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The HealthAgents ontology: how to represent the knowledge behind a brain tumour distributed decision system

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Abstract

In this paper we present our experience of representing the knowledge behind HealthAgents, a distributed decision support system for brain tumour diagnosis. Our initial motivation came from the distributed nature of the information involved in the system and has been enriched by clinicians’ requirements and data access restrictions. We present in detail the steps we have taken towards building our ontology starting from knowledge acquisition to data access and reasoning. We motivate our representational choices and show our results using domain examples employed by clinical partners in HealthAgents.

1 Introduction

HealthAgents (Arús et al., 2006) is an agent-based, distributed decision support system (d-DSS) that employs clinical information, Magnetic Resonance Imaging (MRI) data, spectral output from Magnetic Resonance Spectroscopy (MRS), high-resolution magic angle spinning spectroscopy (HR-MAS) and cDNA Microarray gene expression data. The aim of this project is to help improve brain tumour management by providing non-invasive alternatives to biopsies for diagnosis. A predecessor project, INTERPRET (Julià-Sapé et al., 2006b), has shown that single voxel MRS data can aid in improving brain tumour classification. HealthAgents builds on these results and further employs multi voxel MRS data, as well as HR-MAS and gene expression data for a more comprehensive picture to guide diagnosis. Moreover, HealthAgents has built a distributed decision support system. This allows the system to benefit from the participation of other clinical centres than those originally contributing data to the project. In this way the evidence base for enhanced classification performance is increased.

The HealthAgents system is designed and built as a multi-agent system, with great emphasis on declarative representations for agent interfaces to data, other agents and human users. The user requirements bring up a diverse set of concerns which are accommodated in the knowledge representation schemes developed.

The user requirements directly applied to the problem of representing knowledge inside the system encompass the following main aspects:
Knowledge Representation for Brain Tumour Decision Support

- System functionality: given the distributed nature of the system, the ontology has to function primarily as a common inter-lingua for the different knowledge bases involved. While this functionality could be achieved via an encompassing database schema, using an ontology makes expressive knowledge encoding easier. Indeed, while the project now functions with a comprehensive range of methods for brain tumour diagnosis (such as MRI, MRS, HR-MAS, gene expression profiles) which are being flexibly added to the diagnostic mix in different clinical centres, it is likely that other modalities will be added in the future. Since an ontology makes these ingredients explicit, it is used in this project to serve as a common vocabulary and provide access to databases in an integrated manner.

- Clinician terminological requirements: following on from the previous requirement the ontology has to act as a shared conceptualisation of the application needs\textsuperscript{1}. This means that the terminology employed has to be validated by the clinical users of the system, and the tests leading to the validation cut across hierarchical abstractions introduced in knowledge engineering, and often focus on the use of familiar terminologies in specific work-spaces. Moreover, different hospitals might use standard nomenclature that refer to the same object in different ways. As a consequence, the nomenclature decisions have to be taken in close collaboration with the clinical partners.

- Legacy system integration: A consequence of the two above mentioned requirements, but still an important element in itself is the smooth translation from existing data descriptors (such as database files, application dependent parsing files etc.) towards the agreed nomenclature. This is not a straightforward process and its difficulties (both from a semantic tradeoff view point and a technological viewpoint) have to be carefully analysed and addressed. This additional requirement is one of providing mappings between the ontology for the system and the various legacy database schemata of institutions that join the network.

This paper reports on the process of meeting the above mentioned requirements, addressing the principles and the pragmatism that has shaped their development.

1.1 Technical Background

Brain tumours remain an important cause of morbidity and mortality and afflict a large percentage of the European population. In children over 1 year of age, brain tumours are the most common solid malignancies that cause disease-related death.

Diagnosis using MRI and MRS is non-invasive, but only achieves variable, 60-90% accuracy depending on the tumour type and grade (Julià-Sapé et al., 2006a). The current gold standard classification of a brain tumour by histopathological analysis of biopsy is an invasive surgical procedure and in addition to health care costs and stress to patients, incurs a high risk of morbidity. Studies have shown that stereotactic brain biopsy has significant risks, with an estimated morbidity of 2.4-3.5% (Favre et al., 2002; Hall, 1998) and a death rate of 0.2-0.8% (Favre et al., 2002; Field et al., 2001). For tumours that evolve slowly (e.g. pilocytic astrocytoma in children), repeated biopsies may not be advisable nor practical. Non-invasive methods to monitor tumour progression become necessary, so the classification accuracy of methods based on MRS data needs to be improved with the help of additional information coming from HR-MAS and gene expression data. This falls under the ambit of HealthAgents.

A centralised Decision Support System (DSS) based on MRS data and histopathological diagnosis for classifier labels, is already available from the INTERPRET project. HealthAgents

\textsuperscript{1}In this paper we follow the distinction between domain ontology, upper ontology and application ontology (Hu et al., 2007). While the first concentrates on modeling a specific domain of interest; the second focuses on the common objects that are generally applicable across a wide range of domain ontologies. The third provides a core descriptive scaffold articulating the needs of the application on hand. This specificity requires the introduction of concepts that do not necessarily occur in upper domain ontologies, although they might encompass several domains of application.
aims to decentralise the process in a distributed decision support framework that supports multi-site data partitioning and sharing. Agent technology is used to power the distributed DSS (d-DSS).

Agents encapsulate core chunks of functionality, and the combinatorial possibilities of joining the output of one agent to the input of another generates the overall behaviour of the system aligned to functional specification that users require. As such, the interfaces between agents themselves, between agents and end users and between agents and the clinical data, that require agent-based processing, need to be carefully designed. In a multi-site development environment such as that required for HealthAgents, it is these interfaces that can hinder or foster system integration and correct behaviour. Declarative specification of these interfaces help separate platform dependent details of message passing elements from the functionally specific constructs that individual agent developers at remote locations use. This aspect is directly related to the system functionality requirements mentioned in the previous section.

In order to describe the data acted upon by the intelligent processing and classification algorithms at the heart of HealthAgents’ success, as well as the categories that earmark the output types of these algorithms, we construct an ontology (HaDOM) as the knowledge representation framework. One of the guiding features of this work was the need to ensure that the domain ontology’s concepts and relations could be mapped with relative ease onto database schemata typically used in clinical settings. At the very least, an ontology devised to support intelligent information processing must be capable of answering the same queries that a database-driven system can. This corresponds to the last item of system requirements, namely the smooth transition between the legacy terminologies as employed by various representations and the ontology used by the system. Below we shall describe how we can view an ontology as a construct that organizes the set of questions one can ask of a particular domain of knowledge. Syntactical support for this equivocation between declarative definition and interrogative procedures will be discussed at some length. In this context, curation and maintenance of referentially consistent descriptions in the face of variation in terminological practices is an issue that concerns our work from the very outset, and interfacing legacy databases is addressed as an integral part of this knowledge engineering exercise. This will be discussed further in the sequel, and the structure of the ontology will reflect such pragmatic requirements which are not necessarily addressed by a first-principles description of the domain of brain tumours. This process will be detailed from the light of addressing the second requirement, namely the terminology used throughout the system based on the different standards relevant to the domain and the corresponding usage.

The third aspect of interfacing is about offering end users access to the processing and functionalities built into the software, whether as elementary as data retrieval or involving a range of diagnostic queries that experienced clinicians would want to target at the available data. It is inevitable that there could be several different requirements that different types of clinical users might have. For instance, the requirements of neurooncologists specialising in children’s diseases seem to differ from those of adults in the nature of the details they require of a graphical interface to the information. Once again, the ability to manipulate content using concepts and descriptors from the relevant domains, independent of how the content might be rendered on screen is a requirement that feeds into the ontology design exercise. This last point will also fall under the third requirement by concentrating on the technological difficulties of migrating from existing notations for information and data to the new vocabulary part of the ontology.

1.1.1 Modelling Language
Several structured modelling languages (such as RDF (Lassila and Swick, 22 February 1999), Topic Maps\(^2\), Concept Maps\(^3\)) have been considered in order to represent the HealthAgents domain ontology (HaDOM). The Web Ontology Language (OWL) (Bechhofer et al., 2004) is used

\(^2\)http://www.topicmaps.org/
\(^3\)http://cmap.ihmc.us/conceptmap.html
for the reasons enumerated below. Please note that the choice of the modelling language has also been analysed from the viewpoint of the user requirements: project functionality (F) and clinical terminology compliance (T) and the migration from existing terminologies to the ontology (M).

1. OWL is XML compliant. Terms in HadOM are to be transferred from one agent to another across the internet. An XML compliant language allows us to reuse existing parsers and interpreters. (F)

2. OWL is widely used and adopted as a W3C standard. It is expected that being accepted as an organisational standard would give OWL more advantages than other languages, including extensibility, continuity and technical support. For instance, a rule enhanced version of OWL, SWRL (Horrocks et al., 2004), is under development and this might prove useful when further extending HadOM. (M)

3. OWL is expressive. OWL provides universal and existential quantifications to restrict terms in HadOM. OWL-full also allows one to use enumerations – case-based aggregation of umbrella concepts. These constructs facilitate compositional definition of complex concepts. Furthermore, OWL provides support for declaring concepts disjoint, an expression useful for drawing distinctions between conceptual categories when the same name may be used to describe them in different contexts. This is particularly relevant when legacy database schemata are being mapped onto our ontology. Finally, OWL separates the so-called TBox containing mainly concepts and axioms from ABox consisting of instances. OWL-full allows defining concepts by directly referencing instances, effectively combining ABox and TBox. This is a necessity when enumerating possible status of patients or variants of a particular tumour type. (T)

4. OWL supports reasoning. Based on Description Logics (Baader et al., 2003), OWL provides automated classification with regard to defined concepts. At design time, such a capability helps to detect inconsistencies and modelling errors. Although the increased expressivity of the language normally results in high computational complexity of reasoning, logic-based inferences on HadOM are normally carried out off-line and thus complexity is not an issue. (F)

5. OWL separates the knowledge model and instance data as T-Box and A-Box. This separation helps to maintain integrity of HadOM. (T)

Since it is possible to work with the Resource Description Framework (RDF) structure within an OWL-based representation, we make use of such graphical representations to simplify much of the interfacing work between different formats and their models. Tools that support RDF graph manipulations, such as RDQL (RDF Data Query Language) are considered part of the modelling toolkit that HealthAgents relies on.

1.1.2 Mapping Languages
The interface between HadOM and legacy relational databases is currently implemented using D2RQ (Bizer and Seaborne, 2004). D2RQ aims to provide a bridge between relational databases and RDF graphs. Databases can then be manipulated using RDF toolkits such as Jena\(^4\) and Sesame\(^5\). The current version of D2RQ only provides one way mapping, i.e. relational databases are considered read-only. A fragment of a typical D2RQ mapping file is shown in Figure 1.

In HealthAgents, the functionality of the federated architecture is driven by agents with well-defined tasks. Hence, the mapping languages are native to those agents which perform the mapping tasks. While this will be elaborated later on, we point out that the fragments in Figure 1 are examples of D2RQ scripts which are employed by DatabaseAgents to translate an RDQL query into an SQL query. This allows a term to be mapped between the RDQL references tables and SQL tables.

\(^4\)http://jena.sourceforge.net/
\(^5\)http://www.openrdf.org/
# D2RQ Namespace

```r
@prefix d2rq: <http://www.wiwiss.fu-berlin.de/suhl/bizer/D2RQ/0.1#>.
@prefix : <http://www.healthagents.net/hadv.owl#> .
@prefix db1: <http://www.example.net/dbserver01/db01#> .
@prefix rdf: <http://www.w3.net/1999/02/22-rdf-syntax-ns#> .
@prefix rdfs: <http://www.w3.net/2000/01/rdf-schema#> .
@prefix xsd: <http://www.w3.net/2001/XMLSchema#> .
@prefix owl: <http://www.w3.net/2002/07/owl#> .
```

#----------------------------------------------- # Database

```r
db1:healthagents_db rdf:type d2rq:Database;
  d2rq:jdbcDSN "jdbc:mysql://localhost/healthagents_db";
  d2rq:jdbcDriver "com.mysql.jdbc.Driver";
  d2rq:username "ha";
  d2rq:password "ha";
```

# ----------------------------------------------- # Mapping

```r
db1:mri_cm rdf:type d2rq:ClassMap ;
  d2rq:class :MRI_Series_Image;
  d2rq:uriPattern "http://www.healthagents.net/hadv.owl#mri_img_@@MRI.IDCASE@@_@@MRI.IDF@@";
  d2rq:dataStorage db1:healthagents_db.
```

```r
db1:has_filename rdf:type d2rq:DatatypePropertyBridge;
  d2rq:property :has_file_name;
  d2rq:belongsToClassMap db1:mri_cm;
  d2rq:datatype xsd:string.
```

```r
db1:has_description rdf:type d2rq:DatatypePropertyBridge;
  d2rq:property :has_description;
  d2rq:belongsToClassMap db1:mri_cm;
  d2rq:datatype xsd:string.X
```

#-----------------------------------------------

Figure 1 D2RQ mapping fragment

## 2 HealthAgents Domain Ontology

We distinguish domain ontology from other ontologies, e.g. the one for communication, and we focus on ontologies which aim to facilitate particular applications such as the HealthAgents system instead of general purpose ones, e.g. UMLS Metathesaurus\(^6\) and MeSH\(^7\). Generally speaking, the HealthAgents domain ontology is used to determine what in the domain of discourse of the HealthAgents system – kinds of data, patient records, types of tumours, parts of the brain, etc. This is different from the HealthAgents Language (HAL) which prescribes how the agents communicate. Two of the main components using the domain ontology are:

- The ClassifierAgents which describe their inputs using metadata that corresponds to concepts defined in the ontology and output diagnostic class labels which are defined as subconcepts of Diagnosis and Histopathology, as histopathological descriptors of biopsied tissue are considered a gold standard for classification.
- The DatabaseAgents which retrieve data from (legacy) databases. DatabaseAgents populate the ontology using the retrieved data. Wherever a mismatch is identified between database fields and ontological concepts, a local mapping is used to resolve the discrepancy.

Communication between agents using the HealthAgents domain ontology requires the initiating agent to extract the necessary terms from the domain ontology. This can be done in two ways: i) parsing the ontology on request and traversing the concept hierarchy to locate the right concepts or terms; and ii) extracting and reusing the concepts or terms off-line. The targeted agent needs to understand the meaning of the used terms (e.g. Astrocytoma or has_date) by consulting the

\(^6\)http://www.nlm.nih.gov/research/umls/

\(^7\)http://www.nlm.nih.gov/mesh/meshhome.html
ontology. This process is illustrated in Figure 2 showing that two agents, one of which is the database agent, communicate by referencing the domain ontology.

![Diagram](image_url)

**Figure 2** Communicating through domain ontology

### 2.1 Purpose of the domain ontology

Ontology, in the philosophical sense, is the study of what is — entities, and the relationships among the entities. Basically, it tries to answer questions such as “what exists or can exist in the domain of discourse?” and “what are the relations between the objects in the domain of discourse?”. This view of ontologies has been revised and modified by the knowledge engineering and artificial intelligence communities in order to fit better with the goals of knowledge acquisition and knowledge management. In knowledge management, an ontology is a compendium of organised terms and concepts that drive actions, and has a praxis-oriented structure. In knowledge acquisition of the domain specifics, they reflect the epistemological stance that the knowledge engineer takes up in completing this task. In either form, a standard definition — an explicit, consensual specification of a conceptualisation of a domain (Gruber, 1993) — provides a suitable working definition. In this paper, we do not commit to what an ontology is, merely how it is that an ontology circumscribes what may be used in the HealthAgents system. Following Quine, we state that “to be is to be the value of a bound variable,” (Quine, 1953) but the variable is very much a part of the symbolic order of the software system, and despite its declarative formal foundation, this representation is given meaning in use. Glimpses of this approach show up in mapping issues discussed in the paper, in retrieving answers to queries (binding variables in quantifiers) and so on. As such, in this project we eschew refinements and extensions of upper level ontologies in favour of a more pragmatic approach of ensuring that the declarative framework met the requirements of the application domain, and the validation that we sought was framed in that context. Indeed, the adequacy of the representation scheme, its fidelity to the relevant parts of (say) the neurooncological domain as conceived by its practitioners, rests upon the interpretations it supports and promotes in the context of clinical practice.

HealthAgents Domain Ontology (HaDOM) follows this more opportunistic approach to defining “things” in HealthAgents. In other words, HaDOM captures the expertise and information necessary to facilitate diagnosis and prognosis of different types of brain tumours and management issues of brain tumour patients. Such knowledge is elicited and formalised in a machine-processable manner and with explicit definitions, providing the ground on which consensus can be described and verified. This is particularly important for a distributed environment such as the one envisioned by HealthAgents, since it is not rare in such environments for a meaningful conclusion to be drawn upon suggestions and observations by experts with different background knowledge and using different terminology.

While the inclusion of clinical practitioners in system usage serves to ratify the faithfulness of domain representation, its use amongst software agents to facilitate interoperability requires stringent regimentation. Software agents and human users share the load of pattern recognition and diagnosis encoded. Hence the knowledge representation scheme needs to be both expressive...
and sound, (cf. the above discussion on OWL). When we give instructions to software agents and when software agents communicate with each other, HaDOM would specify the terms of reference in the language spoken by all participants for conveying the intended messages. Examples of such conversations are “retrieve cases of all patients under age 5” and “fetch a case of glioma from Hospital A” where underlined words are concepts from HaDOM.

A domain ontology, however, is not sufficient for establishing consensus among software agents. HaDOM defines what software agents talk to each other about, but not how they talk — how the messages are composed, what speech acts are accommodated and so on. This is beyond the scope of a domain ontology. In HealthAgents, a separate ontology defines the concrete means for passing the information encoded in HaDOM. This communication language (HAL) defines the format of different types of messages that are sent back and forth among agents, parameters that are necessary to reconstruct agent behaviour, the encoding and decoding methods for extracting information from such messages and house-keeping information with respect to messages. For instance, a classifier agent might submit an instance of Database_Request_Msg to a database handling agent to “retrieve a validated case with feature X, Y, and Z”. How the message itself is interpreted is regulated by HAL while the actual content — “retrieve a validated case” with the specified features — would be composed using instances of HaDOM.

In practice, each agent is equipped with an ontology parser to understand the domain ontology/terminology. Upon receiving a request, the agent first consults HaDOM for the meaning of different terms appearing in the request. It then carries out the tasks that it is instructed to perform, e.g. retrieving data from a database, classifying data against a set of labels, etc. When it finishes, the agent composes an answer/response to the request using concepts/terms defined in HaDOM.

HaDOM benefits from the reasoning capabilities inherent in the selected knowledge representation and reasoning formalisms. For instance, a Description Logic based formalism can provide automated subsumption-based inference. Melanocytic Tumour is a subcategory of Meningeal Tumour. HaDOM, however, does not contain knowledge of problem solving methods. That is to say, the domain ontology captures only the static model rather than the inference procedures. Typical examples of the former are “patient”, “a particular type of tumour”, “MRS scans with their parameters”, etc. while examples of the latter are “due to the fact that . . . the tumour is malignant” or when referring to MR spectra, “all peak areas with . . . characters suggest . . . ”. Such separation is based on both theoretical and practical considerations. On the one hand, such inferences are built using handcrafted rules, machine learning techniques, etc. which, currently, are not ready to be built into a declarative knowledge representation formalism. On the other hand, a medical diagnosis is typically a complicated process with ambiguity and uncertainty for which a framework for logical inference that is streamlined for taxonomic knowledge is hardly adequate (Rector, 1999). This, however, does not preclude building a reasoning system on top of HaDOM; indeed the classification tasks within HealthAgents exemplify the use of non-deductive reasoning while being grounded in terms for which a deductive, declarative formalism has been created. Other reasoning mechanisms, based on ontological concepts could be used to switch between different classification protocols. For instance, if certain patterns are present in a patient’s MRI and/or MRS scans, an inference may be made to suggest the use of pattern-specific classifiers and even exclude certain possibilities from the final diagnosis if they are eliminated by clinical knowledge or perhaps an oncologist’s understanding of the nature of the biochemical pathways involved. Such reasoning systems should rely on HaDOM to express the underlying knowledge model and be developed in close collaboration with clinical specialists, a task we have made preliminary investigations into, but have not integrated into the current implementation.
2.2 Structure of HaDOM

HaDOM defines information related to brain tumours (and tumours affecting the central nervous system), e.g. brain tumour diagnosis, prognosis, patient management, etc., in the context of the HealthAgents project. The primary goal of HaDOM is to address the functionalities that are envisioned in HealthAgents and drive such functionalities smoothly. The HealthAgents project has been strongly influenced by several other projects, namely, the INTERPRET project and the ongoing eTUMOUR project. The impact of these two projects on HealthAgents is reflected in the legacy terms in HaDOM that facilitate a smooth migration of INTERPRET data into HealthAgents databases.

Figure 3 HaDOM modules

HaDOM comprises several relatively independent modules (Figure 3), each focusing on a particular aspect of diagnosing brain tumours. Figure 3 also indicates the dependability among different modules. For instance, Medical Control consists of five medical imaging modules and Diagnosis relies on anatomic information, WHO classification, symptoms and results from medical controls. Some top-level concepts of HaDOM are listed here and certain concepts will be further discussed in detail in the following Sections. When defining the conceptual structure and concept names of HaDOM, we worked very closely (ontology validation meetings every 3 months throughout the whole duration of the project, joint demo programming workshops every 6 months etc.) with domain experts such as neurosurgeons, biochemists, and oncologists, to build up a picture of how a person is first recommended to the hospital, how he/she goes through all the medical exams and tests, how knowledge from different domains are projected upon this patient, and how a patient is managed during his/her treatment. The multiple domains of expertise – from neurooncology, medical imaging and spectroscopy, gene expression, and so on – address different levels and scales, both temporally and spatially. As such, tying together the knowledge modelling

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8 [http://azizu.uab.es/INTERPRET](http://azizu.uab.es/INTERPRET)
9 [http://www.etumour.net/](http://www.etumour.net/)
of each of the domains into a single domain ontology would require bridging relations which are placeholders for as yet unspecified scientifically validated explanations. In this context, patient identity offers a conceptual handle as a site for knowledge integration, wherein these multiple discourses bear meaning in the context of aetiology and progression of a type of disease Mol (2003). Thus a meta-level organising structure for the ontology can be viewed as a star-shaped graph with Patient_Record at the centre linking together all the related information about the patient coming from different domains of specialism. Again, such a choice for knowledge modelling is influenced by the nature of clinical practice, rather than a description of knowledge about cells and tissues from physiological and spatio-anatomical perspectives. The latter, physical reality of biomedicine might have had a closer fit to the sense of ontology as a study of “what exists,” as the underlying, causal organisers of medical intervention and management protocols.

- **Patient_Record** also known as electronic health record (EHR) is the most important concept in HadOM. It acts as an entry point into the ontology, specially when the task of rendering information onto graphical user interfaces is undertaken. It connects a particular patient to his/her examinations, diagnosis, treatment, prognosis, etc.
- **Patient** is a non-clinical concept. It is introduced to establish links between current EHR with chronological or historical records. It holds the necessary information regarding a patient needed for the purpose of diagnosis, treatment, and patient management. It can also facilitate the anonymisation process by creating a unique URI for a patient without exposing his/her identity.
- **Symptom** is a clinical concept. It is defined with attributes has_date and has_description. An instance of Symptom should be referred to by instances of Patient_Record when symptoms of a patient need to be recorded.
- **Clinical_Centre** is referred to by the Patient_Record concept. Information regarding clinical centres becomes necessary when the origin of medical examination data needs to be recorded.
- **Clinical_Intervention** is introduced to be compliant with INTERPRET and/or eTUMOUR database schemata. Clinical_Intervention is the parent concept of various methods used to treat patients with a diagnosed tumour. Sub-concepts of Clinical_Intervention include Therapy which in turn has Chemo_Therapy and Radio_Therapy as sub-concepts; Adjuvant_Method that might aid the tumour treatment; and Surgical_Removal as the surgical removal of cancerous tissue. Definition of Clinical_Intervention and descendant concepts are subject to further refinement.
- **Machine** records the manufacturer of the equipment used to acquire (multi- and single-voxel) MRS spectra and HR-MAS spectra and the version of the software used by such equipment.
- **Medical_Agent** is an umbrella term for substances used in examination and treatment. For instance, in HadOM, the treatment of brain tumour requires Anaesthetic_Agent, Anti_Convulsant and Steroid which are sub-concepts of Medical_Agent; the MR imaging model might require injection of contrast enhancing substances. The medical/biochemical agent used in a particular treatment will be introduced as instances of Medical_Agent or one of its sub-concepts. Names and the administered dosage will be recorded.
- **Medical_Control** is the parent concept of all the medical investigation models including Biopsy, HRMAS, Magnetic_Resonance, and Microarray. Among such different models, Magnetic_Resonance has child concepts MRI and MRS and Biopsy has child concept Stereotactic_Biopsy.
- **Medical_ControlOutcome** records all the information produced by and interpreted from a Medical_Control module. Images and binary voxel data are the expected outputs.
- **Region_Of_Interest** is a non-clinical concept. It is the area in or related to a patient’s central nervous system that arouses clinician’s concerns. It is normally instantiatiated as a mass, enhancement, or highlighted area in medical images or as a tissue to be examined ex vivo.
- **CNS_Anatomic_Structure** describes the major organs and parts of organs related to the human brain. We use separate concepts for the functional aspect (e.g. Brain_Stem) of a particular
organ and its structural aspect (e.g. Brain_ Stem_ Structure). A few properties are introduced to describe the spatial relationships, e.g. spatial_connected_to and spatial_within.

- CNS_Tumour_Grading introduces the four-level WHO tumour grading system and the Daumas Duport grading schema for convenience and compatibility.
- Diagnosis refers to terms in WHO CNS Tumour classification. An instance of Diagnosis is reported in a Patient_Record and is associated with a particular instance of Region_Of_Interest as an instantiated relation of the anatomical structure in the ontology.
- CNS_Tumours is the WHO classification of Tumours affecting Central Nervous System. The hierarchical structure of WHO classification is faithfully re-constructed in HaDOM. Further extension and modification will be made compliant with WHO classifications. Indeed, we have both the 2002 and 2007 classification indices in the ontology.

The above categories are the top level concepts that are defined as the direct sub-concepts of the root concept, \( \top \) (e.g. \( \langle \text{owl:Thing} \rangle \)). Note that several categories are introduced in order to accommodate legacy terms and concepts from existing databases schema, such as the INTERPRET databases.

2.2.1 Patient record

Instances of patient record should be regarded as the point of reference of a system that uses HaDOM (as shown in Figure 5). Normally, when a new patient \( P \) is admitted or reported, a new instance of Patient_Record is created which includes a reference to an instance of Patient concept to record personal information of \( P \). Instances of Symptom are created to describe the complaint of \( P \). Instances of Medical_Control are introduced including instances of different imaging models to document information regarding the examinations that \( P \) has undertaken. Instances of Diagnosis are used to note down diagnosis details while and instances of Clinical_Intervention serve to keep details of treatments and surgeries.

To retrieve information with respect to a particular patient, an instance of Patient_Record is the main entry point and bridge. For instance, assume that one wants to find all the patients who have astrocytic tumour. The user “glues” different instances using instance of Patient_Record as in the following query.

```
SELECT ?patient WHERE
(?pr, hadv:record_of, ?patient) AND
(?pr, hadv:diagnosis, ?diag) AND
(?diag, hadv:is_who_class, ?tumour) AND
(?tumour, rdf:type, Astrocytic_Tumour)
```

A particular visit of a patient identified by the URI \( x \), results in the creation of an instance of Patient_Record with a unique URI. Therefore, the clinical history of the patient is accessed using the following pseudo-RDQL query.

```
SELECT ?patient_record WHERE
(?patient_record, hadv:record_of, ?x)
```

2.3 Medical control and relevant concepts

A number of technologies are employed in brain tumour diagnosis. In HaDOM, we enumerate the following approaches and defined them as sub-concepts of Medical_Control:

1. Biopsy
2. HRMAS
3. Magnetic_Resonance
4. **Microarray**

For each of the above concepts, necessary information is recorded, e.g. has_date property keeps a time-stamp on every medical examination.

*Magnetic Resonance* is the major concern of HealthAgents project. It has MRI and MRS as sub-concepts. An MRS instance produces pre-processed Raw\_MR\_Data and might contain the post-processed Processed\_MR\_Data. Therefore we have:

\[
\text{Magnetic Resonance} = \text{Medical Control} \sqcap \ldots
\]
\[
\forall \text{produce data}\_\text{MR Data} \sqcap
\exists \text{produce data}\_\text{Raw MR Data} \sqcap \ldots
\]

A medical control instance produces outcomes that are defined as *Medical Control Outcome* including Medical\_Image, Textual\_Report, and data concepts for each of different test modules (See Figure 4). Medical\_Image is the umbrella concept of both MRS and MRI images, the latter of which is actually a series of images taken at fixed intervals. Textual\_Report refers to a paper or the electronic reports generated by clinicians. It might contain the conclusions and descriptions on a set of images taken with regard to a particular patient.

![Figure 4](image)

The actual MR data might be in two forms: processed data and raw data. In order to trace diagnosis, it is necessary to have both forms of data available and linkable from a particular patient record. The actual data file and relevant information are kept as instances of MR\_Data:

\[
\text{MR Data} = \ldots \sqcap \forall \text{has description}\_\text{String} \sqcap
\forall \text{has file name}\_\text{String} \sqcap
\forall \text{has creation date}\_\text{String} \sqcap
\forall \text{has creation id}\_\text{String} \sqcap \ldots
\]

3 **Structuring HaDOM to fit praxis**

A declarative knowledge representation is an enabler of separation of knowledge from particular models of its use. However, streamlining the ontology for efficient use in the context of a particular application such as HealthAgents must be balanced against the need to have the ontology serve as a vehicle for knowledge sharing independent of it. The ontology developed reflects these contrary pulls, and we address such ontological features in this Section.

3.1 **Modularising HaDOM**

Many technologies and methods used to detect and diagnose brain tumours are yet to reach a mature stage. This is made explicit in the fact that in 2007, halfway through the HealthAgents
WHO released a new classification of tumours affecting Central Nervous System with major changes to the terminology as well as the taxonomies (http://www.who.int/en/). In light of further changes being highly likely, we revise HaDOM into a modular structure that confines changes locally to a module. HaDOM is designed as a modular structure with a core kernel haCore.owl and five modules. haCore.owl contains the essential concepts from the domain and the top level conceptual relations between these concepts. haCore defines the skeleton of HaDOM and the five modules below are attached to this structure.

- haMedCrtl extends the core HealthAgents ontology with concepts detailing the various medical examination methods, the results generated, and materials used in such examinations.
- haClassifier enhances the core HealthAgents ontology with knowledge prescribing how the input and output types of automated classification methods should be constrained in the HealthAgents framework.
- haSecurity introduces a layer of system security-specific concepts and properties. When designing a health care system, one needs to not only accommodate the needs for clinical use but also observe patient privacy and safety issues, especially in a distributed environment as envisaged by the HealthAgents Consortium. Reflected in HaDOM is a dedicated module for security concerns. We exercise a policy rule based security model regulating the access right of HealthAgents users. Basic concepts to facilitate such an approach are
  - Access_Rights regulating who can manipulate the data and how;
  - Users which can be further divided into Software Agent, Clinician, Patient, and System_Admin;
  - Resource as the data and methods available to users of HealthAgents system.
• **Brain Structure** presents in details the anatomic structure of the human brain and central nervous system.

• **CNS_Tumour** gathers tumour types with or without histopathology results. **Paediatric_Non_Histo** is the parent concept for tumours. This concept is not necessarily required under histopathological studies. On the other hand, the WHO 2002 classification and the WHO 2007 classification co-exist under **CNS_Tumour_Histopathology**. With the help of clinical experts, we mapped the 2007 classification against the 2002 one and marked tumour types from 2007 with deletion, creation, split, merge, generalisation, and specialisation, similar to the types of changes proposed in (Noy and Musen, 2004). With such a markup, we can establish correspondences between different WHO classifications and easily “revive” legacy patient records dating back to 1950s\(^{10}\). Note that a change between the two classifications may lead to marking a concept with different actions. For instance, the changes on **Choroid_Plexus_Carcinoma** suggest creation of “Neuroepithelial tissue tumours” in 2007, deletion of “Choroid plexus tumours” in 2002, specialisation of “Choroid plexus tumours” under “Neuroepithelial tissue tumours” in 2007 and deletion/creation of all the sub-type of “Choroid plexus tumours” including “Choroid plexus carcinoma”.

Moreover, we refine tumour types with tumour grading systems. Two different grading schemata are introduced in HaDOM: the **Dauma Duport Grade** and the **WHO Grade** as instances of **Dauma Duport Grade** and **WHO CNS_Tumour Grade** who are in turn sub-concepts of **CNS_Tumour Grading**.

### 3.2 Modelling Anatomical Structure of Central Nervous System

The anatomy model has been extensively studied and many different models have been proposed including the comprehensive Foundational Model of Anatomy (FMA) (Rosse and Mejino, 2003) for humans and the Edinburgh Mouse Atlas Anatomy Ontology\(^{11}\). In HaDOM, anatomical knowledge is used to establish the connection between diseases and human organs and we focus on anatomical knowledge of the central nervous system only. When constructing an ontology, establishing connections with existing ontologies such as FMA is recommended so as to maintain consistency with regard to the latest advances in the domain of discourse. This is not strictly applicable in HaDOM for the following reasons. In order to connect diseases and human organs, part-whole relationships are necessary to infer potential damages to other neighbouring organs and to the neural functions that the entire organ presents, of which the organ under consideration is only a part. FMA uses a separate spatial ontology and models the partonomy information in the Anatomical Structural Abstraction model. Specialist reasoning systems other than a description logic based one are needed; this makes the implementation unnecessarily complicated.

Using (Damasio, 1995) as a reference, we sought a balance between a knowledge model containing an exhaustive and refined coverage of human CNS and a parsimonious construction that is sufficient for the HealthAgents framework. The fine line between domain and application ontology is identified with the help of clinical experts working closely with the HealthAgents development team. The criteria for opting to place a part of CNS in or out of the anatomical model is whether it is mentioned in the patient’s EHR, whether its neighbouring parts are referred to in patient’s EHR, and whether its subparts are used in the patient’s EHR. Using \(T_{EHR}\) is the set of anatomical terms that appear in patient EHRs, this choice criterion is formalised thus:

\[
\text{Brain Structure} = \{C | C \in T_{EHR} \lor (\exists D \in T_{EHR} \land \text{adjacent}(C, D)) \lor (\exists D \in T_{EHR} \land \text{partof}(D, C)) \}
\]

We refine adjacent\((x, y)\) to be spatially left_to, right_to, beneath, above, connected_to, inner, outer, restriction_surround, etc. A brain tumour might damage brain tissue which inevitably

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\(^{10}\)Available from UK West Midland Brain Tumour Registration

\(^{11}\)http://genex.hgu.mrc.ac.uk/
affects the corresponding neurological functions. In HaDOM, a series of neurological functions are defined as instances of concept \textit{Nerve Function} and are associated with brain anatomical structure using property \textit{has function}. By doing so, one is then able to infer potential damage to normal muscle movements and senses based on the location of the brain tumour and other tumours of the central nervous system, and thus cross check with a patient’s observed symptoms.

In HaDOM, we adopt the approach to modelling part-whole relationships in (Hahn et al., 1999) using only the subsumption relationship \textit{is-a} inherent in description logic. Partonomy is emulated with \textit{is-a} hierarchies of concepts introduced particularly for representing structural knowledge. CNS is viewed as a series of three coexisting concepts: the structural concepts which are normally with suffix \textit{“Str”}, the anatomical concepts themselves and the part concepts which are normally with suffix \textit{“Prt”}. For instance, brain stem is defined by the combination of Brain\_Stem\_Str, Brain\_Stem and Brain\_Stem\_Prt with two subsumption relationships, i.e. Brain\_Stem \sqsubseteq Brain\_Stem\_Str and Brain\_Stem\_Prt \sqsubseteq Brain\_Stem\_Str. Among the triadic combination, Brain\_Stem is the one holding all the taxonomical knowledge while Brain\_Stem\_Str and Brain\_Stem\_Prt are the bridge to establish partonomial chain of anatomical structures.

Based on this triadic combination, the left cerebral hemisphere is defined as

\[
\begin{align*}
\text{Left Cerebral Hemisphere} & \sqsubseteq \text{Left Cerebral Hemisphere Str} \\
\text{Left Cerebral Hemisphere Prt} & \sqsubseteq \text{Left Cerebral Hemisphere Str} \\
\text{Left Cerebral Hemisphere Str} & \sqsubseteq \text{Cerebrum Prt} \\
\text{Cerebrum Prt} & \sqsubseteq \text{Cerebrum Str}
\end{align*}
\]

Hence, if a tumour is identified within Left Cerebral Hemisphere, we can safely infer along the partonomical chain that it is also within Cerebrum structure and thus is part of Main Brain structure. For simplicity, we define anatomy specific knowledge belong to the entire structure at \textit{“xxx Str”} and use the anatomical concepts to usher in references to conventional anatomy terminology.

3.3 \textit{DICOM’ising HaDOM}

The Digital Imaging and Communications in Medicine (DICOM)\textsuperscript{12} standard was initiated by the American National Electrical Manufacturers Association (NEMA)\textsuperscript{13} to regulate the distribution and viewing of medical images, and later become a global standard adopted by clinical authorities and manufacturers from major European and North America countries. DICOM has become an increasingly common format for receiving scans from a hospital. Therefore, even though DICOM descriptors are tied closely to implementation details, i.e. how image files are composed, stored, transferred, etc. rather than at the conceptual structure of the domain of discourse, we enrich HaDOM with a DICOM reference module to enable smooth migration to DICOM compatible system.

Among DICOM standards, the Image Information Object Definitions (IOD) impinge on the HealthAgents domain ontology. IOD impose a standard format when transferring medical images. Depending on the purposes of medical studies and the nature of associated data, IOD differentiate \textit{Patient Module} for patient data, \textit{Series Module} for information related to particular imaging modules, \textit{Study Module} for information about the entire medical study, etc. Correspondences are manually crafted to facilitate inspecting HaDOM concepts in a DICOM apparatus. More specifically, \textit{Patient Module} in DICOM perfectly matches the \textit{Patient} concept from HaDOM with nearly one-to-one correspondence between DICOM and HaDOM properties. \textit{Study Module} is translated into \textit{Patient Record} in that HaDOM’s patient record comprises all the information

\textsuperscript{12}http://medical.nema.org/
\textsuperscript{13}http://www.nema.org/
concerning a patient on a particular disease from the first visit that he/she made to one of HealthAgents member hospitals until the end of his/her treatment. Series Module stays one level below Study Module and is mapped to Case Record including information of a particular visit of a patient. Image Module details how images are taken. Depending the image types, Image Information is saved in sub-concepts of Medical Control and Medical Control Outcome.

4 Facilitating Data Interoperability with HaDOM

In the HealthAgents framework, a domain ontology is the locus of reference for participating agents and institutions to align their local vocabularies. Hospitals joining the HealthAgents network can either adopt the ontology-derived database schema provided, or they can retain their local database schemata and data gathering processes based on such schemata. In the latter case, a mapping between these local databases and the HealthAgents central domain ontology is needed to enable communication between the hospitals and the HealthAgents system. This, in turn, will allow information to be read in from the local hospital databases to the HealthAgents system and be compliant with the HealthAgents central ontology, and thus feed into the goal of building and refining classifiers.

The mapping between the database schemata and the ontologies, at present, cannot be automatically generated. Instead, a manual or semi-automatic method will be performed during the installation process of the HealthAgents software. In order to help creating such mapping, a user friendly interface is being developed. It should be noted that the mapping will require a person with considerable database and clinical knowledge if the installation is to be successful. We have undertaken the task for database schemata used in hospitals in Spain and the UK and have created a tool that facilitates this mapping procedure. The successful deployment of the system across these heterogeneous networks is validation of the ontology and mapping tools' representational adequacy.

4.1 Communicating with HaDOM

HaDOM is used as the common reference point among different hospitals which maintain their own vocabularies and database schemata. As illustrated in Figure 6, such a design seeks to respect the integrity and independence of legacy databases. The discrepancy between such schemata is, however, resolved by dedicated interfaces between each individual schema and the common domain ontology/vocabulary HaDOM.

A typical scenario of using HaDOM starts with the visualisation of a particular patient record read from the local database. The visualisation is driven and regulated by the domain ontology/vocabulary. Information read from local database is translated into a format compliant with HaDOM via relational database (RD) to RDF interface to create an instance of HaDOM. Such an instance is then classified and displayed at the allocated sections in the HealthAgents graphical user interface (GUI).

Agents, such as an Administration Agent, Classifier Agent, Audit Agent, etc., are equipped with parsers understanding HaDOM. The communications among different agents are fully compliant with HaDOM (see Figure 8). For instance, when querying a classifier, the handling agent would submit queries composed using terms explicitly defined in HaDOM. The RDQL query illustrated in Figure 7 retrieves all the patients that are diagnosed by hospital “BCH”.

4.1.1 Mapping between HaDOM and database schemata

HaDOM provides a common reference point that local vocabularies and legacy database schemata can exploit to achieve data interoperability within HealthAgents consortium. Mapping between ontologies and database schemata, however, is not an easy task. Although extensive research has been done (Kaloglou et al., 2005), the problem is far from solved. Apart from the general issues associated with independently developed knowledge models, a major obstacle lies in
the fact that the conceptual structure of ontologies and database schemata are significantly different. Ontologies tend to see the world through layers of abstractions while database schemata work better in a world with vertical partitions (columns for attributes of an entity) instead of horizontal layers (representing hierarchical abstractions supervening on the same set of
instances). Automated methods thus far are still not comparable against human data curators crafting mappings manually. In the scope of HealthAgents, we evaluated several existing mapping algorithms to automatically identify correspondences between HaDOM concepts and database schemata currently installed in HealthAgents member hospitals. The results are summarised as follows.

- String (edit) distances algorithms (e.g. those discussed by Cohen et al. (2003)) gave the best results. An obvious reason is that the domain of discourse of HealthAgents is fairly small with well studied and well documented knowledge. It is expected that similar names are used for both concepts and database tables/columns. String distance methods failed to handle acronyms, synonyms and names in different natural languages where the later, though not common in HealthAgents domain, might become more evident when HealthAgents framework is deployed widely to work legacy databases from different countries. For instance, when processing data from existing databases, patient’s gender may be “hombre” in Spanish, “männlich” in German, or “man” in English, all of which bear limited resemblance.

- Although algorithms based on WordNet solve the synonymy problem, they fail to achieve much better results on acronyms and terms from multiple natural languages.

- Structure-based and many other so-called semantics-enhanced matching algorithms (Rahm and Bernstein, 2001)(Kalfoglou et al., 2005) are not applicable. Such algorithms perform deep structure comparison between the source and the target knowledge model. However, HaDOM concepts and database tables might be conceptually different and thus do not provide many hints for structure based matching.

The above limitations/weaknesses rule out automated mapping methods in establishing connections between central ontology and local database schemata. Manual mapping becomes inevitable.

4.1.2 Making mapping easier

Database interoperability has been studied by both conventional database community and the new semantic web community (Benslimane et al., 2007)(Doan et al., 2001)(Bussler et al., 2005). It is our contention that although many algorithms have been proposed and implemented, data interoperability between ontologies and databases is far from satisfactorily addressed. Before a mature automated mechanism can be found, mapping between ontology and database schemata is still a human labour intensive task with heavy involvement of domain experts. Manually crafting mappings is not straightforward. Concepts in HaDOM can be mapped to tables in HealthAgents databases, columns from a particular table, or columns from several tables. Similarly, although concept properties are frequently in one-to-one correspondence with table columns, they can also take values from several columns across tables or be merged into one column. While HaDOM constrains domain vocabulary, its effective use requires instantiating its concepts with entries extracted from databases. Unstructured database schemata makes translating values in table cells difficult. In practice, we cannot presume values in table cells are always predictable. Ideally, if when defining the database schema, one enumerates all the possible values for table columns (e.g. Patient.Gender = \{"Male", "Female", "M", "F"\}), only a handful possible values need to be coded in the mapping scripts. If, however, one does not enumerate the values but rather constrains the values as any string of length 4 - a common practice in hospitals, cells can take up any arbitrary strings. Such a scenario becomes more likely when the HealthAgents framework is widely deployed and takes in legacy databases from newly joined members.

In order to simplify the mapping process, we restrict ourselves to map concepts in the ontology only to tables or parts of tables and properties to concatenations of table columns. We observe the independence of tables to avoid using many database join operations which significantly impinge on the efficiency of database querying. This design principle was reinforced by introducing a housekeeping property to every concept. This property gathers all the information unable to map
to any ontological entities as a string separated by “+”. For instance, when mapping databases from Birmingham Children Hospital (BCH), Patient is extended as

\[
\text{Patient} = \ldots \sqcap \exists \text{id}.\text{String} \sqcap \exists \text{name}.\text{String} \sqcap \exists \text{gender}.\text{String} \sqcap \exists \text{concept identifier}.\text{String} \sqcap \ldots
\]

where concept identifier gathers the information that is unique to each hospital. In case of BCH, it has the following D2RQ code “BCH@+@@PATIENT_TBL.P_EU_ID@@+…” to collect information useful only to BCH.

When addressing the discrepancies introduced by ambiguous database schema specification, we use the Jena ARQ package\(^\text{14}\) to keep mapping scripts less database dependent. A Java property file stores all the locale information and is continuously extended once new values are identified. Human data curator, normally being the person maintaining databases, is necessary to update the property file.

4.1.3 The HealthAgents OntoDB Mapping Tool

The HealthAgents Mapping Tool is a software application developed for mapping between a given relational database and a given OWL ontology. Motivated by the idea of automating the mapping process between an ontology (concepts and properties) and a relational database schema, we designed a tool with a “drag and drop” feature to facilitate ease of use. This tool allows the user to relate concepts in a given ontology to entities present within a relational database with the final goal of obtaining a mapping description, using the D2RQ language for its representation.

The D2RQ framework contains a mapping language for treating non-RDF relational databases as virtual RDF graphs, and a platform that enables applications to access these graphs through the Jena and Sesame APIs, as well as over the Web via the SPARQL protocol and as linked data. The D2RQ language offers great flexibility from the point of view of mapping relationships, since it allows for a great range of properties and relations between concepts to be represented. The full specifications of the D2RQ language as well as the description of the entire platform are described in the D2RQ specifications web page\(^\text{15}\); where all the concepts, properties, and relationships are represented within a mapping description created using this language are presented.

The mapping description introduced above allows any given user, who does not need to know the organisational schema of the database, to query the database via the SPARQL language on the ontology. The tool facilitates the production of mapping relations between an OWL ontology and a relational database. This need for automated mapping tools is even greater in a Semantic Web era when ontologies are commonly used for interoperability and most of the data still resides in local database schemata.

In the following, we present the functionality of the tool and its usage in a practical setting. This allows us to illustrate the approach taken for its design, and also conveys the full extent of the tool’s capabilities. In doing this, we start by roughly describe a typical workflow of a user working with the application. The user is presented with the option of loading an OWL ontology visualised through the built-in interface. At the same time, the user can load a relational database schema specified either by an XML file or by access to the location of the actual database server. The database schema is visually available through the interface provided by the application. Once the ontology specification and the database schema are loaded into the application, the workflow begins by presenting the user with a directed graph that shows the entities (nodes) within the database and the relationships (e.g. foreign keys) amongst them. Apart from this, a series of windows appear which are used to specify the concepts and entities to be related in by dragging graphical renderings of related items and dropping them into a common space to articulate their association. Figure 10 shows a screenshot of the application with an ontology and a database loaded. At the center of the window, the graph representing the database schema is displayed.

\(^{14}\)http://jena.sourceforge.net/ARQ/

\(^{15}\)Available at: http://www4.wiwiss.fu-berlin.de/bizer/d2rq/spec/
For the sake of clarity, in order to improve the usability of the application, the workspace is divided into four different areas used to present the different type of information involved in the mapping process:

- **The ontology area** shows, in two windows, the concepts available within the ontology, and the attributes of the currently selected concept;
- **The visualisation area**, apart from the graph mentioned above, presents two more tabs, displaying: the D2RQ file being generated by the mapping process, and a table presenting the data available on the database for the selected entities over the schema;
- **The database area** shows the schema of the specified database (tables and their fields); also makes available a window with suggestions of database schema tables for the mapping of the currently selected ontology concept;
- **The mapping area** displays the D2RQ specifications and the way of presenting the information of the mapping. In this space all the D2RQ specifications can be filled in to obtain a complete mapping description. This area also fosters two subspaces: one on the side of the ontology (ontological concepts and properties), and the other on the side of the database (database tables and fields, that are being related within the current mapping description).

For illustration, Figure 9 shows the different organisational areas used for the presentation of the information within the application. Within the Figure, the top left screenshot shows the ontology area, the top right screenshot shows the visualisation area, the database area is presented on the bottom left screenshot, and finally, the bottom right screenshot presents the mapping area.

Given the intuitive character of the application’s interface, the only thing to be done in order to relate a concept in the ontology (or any of its attributes) to an entity within the database is to
select the desired object, drag it to the correct window within the mapping area, and do the same for the corresponding object in the database. Figure 10 shows how easily the mapping process is carried out, with a few concepts already mapped and an ontology concept being dragged to the mapping area to relate it with its counterpart within the database.

Figure 10  The mapping process. Dragging an ontology concept to the mapping area.

In order to achieve the completion of the mapping description the user must repeat the action described above for each one of the concepts on the ontology that need to be mapped. At any time during the development of the mapping, the user is allowed to visualise the final D2RQ file, which stores the mapping description. Another useful functionality is the possibility of querying the database, at any time, using the tab window provided for that specific purpose. In doing this we illustrate a statement, articulated in the introduction, that an ontology provides a conceptual integration of the range of questions one would expect to have answered about a domain. As such, the meanings of terms get explicated with reference to the answers obtained from queries which involve these concepts. This helps the user to decide, based on the information stored in the database, to which concept on the ontology any given entity within the database is related.

Although the mapping is done complying with the minimum specifications of the D2RQ declarative language, the application offers the possibility to create a complete mapping by presenting the user with a complete set of relations and attributes to be specified for each of the concepts mapped (following the D2RQ language specifications).

At the end of the mapping process the user has, within a D2RQ file, all the mapped concepts and the corresponding relationships with the original database entities, i.e. the mapping description (Figure 11 shows an example of the D2RQ file).
4.1.4 Accessing data functionality

The mapping of a database into the HaDOM ontology is carried out by the Database Agent using a mapping file containing the matching between the database and the HaDOM ontology.
The Database Agent is also responsible for checking permissions before the secure delivery of the requested information. This process is made through the validation of the user who sends the SPARQL petition to the Database Agent through the GUI Agent. Each user has an unique ID which is obtained and maintained by the GUI Agent and attached to all the messages containing SPARQL queries sent to the Database Agent. If the user has enough privileges to see the medical cases retrieved by the Database Agent of a particular clinical center, and the requested cases are marked as public then the results are passed to the GUI Agent and are shown to the user. Figure 12 shows the described flow of information between a HA client node with all the other client nodes in the network. Further details of the security arrangements are provided in a companion paper in this issue.

Each HA node owner of a database with information to share must also have its own Database Agent with the corresponding mapping file. Nevertheless, any HA node can also join to the HA network even if the node does not have its own database (the dotted components within the client node are optional as is shown in Figure 12) but may want to retrieve information from the databases of other medical institutions.

In order to execute the HealthAgents DSS at a clinical node, the HA Framework needs to be running and the Data Collector Agent invoked. If this initial requirement is satisfied, then the DSS can be started and the first screen is used by the user to log on into the system (Figure 13).

During the log on process, the user is authenticated according to his/her security permissions and if the user name and password are correctly registered, then the GUI Agent is started. The first task of the GUI Agent is to know if the node of the user has its own Database Agent. If a Database Agent exists, then the GUI Agent builds a SPARQL query to get some fields that are presented on the next screen. This information contains data such as the possible values for

![Figure 13 HealthAgents DSS login screen.](image-url)
the age, gender of the patients, all the values for the patients’ geographical origin and tumour locations. The values retrieved are used to fill the combo boxes that the user can manipulate to define a search criterion for a patient’s case notes (see the search neurooncological cases screen on Figure 14).

Figure 14 HealthAgents DSS screen for search neurooncological cases.

The next screen after the authentication is where the user can request for the neurooncological records from his/her own database (if it exists) or from all the available external clinical centers. As stated before, in this screen the user can define the search criteria to filter all the medical data available on the HA network. These parameters include specific information of the patient such as the gender, the range of age, the geographical origin or the tumour location (if it is already available). Other filter criteria are the echo time of the patients’ MRS: long echo time (LET) or short echo time (SET). The user can also define in the search if the medical records should be present in all the clinical nodes of the HA network or only in the local database.

Once the user has set the parameters for the search, the GUI Agent builds the corresponding SPARQL sentence which is sent to the Data Collector Agent. As explained in Section 3, the Data Collector Agent distributes the query and collects all the results retrieved from all the Database Agents. After the GUI Agent receives all the collected data, it presents the obtained neurooncological records to the user. The data shown on Figure 14 were obtained in a test using three distributed clinical nodes, two of them with a different database schema and running with different database engines (MySQL and Oracle ver. 10). The neurooncological records listed in the results were obtained from two of the three nodes (those with different DB schemata and engines) while the results of the third clinical node were hidden given the lack of user’s permissions.

As can be seen in Figure 14, the neurooncological records are presented, grouped by the name of the node, and then the user could also use the criteria to filter only the data belonging to a
specific clinical institution. The data retrieved and shown in this screen includes not only patient-related information but also some other data such as the date of the medical control and/or the date of the spectrum measurement. Using the records listed in this screen, the user may also select one of them for classification purposes. Depending on the input selected, the available Classifier Agents are shown (each one of them using a specific classification algorithm) and the user needs to select which Classifier Agent(s) to use. After selecting the Classifier Agent(s), the GUI Agent presents the results of the classification to the user (see Figure 15). This screen includes a graph of the obtained probabilities in the tumour type classification of the selected patient (graphs shown in the right side of Figure 15) and the spectrum of the case compared with the inferred shape of the spectrum of three tumour types: aggressive, low grade glial and meningioma (see the graphs in the left side of the screen in Figure 15).

5 Reasoning with HaDOM

5.1 Subsumption, instance classification, and other ontological reasoning

HaDOM provides a controlled vocabulary for the use of the classifiers and the construction of GUIs. For instance, the HaDOM ontology simplifies the development of an adaptable GUI, depending on the requirements of the user, whether they be a radiologist or surgeon or oncologist. The HaDOM ontology provides a well-structured model to simplify the development of adaptable user interfaces. Similarly, while the HealthAgents classifiers take data from the data providers and generate classification labels using pattern recognition methods, HaDOM is used to regulate the input and output labels for the classifiers by offering a controlled vocabulary as a uniform communication interface. Classifiers are developed at different centres using different data sets and with the goal of resolving different questions. So, for instance, there may be classifiers developed to distinguish between low grade meningiomas and aggressive tumours, which include high grade

Figure 15  HealthAgents DSS screen of classification results.
glioblastomas. The terminology belongs to the set of terms sanctioned by the WHO classification, and these classification labels reflects their actual usage amongst clinical practitioners. However, from a knowledge engineering viewpoint, such mixing of attributes of tumours (aggressive, or grade, or whether they have undergone metastasis) and its principal conceptual identity (glial tumours) has to be disentangled to create the conceptual hierarchical structure. Else, idiosyncratic usage in different clinical centres would make the job of coordinating the outputs of classifiers developed in one centre, but deployed elsewhere in the HealthAgents network difficult for agents. Using the capabilities for logical reasoning offered by ontologies built using OWL, identification of clusters of concepts used across the HealthAgents network in diagnosis offers potential future benefits for medical advances in this domain as well.

The domain ontology brings along with it valuable reasoning capabilities. In this context, reasoning is defined as making explicit statements that are implicitly encoded in the representation. In the following, we will present reasoning capabilities of HaDOM. Generally speaking reasoning mechanisms supported by the HaDOM relate to subsumption. More precisely, the ontology allows for one to infer out of (i) “A is a subclass of B” and (ii) “x is a member of A” that “x is also a member of B”. If, for example, “Glioblastoma Multiforms” is considered with a subclass of “Astrocytoma” and an unknown mass is classified as “Glioblastoma Multiforms” based on its appearance and bio-chemical characteristics, then we can automatically infer that this unknown mass is an astrocytoma and bears all the features defined on an astrocytoma. Another reasoning pattern is the inheritance of properties along the conceptual hierarchy. An ontology allows one to infer from (i) “A is a subclass of B” and (ii) “B has property P” that “A has property P”. In the previous example, this unknown mass will automatically inherit the necessary constraints defined directly on the Astrocytoma class. Defaults and exceptions might be applicable in this case when the complete domain knowledge is not available. Building upon the above mentioned mechanism we can utilise reasoning to ensure the correctness of the knowledge acquisition process. If, for example, it is known that a patient is characterised by three properties: age, sex and location and a database query only retrieved two of such fields, then missing information is flagged up and notification of appropriate action provided.

5.2 Better information accessibility

HaDOM underpins the HealthAgents Evidence-based Search System (EbSS)(Matthews, 2008) for well-targeted information extraction from on-line literature and patient databases. In evidence-based medicine (EBM), pieces of evidence from various scientific studies are evaluated and applied to ensure that the best outcomes can be expected based on the current status of knowledge. Hence, in EBM, identifying and retrieving appropriate information is critical. In many cases, such information is not readily available and the clinicians and other information requestors are overwhelmed by a large number of publications from online repositories such as PubMed\textsuperscript{16}, emedicine\textsuperscript{17}, etc. Mining useful information from such sources could be time consuming and inefficient. Classifying clinical research against a domain ontology imposes a schematic view over the information sources that helps the requestors to quickly zoom in and identify the most relevant information. For instance, when searching for diagnosis and prognosis information with respect to Choroid Plexus Carcinoma, HaDOM allows one to extend queries to not only the parent classes of this particular type of brain tumour but also the new tumour type defined in WHO 2007 classification by means of the links/properties among HaDOM concepts. Similar systems based on general ontologies have been successfully commercialised (c.f. goPubMed\textsuperscript{18}). HealthAgents EbSS, different from such general-purpose information portals, takes advantage of HaDOM in generating queries and filtering search results that tuned specifically against HealthAgents domains, namely brain tumours and associated imaging modalities.

\textsuperscript{16}http://www.ncbi.nlm.nih.gov/pubmed/
\textsuperscript{17}http://emedicine.medscape.com/
\textsuperscript{18}http://www.gopubmed.com/
Rendering information in a meaningful way also has implications for how well information is conveyed and apprehended (Herman et al., 2000). In the HealthAgents system, information is collected from different sources and is displayed based on the nature of the request and identity of users. This lays down two requirements on HealthAgents user interface, namely integrating and role-based information provision. When implementing the HealthAgents system, the integrating requirement is facilitated by annotating clinical data using concepts from HadOM and projecting it onto patients’ EHRs in a chronological manner. From EHR, therefore, users can navigate to clinical history of a patient, the various clinical investigation performed on him/her, etc. It is also possible to retrieve clinical research information via HealthAgents EbSS displayed alongside patient’s EHR. The HealthAgents system also practices a strict information filtering process based on the roles of users. Currently, HadOM defines a list of roles that can be played by a human user or a software agent. Associated with each role is its rights and authorisation that are used to annotate fragments of patient data. When browsing and navigating through a patient’s EHR, one is presented with the data that he or she has clearance for and prohibited to view or modify those for which he or she has not been granted access right.

6 Evaluation and discussion

The ontology presented in this paper is currently functioning as the inter-lingua between the different agents within the HealthAgents system. This application-centric role of the ontology means that the evaluation has to look at how this shared conceptualisation benefits the system from a communication view point. However, as explained above, the ontology serves to specify what information is passed around. This means that the evaluation will also have to take in consideration the application’s domain of expertise. Regarding the first point, a measure of how effective a particular ontology is in the context of an application, will need a number of similar, but different, ontologies to be compared against. However, this application-based approach to ontology evaluation is not suitable given the fact that the ontology is only used in one particular way for one particular task, and it is difficult to generalize this observation. Also, given the novelty of our project a comparison with related ontologies is not possible on a large, integrated scale. A very small number of different modules developed for describing brain structures or general tumour classes could be related as separate modules. However, such modules are relevant for evaluation more in the context of the second raised point and namely the domain of expertise. Unfortunately when trying to evaluate our ontology from a “domain” view point another problem occurs. It is quite hard to determine who the right users are, and what criteria to propose for their evaluation. Indeed, in this case, given the main purpose of the ontology it is not clear who the right users are and what such qualitative evaluation means (see (Brewster et al., 2004)). Moreover, comparing such different ontologies is only possible if they can all be plugged into the same application and this takes us back to the initial point detailed above.

Given this rationale we will evaluate our work by validating the ontology with respect to its purposes. According to Gangemi et al. (2006) an ontology validation needs to look at three different aspects: task assessment, agreement assessment and topic assessment. These three points correspond to the initial requirements presented in Section 1. Indeed, the system functionality validation will ensure the task assessment, meeting the clinician terminological requirements addresses the topic assessment and the smooth transition from existing data nomenclature towards the agreed nomenclature will allow for agreement assessment. Thus, in validating HadOM we will assess the work presented in this paper with respect to:

- System functionality. In the light of this requirement we have demonstrated how the ontology functions as a common vocabulary amongst the different databases in the system and how it is used by various agents within HealthAgents.
- Clinician terminological requirements. We have validated the ontology throughout the duration of the project by having regular meetings with the clinical partners in order to
discuss both the terminology used and how it will impact on the development of the system. The terms used in HaDOM are terms that have been agreed upon with the domain experts and which are consistent with the envisaged use of the system.

- The smooth translation from existing data nomenclature towards the agreed nomenclature. This has been demonstrated by the development of the Mapping Tool detailed at length in the previous Section. Not only that this tool will facilitate creating mappings between legacy databases and the HealthAgents system but also, without such system, the manual creation of such scripts would be impossible for the new clinical partners joining the system in the future.

6.1 System functionality

The HealthAgents system is effectively running with data nodes residing in both Spain (i.e. Universitat Autònoma de Barcelona, UAB, and Universitat de València, UV) and the United Kingdom (i.e. The Birmingham Children’s Hospital, BCH). Each data provider is allowed to keep the integrity and continuity of their legacy data to avoid disturbance to existing tools and systems. In the meantime, the heterogeneity inherent in the independently collected data is tackled by means of the domain ontology. Although further evaluation of the HealthAgents system is necessary, usability and reliability studies of the current release of the HealthAgents system have confirmed that:

- HaDOM is sufficiently expressive to cover the legacy data from all participating hospitals and clinical centres. Data has been faithfully converted and no knowledge loss has been reported.
- HaDOM is capable of representing inputs and outputs of classifiers and other data processing agents. HaDOM serves as the unified language to ensure service and data interoperability within HealthAgents.
- Modularised HaDOM enhances the extensibility of the HealthAgents system and enables specialist software agents. For instance, data anonymising agents can be developed against each imaging and clinical module with their outputs projected upon HaDOM for alignment.

In summary, HaDOM successfully facilitates an unobtrusive mechanism to transfer heterogeneous data among different sites without requiring the active engagement of human users. On the other hand, a major disadvantage of HaDOM has been revealed during the evaluation. The HealthAgents classifiers normally offers class labels together with numeric values to justify and contextualise the classification. Thus far, HaDOM uses a URI to point to a data file holding such values (e.g. matrices) or treats them as strings using string data type properties (e.g. hasParameter). While such approaches have been demonstrably successful in leveraging diagnostic classification tasks to be executed over the HealthAgents network, they offer access to the patterns in the data only through their algorithms and interfaces. This precludes any possibility of combining reasoning based on these numeric values directly with ontology based inferences. Although conceiving a new reasoning algorithm enhancing ontology with reasoning on concrete data is beyond the scope of HealthAgents project, research on integrating logic based knowledge representation formalisms with uncertainty is relevant to this task (c.f. (Łukasiewicz, 2008)(Costa, 2005)).

6.2 Clinical terminology

The diversity of the HealthAgents consortium offers a good test bed for HaDOM. The first version of HaDOM was mainly based on published literatures, interviewing various domain experts from UAB and observing the daily work of selected domain experts with the think-aloud protocol (Nielsen et al., 2002)(Wright and Monk, 1990). This draft version is then reviewed by domain experts (potential HealthAgents users and clinical consultants) from UV and BCH in three consecutive steps. Firstly, the domain experts were given a pre-interview so as to build up
essential knowledge on HaDOM and to introduce them to the idioms of knowledge representation languages (namely Description Logic constructs). They then walked through the ontology with or without the help of knowledge engineers. A post-interview was performed against a questionnaire to collect their questions, comments, and observations. This variant of the usability evaluation method (Rubin, 1994) is based on practical considerations — the limited availability of clinicians prevents a prolonged interview and thus a guided one could ensure that necessary feedback was duly gathered. Expert feedback was used to revise HaDOM.

Moreover, HaDOM revision was reviewed against the eTUMOUR data model. One of eTUMOUR’s objectives was to collect real patient data for establishing effective clinical decision support methods. eTUMOUR consortium overlaps with HealthAgents consortium and was expected to share a large amount of data with HealthAgents. Therefore, HaDOM should be compatible with the database schemata from eTUMOUR. One of the consequences is that HaDOM’s naming and modelling conventions have to accommodate the design consideration in eTUMOUR. Such a link was made through the development team in MicroArt which was responsible for database design in both projects.

Finally, HaDOM was further evaluated through manually constructing mappings between the domain ontology and legacy database schema by domain experts. A major assumption behind such an approach is that one can safely conclude that HaDOM satisfies the applicability and usability requirements if a domain expert with limited knowledge on ontology engineering could establish the mappings correctly. Two experts from BCH responsible for handling patient data were summoned for the study. With guidance from knowledge engineers, mapping was successfully constructed. Feedback from the two domain experts led to further changes on HaDOM including new names and conceptual structures.

6.3 Facilitating translation

The last phase in evaluating HaDOM was done with the help of the graphical mapping tool developed within HealthAgents. Thus far, many mapping tools are available to suggest candidates between ontologies and database schemata (see for instance the survey by Rahm and Bernstein (2001)). A strong argument against adopting such automatic mapping methods in HealthAgents is that although labelled with “semantics”, most approaches fail to inspect semantics in terms of cognitive expectations that emanate from working within established working practices within institutions. In addition, these cognitive biases get shaped within different perspectives and implicit conceptual models rooted in the users’ educational, cultural and societal background (Fodor, 2004). It is unrealistic to expect effective automation for ironing out these potentially distinct conceptions, and need to accommodate these discrepancies when constructing mappings. The situation is aggravated when mapping HaDOM against legacy database schemata due to the fact that we have to observe the integrity, specificity and historically acquired idiosyncrasies of the latter.

Furthermore, in practice, we found the following difficulties prevented use from adopting automated mapping tools. Firstly, the diversity of the legacy database schemata made automated approach less appealing. There were cases that one HaDOM concept was mapped to more than one database table combined through a series of join operations; one HaDOM concept was mapped to a number of columns that did not have obvious relations one could rationally describe; one HaDOM property was mapped to multiple table columns depending on whether or not it satisfied certain auxiliary conditions; etc. Secondly, many well-performed automated mapping tools rely on external data sources, e.g. WordNet (Miller, 1995), reference ontologies, or instance data. Such information was either not available from the legacy databases due to patient privacy concerns or not applicable because of the existence of a large number of hospital specific abbreviations and acronyms. Using an automated mapping tool would require tuning the tool against individual hospitals and prolonged validation phases. Thirdly, even if an automated tool had been used, human involvement would have been inevitable due to strict patient safety
requirements. The benefit of adopting such tools was not evident giving the size of the problem—after modularisation, each domain expert, with even a rudimentary understanding of the meanings of the entries of the database schema, would not find it difficult to map and review mappings of about 30 concepts. The HealthAgents mapping tool, however, leverages basic string similarity metrics to recommend potential mapping candidates.

A preliminary usability study of the graphical mapping tool was carried out. Four people with different computing skills and different backgrounds were selected. They were presented with the HaDOM ontology and one of the real-life legacy database schemata and were asked to map a few preselected concepts against table columns. The feedback on the user interface and the automated generated D2RQ script was positive, suggesting that the layout was intuitive and significantly reduced typos and human errors. Negative comments include the confusing visualisation of the ontology, the difficult of navigating through different tabs and windows and the lack of “intelligence” of recommendations. We expect to carry on development of the graphical mapping tool and perform formal usability and design studies beyond the HealthAgents project in order to enhance its usefulness.

6.4 Concluding remarks

In conclusion, this paper presents our efforts towards building an ontology for HealthAgents. Our main motivation behind the work was driven by a desire to provide a declarative framework to separate the functionality of the system from an articulated interface derived from user requirements that were informed by frequent meetings for validation with the clinical partners. We have shown how we implemented the ontology, as well as the mechanisms for accessing the data using the ontology by domain specific examples. The main contribution of the paper is two fold. On one hand we show a “hands on” example of building an ontology in practice, and how making it work in distributed settings requires translations and intermediate placeholders in order to include legacy representations. This is especially important in an era where more and more information is acquired and annotated with metadata so that methods for their (semi) automatic informed manipulation become essential. On the other hand we make explicit the implicit modeling choices when building an application ontology for a given domain. This has been an interesting process that could serve as a future reference point for similar work.

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References

Knowledge Representation for Brain Tumour Decision Support


