

Mémoire: Case Based Reasoning Meets the Semantic Web in Biology and Medicine

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Abstract. Mémoire is a framework for the sharing and distribution of case bases and case based reasoning in biology and medicine. Based on the fact that semantics account for the success of biomedical case based reasoning systems, this paper defends the suitability of a semantic approach similar to the semantic Web for sharing and distributing case bases and case based reasoning in biology and medicine. 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. This paper presents the components of Mémoire for the representation of cases, case structure, and case based ontologies in biology and medicine. The approach could be extended to other application domains of CBR.

1 Introduction

The semantic Web has been defined as "an extension of the current web in which information is given well-defined meaning, better enabling computers and people to work in cooperation." [1]. The semantic Web is typically described as a framework for spreading and distributing information/data, information/data structures, and information/data about articulation between ontologies. In this article, we hypothesize that the same 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. Taking as examples several case based reasoning (CBR) systems in biology and medicine, it becomes obvious 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, shared case bases in medicine and biology. This paper introduces the Mémoire project, as a framework for the sharing of case bases and distributed case based reasoning in biology and medicine.

In the second section, we will introduce the reader to the semantic Web, then to the semantic Web current work in biology and medicine. The fourth section explains how biomedical case based reasoning makes use of semantics. The fifth section presents the Mémoire system, which is essentially a framework for sharing case bases in biology and medicine. 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” [6]. 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.

The semantic Web currently has three main components:

1. **Information/data in HTML or better XML format.** XML is a common language to represent Web content, and using it facilitates integration of Web documents from different sources, in particular via XSLT transformation language. Nevertheless, the meaning of the different tags across applications is not provided in XML, so that another layer needs to provide that semantic mapping.
2. **Information/data structures in a semantic Web format such as RDF.** Resource Description Framework (RDF) [14] 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 describe 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 [7] and OWL [13], permit to represent ontologies of terms (thesauri) and concepts in hierarchies expressing how these terms relate to one another.

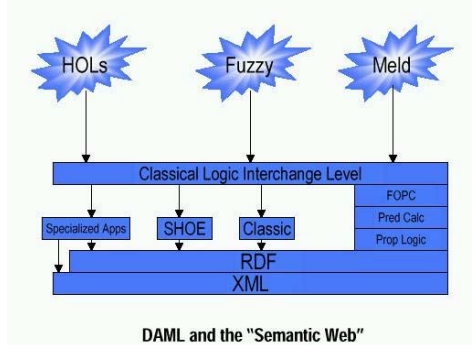


Fig. 1. DAML and the Semantic Web

Semantic Web framework enables so called Web services 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: 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 entering an order, and the orchestration of the other services providing the solution as the supply chain at work [11], and a complete delivery plan to the right plants of company A.

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* [9]. Specific languages and technologies have been developed for that purpose of representing and reasoning at a semantic level, such as first RDF [14], then DAML+OIL [7], and now OWL [13]. 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 (W3) in 2001, and accepted as a standard in 2002 under the name OWL, then as recommendation for Web Ontology Language on February 10th, 2004.

Table 1. Index of all DAML language elements

Cardinality	hasClass	Range
Class	hasValue	Restriction
ComplementOf	imports	sameClassAs
Datatype	intersectionOf	sameIndividualAs
DatatypeProperty	inverseOf	samePropertyAs
DatatypeRestriction	ObjectClass	subClassOf
Datatype value	ObjectProperty	subPropertyOf
DifferentIndividualFrom	ObjectRestriction	toClass
DisjointUnionOf	oneOf	TransitiveProperty
DisjointWith	onProperty	UnambiguousProperty
Domain	_Ontology	unionOf
EquivalentTo	_Property	UniqueProperty

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

Since building semantic systems is a very ambitious task, we focus in this article on case bases and case based reasoning in biology and medicine, which is already a consequent domain. Another characteristic of this domain is that it is well studied and formalized, as is presented in this section, such that it is not acceptable in this domain to ignore past 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.

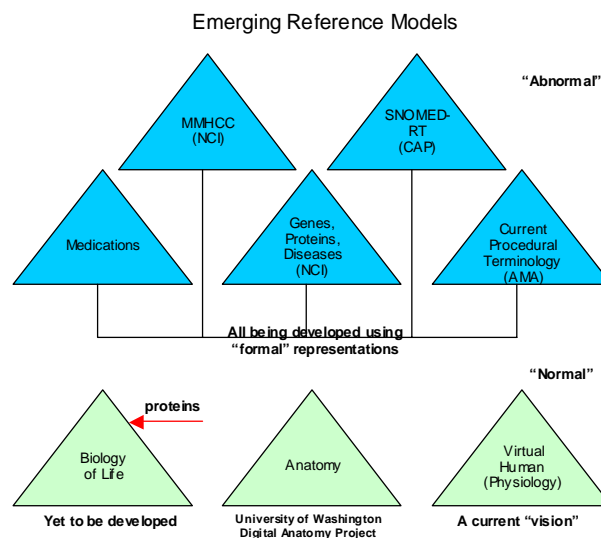


Fig. 2. Emerging Reference Terminologies in Biomedicine [16]

The advantage of biomedicine is that it has several standard terminologies to build on (see Fig. 2) [16]:

- Terminology servers, such as National Cancer Institute's Enterprise Vocabulary Server (EVS).
- GCPRMedications 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 terminologies for eight organ sites in mice, as a model for same sites in humans.

- Genes, proteins, diseases from NCI modeling 250 genes associated with cancer.
- Systematic Nomenclature of Medicine (SNOMED) from the College of American Pathologists (CAP), describing accepted terms of most diseases, symptoms, medications, and organisms.
- Current Procedural Terminology (CPT) 5 from the American Medical Association (AMA) for procedure codes.

A common characteristic of these projects is that they use a Description-Logic based representation [16]. Other reference terminologies are being developed for vertebrate anatomy, and human physiology.

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 [12] is a proposed standard for exchanging semantic messages in health-care, and builds on the terminologies presented above. Another effort is the Unified Medical Language System (UMLS) [17] 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.

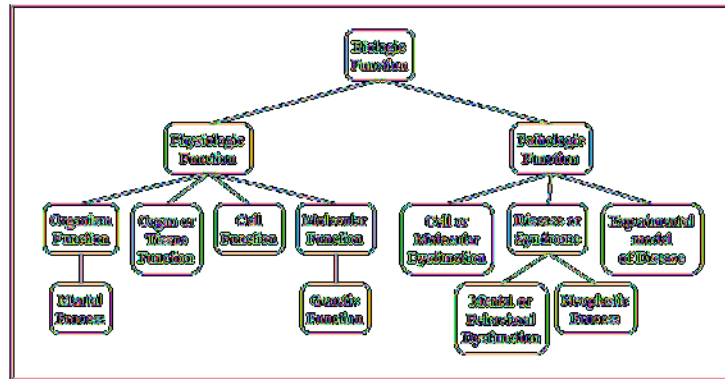


Fig. 3. A portion of the UMLS semantic network [17]

Nevertheless, 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. [5] uses the semantic Web for querying multiple bioinformatics data sources, and [15] for connecting several distributed ontologies.

4 Semantics and Case Based Reasoning in Biology and Medicine

Case based reasoning systems in medicine generally 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, and ontologies. These systems have been successive implementations of the same concept of a case based reasoning system in biomedicine, and thus can be seen each as an improvement from the previous one.

4.1 ALEXIA

Presentation. ALEXIA[2] is 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. Moreover, the dependency relations expressed through the causal model provide a functional point of view that does objectivate the selection of the best analogous.

```
Mr. MARTIN :
      INTAKE          CLINICAL
length-AHT : 6      arterial-tension : (152 118)
gender : male      pulse : 80
resistance-AHT : present    vascular-murmur : present
age : 50          peripheral-pulse : present
observ-problem : absent    BIOLOGICAL
asthenia : present    creatininemia : 99
smoking : present    kaliemia : 2.8
anti-AHT-treatment: present  natremia : 145
sport : absent      bicarbonatemia : 31.0
```

Fig. 4. ALEXIA's case representation (partial)

Case representation. ALEXIA represents its cases along three dimensions: intake, clinical, and biological (Fig. 4). In addition, memorized cases also 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.

Ontology. ALEXIA's ontology is a set of classes and rules associated with the classes in frames. It comprises 20 nodes representing the main hormones regulating arterial tension (Fig. 5), 20 signs and symptoms, 111 observations, 31 complementary exams, and 26 edges.

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, renal artery stenosis, and pheochromocytoma, as well as the etiology by default: essential 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 physiopathological model, and the numeric approach of its case based reasoning.

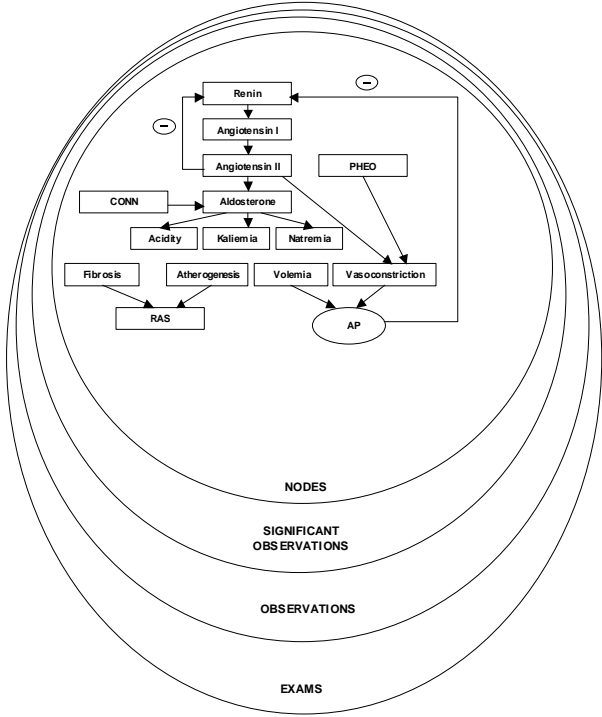


Fig. 5. ALEXIA's causal physiopathological model

4.2 MNOMIA

Presentation. MNAOMIA is a case based reasoning system providing assistance to clinical staff in psychiatry eating disorders for diagnosis, treatment, and research hypothesis recommendation [3]. 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 representa-

tion 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 can be various, and takes advantage of all the components, whether experimental or theoretical. It is strongly constrained by some specialized models in theoretical memory, called the points of view.

Case representation. MNAOMIA represents its cases along several dimensions, namely general, behavioral, somatic, psychic, and biological (Fig. 6).

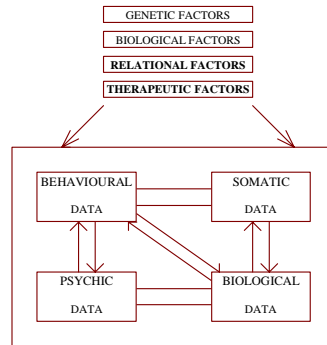


Fig. 6. Representation of a contextual patient's state in a patient's case

Ontology. MNAOMIA's ontology contains diagnostic category prototypes, as described in psychiatry nomenclature, normal subject prototypes, and average subject prototypes, 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 memories structures the information though several points of view, such as biological symptomatology point of view, or cognitive task point of view.

Table 2. Description of the patients for diagnosis evaluation

Patients	Number
Anorexia Nervosa	41
Bulimia Nervosa	30
Anorexia Bulimia	40
Other Eating Disorders	4
Total	115
Schizophrenia	13
Pathological Personality	43
Depression	3

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.

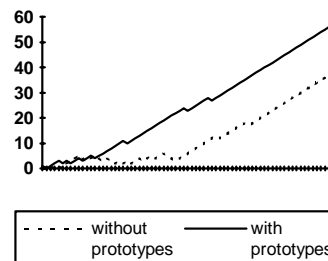


Fig. 7. Accuracy of diagnosis (each ascending line between two X-axis points is a diagnosis success, and each descending line a failure)

4.3 CARE PARTNER

Presentation. CARE-PARTNER is a computerized decision-support system on the World-Wide Web (WWW) [4]. 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.

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.

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, 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), and called clinical pathways.

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 1 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.

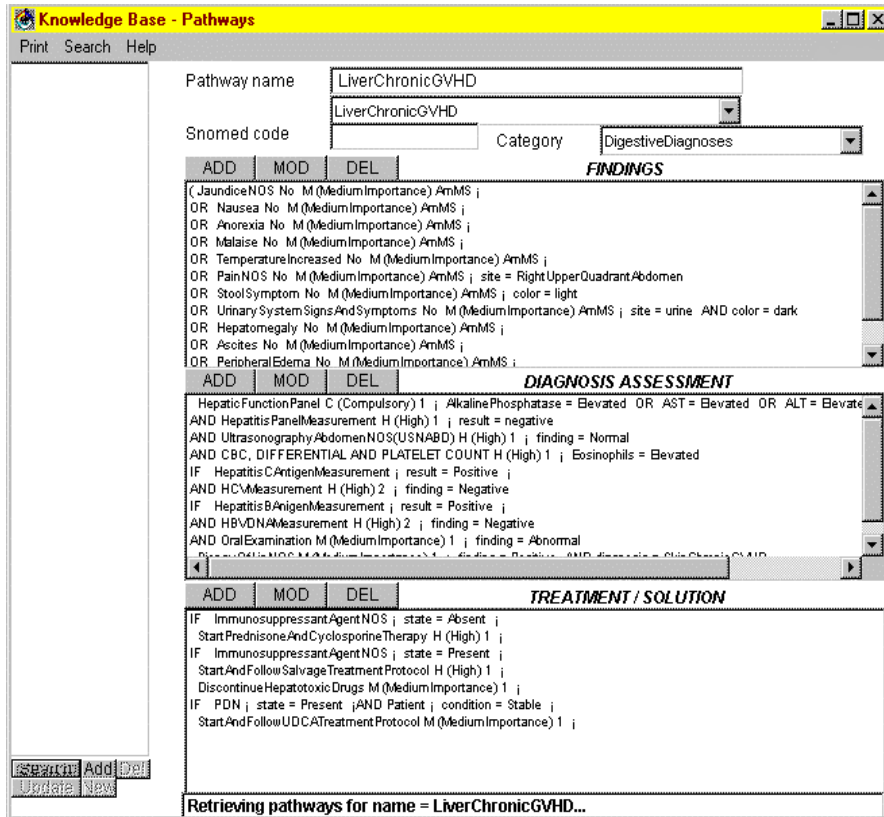


Fig. 8. Example of a LiverChronicGVHD clinical pathway

4.4 Semantics in Biomedical CBR

All these systems show the importance of biomedical ontologies for interpretation of the data, thus proving 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 the previous section.

Table 3. CARE-PARTNER evaluation Form Inter-Rater Agreement and Summary Ratings for Two Raters over Three Patients

	Applicable Cases			Concordant Cases			
	Number	Percent Agreement Rating	Kappa coefficient of agreement	Number	Fails to meet standards	Adequate	Meets all standards
Labs	57	94.7	.71	54	3.7%	3.7%	92.6%
Procedures	70	95.7	.83	67	8.9%	3.0%	88.1%
Diagnosis	79	86.1	.74	68	16.2%	13.2%	70.6%
Treatment	77	92.2	.81	71	9.9%	11.3%	78.8%
Pathways	53	88.6	.71	47	8.5%	8.5%	83.0%
Overall Appreciation	178	91.6	.77	163	5.5%	12.3%	82.2%

5 Mémoire Framework

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 institution, 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 [8, 16].

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 integrated in a common framework for connected applications on the WWW. Mémoire framework should also satisfy the following requirements [10]:

- (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 to distinguish between generic (IS-A) and partitive (PART-OF) relations.

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 in 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` 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).

- **Classes, properties, instances of classes, relationships between classes and instances** permit to define such classes as `Case`, `Prototype` for our prototypical cases, and `Model` and `Concept` for our CBR in Biology and Medicine domain. These classes are subclasses of `owl:Class`, but some domain specific classes, such as `mem:Food` are already defined in owl as an ontology of foods has already been defined, so that many domain specific objects have been defined, 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 specialize 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.

```

<?xml version="1.0"?>
<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://semantic.insttech.washington.edu/memoire/owl#">

  <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="#Model" />
    <owl:disjointWith rdf:resource="#Case" />
  </owl:Class>

```

Fig. 9. Directed Labeled Graph representation of biomedical CBR domain

One limitation found so far in both OWL DL and OWL Full is that they do not support rules explicitly. DAML has 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 [16], 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, InverseFunctional, which were added for a biomedical application before OWL [10].
- **Facts** are used to represent instantiations of class, for instance real patient cases from the `mem:Case` class.

8 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 refine Mémoire framework to represent cases and case bases from other CBR systems in biology and medicine. The success of this work will permit to leverage the development of CBR systems in biology and medicine. First of all, 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, patients often presenting mixed sets of symptoms. 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. It will also provide the basis for developing a CBR shell for rapid development of CBR systems in biology and medicine. Another advantage of having this formalized interchange format is to enable to seamlessly integrate case based reasoning and information retrieval in biology and medicine.

7 Conclusion

The ability to exchange case bases and their ontologies will permit to link not only biomedical CBR systems with one another, but with other intelligent and informa-

tion 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” [1]

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