top-level reasoner, called Mémoire reasoner, capable of dispatching a problem description to the case based reasoner and the rule inference engine, collecting all pertinent memory entities from both, deciding which to reuse, reusing them, and of updating the memory accordingly.

Table 5. Description of the CBR systems that served as testbeds for Mémoire, along with the comparison criteria that were all satisfied by Mémoire framework. The (*) symbols indicates that during follow-up certain data will be repeated, and thus the number of attributes in a case will grow.

<table>
<thead>
<tr>
<th>Comparison criteria</th>
<th>ALEXIA</th>
<th>MNAOMIA</th>
<th>CARE-PARTNER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical task</td>
<td>Diagnosis</td>
<td>Diagnosis treatment planning</td>
<td>Diagnosis</td>
</tr>
<tr>
<td>------------------------------</td>
<td>Diagnosis assessment planning</td>
<td>Treatment planning</td>
<td>diagnosis assessment planning</td>
</tr>
<tr>
<td>Nb attributes in a memorized case</td>
<td>172</td>
<td>2287(*)</td>
<td>1532(*)</td>
</tr>
<tr>
<td>Theoretical knowledge</td>
<td>Qualitative physiopathological model</td>
<td>Prototypical cases</td>
<td>Prototypical cases</td>
</tr>
<tr>
<td>------------------------------</td>
<td>Points of View</td>
<td>Points of View</td>
<td>Clinical guidelines/models</td>
</tr>
<tr>
<td>Nb test cases</td>
<td>18</td>
<td>115</td>
<td>163</td>
</tr>
<tr>
<td>Nb diagnostic categories</td>
<td>3</td>
<td>7</td>
<td>78</td>
</tr>
</tbody>
</table>
6 Evaluation

Mémoire has been evaluated from its ability to reproduce the case based reasoning capabilities of ALEXIA, MNAOMIA, and CARE-PARTNER. Section 4.4 noted that these systems present distinct, and complementary, characteristics, covering a large span of biomedical domains, ranging from those where a complete pathological model exists, such as hypertensive disease, an incomplete formalization, based on prototypes, such as psychiatry, or little formalization besides maybe guidelines, such as stem cell transplantation. Table 4 summarizes the characteristics of the three CBR systems on which Mémoire has been able to reproduce the same results as in the original system, which means that this generic framework and associated tools is sufficient to represent in a standardized manner the full competency of these three systems. An exception is the clinical research assistance provided by MNAOMIA [4]. This feature was based on an incremental concept learning performed during case based reasoning. This competency is left for a future version of the system.

7 Discussion

Although the evaluation of the framework has been so far limited to ALEXIA, MANOMIA, and CARE-PARTNER, a next step in this research will be to test the Mémoire framework to represent cases and case bases from novel domains in biology and medicine.

First of all, the success of this work will permit to leverage the development of CBR systems in biology and medicine. It provides the basis for developing a CBR shell for rapid development of CBR systems in biology and medicine.

Secondly, by the definition of a common representation language for CBR cases, it will become possible to develop Web services and agents to federate the CBR process across several domains of medicine, which will be helpful for patients presenting mixed sets of symptoms. This feature will be particularly valuable in such domains as stem cell transplantation, for which other conditions occur besides the one requiring the transplant.

Another advantage is that this work will permit the reuse of CBR systems outside of their domain of development, and to give them the formalization required for interacting with non-
CBR systems, so that the whole is more than the parts. This formalized interchange format will enable a seamless integration between case based reasoning and information retrieval in biology and medicine.

In addition, Mémoire is well suited for bioinformatics domains, because of its advanced algorithms for processing large case bases and highly dimensional cases. This domain will be an application domain of choice for Mémoire, who will be able to take advantage of GeneOntology in particular.

8 Conclusion

The Mémoire framework will permit to foster the development of case based reasoning systems in biology and medicine. Moreover, the ability to exchange case bases and their ontologies will permit to link biomedical CBR systems not only with one another, but also with other intelligent and information retrieval systems. The perspective of unlimited cooperation between these systems is extremely promising for the improvement of healthcare and biomedical research, as the whole is more than the concatenation of the parts: “Human endeavor is caught in an eternal tension between the effectiveness of small groups acting independently and the need to mesh with the wider community... The Semantic Web, in naming every concept simply by a URI, lets anyone express new concepts that they invent with minimal effort. Its unifying logical language will enable these concepts to be progressively linked into a universal Web. This structure will open up the knowledge and workings of humankind to meaningful analysis by software agents, providing a new class of tools by which we can live, work and learn together” [2]

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References


