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HealthAgents: distributed multi-agent brain tumor diagnosis and prognosis

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Abstract We present an agent-based distributed decision support system for the diagnosis and prognosis of brain tumors developed by the HEALTHAGENTS project. HEALTHAGENTS is a European Union funded research project, which aims to enhance the classification of brain tumors using such a decision support system based on intelligent agents to securely connect a network of clinical centers. The HEALTHAGENTS system is implementing novel pattern recognition discrimination methods, in order to analyze in vivo Magnetic Resonance Spectroscopy (MRS) and ex vivo/in vitro High Resolution Magic Angle Spinning Nuclear Magnetic Resonance (HR-MAS) and DNA microarray data. HEALTHAGENTS intends not only to apply forefront agent technology to the biomedical field, but also develop the HEALTHAGENTS network, a globally distributed information and knowledge repository for brain tumor diagnosis and prognosis.

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Abbreviations

API	Application Programming Interface
DSS	Decision Support System
EbSS	Evidence-based Search Service
FIPA	Foundation of Intelligent Physical Agents
GUI	Graphical User Interface
HAL	HEALTHAGENTS Language
HR-MAS	High Resolution Magic Angle Spinning Nuclear Magnetic Resonance
LCC	Lightweight Coordination Calculus
LDA	Linear Discriminant Analysis
LS-SVM	Least-Squares Support Vector Machines
LTE	Long Time Echo
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MRSI	Magnetic Resonance Spectroscopic Imaging
OWL	Web Ontology Language
RDF	Resource Description Framework
STE	Short Time Echo
SVM	Support Vector Machines
YP	Yellow Pages

1 Introduction

Brain tumors remain an important cause of morbidity and mortality in Europe with a crude incidence rate of 8 per 100,000 inhabitants [9]. Even though it is not the most common type of cancer overall, brain tumors account for a greater proportion of tumors in younger age groups. This leads to them being an important cause of cancer in young adults and children. Indeed, brain tumors are the most common solid malignancies in children.

While medical treatment relies on the accurate classification of a tumor, diverse studies document the difficulties faced by radiologists and oncologists in making a non-invasive diagnosis based on traditional cranial imaging only [2, 13, 19]. The inclusion of innovative techniques, such as Magnetic Resonance Spectroscopy (MRS), gives the opportunity to increase the information available from imaging and potentially improve the accuracy of non-invasive diagnosis. Furthermore, there is emerging evidence that these techniques may provide novel biomarkers of prognosis. The use of histopathology to classify tumors is now being augmented by other investigations on tissue, such as molecular genetics and gene expression, to improve the characterization of tumors and stratify them into groups of varying prognosis.

The metabolite profiling of tissue by High Resolution Magic Angle Spinning Nuclear Magnetic Resonance (HR-MAS) may further improve this characterization by probing the downstream consequences of these genetic alterations. The use of ex vivo magnetic resonance spectroscopy in the investigation of tumors gives the potential to link these studies to in-vivo MRS and hence the non-invasive determination of tumor tissue properties [42]. Moreover, we argue that if advanced magnetic resonance data can be made widely available along with clinical data, in a secure and easily accessible way, this will significantly improve the ability of clinicians to determine non-invasively the diagnosis and prognosis of brain tumors.

The HealthAgents project [3, 47] is engaged in the development of a distributed, agent-based Decision Support System (DSS), which implements a series of automated classifiers based on pattern recognition methodologies for the diagnosis and prognosis of brain tumors.

Our approach builds upon previous experiences in biomedical informatics, particularly in image processing and computer-aided diagnosis, where physiologic and molecular level tumor discrimination are becoming increasingly used for the early detection of tumors [24]; in machine learning for brain tumor classification using MRS [20], where high classification accuracies have been achieved by various methodologies; and in agents, where meaningfully codified descriptions of service capabilities have facilitated the development of protocols for pipelining them in dynamic ways for genome analysis and medical decision support systems [11, 38].

This work documents the first prototype of the DSS, which is comprised of an agent-based architecture, with an associated ontology, data mining techniques, and the protocols for clinical data exchange. It is designed to allow users to preserve their local center policies for sharing information, whilst allowing them to benefit from the use of a distributed data warehouse. Moreover, it will permit the design of local classifiers targeting specific patient populations.

While the DSS provides a clinical environment using MRS, the machine learning techniques will also be applied to ex-vivo chemometrics, micro-arrays and text mining to correlate the transcriptomic and metabolomic information. The use of multiple complementary data sources will enrich the classification of brain tumors and aid the discovery of novel prognostic markers.

All data is stored anonymously and securely through the HealthAgents network of data marts in order to create a distributed data warehouse. This data warehouse contains the collection of such clinical data, that has been properly anonymized from the original clinical data and information acquired and stored at the various participating European clinical centers. This incipient network grants bona-fide access to any qualified organization in return for its contribution of clinical data to the DSS. No personal patient information leaves the local centers.

The rest of this paper is structured as follows. First, we provide some background on the underlying techniques for this project: determination of tumor properties, machine learning, and agents. Then we provide the architectural specification, followed by a description of the implementation. Finally, we conclude by reviewing some related work and providing guidelines on our future work.

2 Background

Nowadays the diagnosis and treatment of brain tumors is typically based on clinical symptoms, radiological appearance and, often, a histopathological diagnosis of a biopsy. However, treatment response of histologically or radiologically-similar tumors can vary widely, particularly in children. MRS is a non-invasive technique for determining the tissue biochemical composition of a tumor (metabolic profile) [26]. Additionally, the genomic profile, determined using DNA micro-arrays, facilitates the classification of tumor grades and sub-types, which may not be distinguished by morphologic appearance.

HealthAgents builds upon three areas of expertise:

1. Determination of Tumor Properties
2. Machine Learning
3. Agents and Ontologies

2.1 Determination of tumor properties

Diagnosis using Magnetic Resonance Imaging (MRI) is non-invasive, but only achieves variable accuracy depending on the tumor type and grade [28]. In addition to its intrinsic healthcare costs and stress to patients, the stereotactic brain biopsy exhibits significant risks, with an estimated morbidity of 2.4–3.5% [14, 21] and a death rate of 0.2–0.8% [14, 15]. For tumors whose grade may evolve over time, repeated biopsies would be needed to establish the current status and these may not be clinically advisable or practical. Furthermore, tumor histopathology does not reliably predict response to treatment or outcome for all tumors and there is an increasing emphasis on the discovery of novel biomarkers of tumor behavior [23].

Hence, there is a need to improve brain tumor classification and non-invasive methods for brain tumor diagnosis and prognosis in order to aid patient management and treatment. In the HealthAgents, three techniques are made available to address the aforementioned requirements:

1. MRS, coupled with conventional MRI, provides metabolite profiles of either a single-voxel of tumor tissue or a grid of voxels, where a molecular image of particular tumor metabolites can be additionally produced Magnetic Resonance Spectroscopic Imaging (MRSI) [26, 45].
2. HR-MAS is applied to biopsies in vitro in order to provide metabolomic characterization which is more detailed than that available from in vivo MRS [4, 36].
3. DNA microarray analysis of biopsies can determine tumor phenotype from gene expression profiles and predict survival more accurately than classical histology [39, 41].

2.2 Machine learning

Defined as the study of computer algorithms which improve automatically through experience, machine learning can be thought as the intersection of computer science and statistics [7]. It uses example data or past experience to optimize a given set of performance criteria. As a field of study in computer science it is sometimes referred to as "data mining", "knowledge discovery from databases", or "advanced data analysis" [40], and entails the solution of a series of sub-problems such as: association, supervised learning (e.g. classification and regression), unsupervised learning, or reinforcement learning [1]. Hence, pattern recognition is often described as a sub-domain of machine learning since its main focus is on supervised and unsupervised learning. Brain tumor research provides several biological domains where both pattern recognition and machine learning techniques can be applied: chemometrics [45], metabolomics, microarrays, genomics, proteomics, and text mining [30].

HealthAgents employs machine learning methods to provide the mathematical and computational mechanisms to infer knowledge in a formal model from specific brain tumor data. HealthAgents samples brain tumor data from a training set (x_i, y_i), where x_i is an input pattern—a metabolic profile—and y_i indicates the class membership—a known pre-diagnosed brain tumor—, with the goal of learning general models from the particular samples. Such models will minimize classification error on future unseen data and, eventually, suggest a brain tumor diagnosis more accurately. In order to address the solution of such classification problems, HealthAgents is developing linear and non-linear classifiers for brain tumors employing Linear Discriminant Analysis (LDA), Support Vector Machines (SVM) and Least-Squares Support Vector Machines (LS-SVM) in combination with feature selection and feature extraction methodologies.

LDA maximizes the ratio between the difference of the projected means and the dispersion within the classes. Ideally, this function should be optimum when the distance between means is maximum and the inside-class dispersions are minimum. SVM are classification, nonlinear function estimation and density estimation methodologies defined in the context of statistical learning theory, kernel methods and structural risk minimization [50]. While SVM define the optimal separating hyperplane between two classes with the maximal margin in a high dimensional space by means of the kernel trick, LS-SVM provide a reformulation of the SVM, where a linear system is solved [44].

2.3 Agents and ontologies

Several modern complex distributed systems are composed of customizable building blocks, known as software agents or, simply, agents. The literature enumerates four important characteristics of agents [10]. First, agents possess an internal knowledge-based state that can be dynamically altered. Second, they have dynamic reasoning capabilities that determine their internal behavior through constraints or goals. Third, they sustain a communication status that enables them to interact with agents or human entities. Last, they feature a unique identity that provides roaming and service advertising capabilities.

Software agent technology offers an increasingly popular paradigm for the design and development of certain types of software system. This is particularly the case for complex distributed systems, in which components need to communicate and reason about the information they exchange. Other approaches, such as those based on web services, offer similar solutions but the clean and high level software abstraction inherent in the agent approach makes agent technology an appropriate choice for this application.

The HEALTHAGENTS scenario is one in which distributed datamarts are being built by widespread hospital groups in various countries throughout Europe. Individual hospitals do not typically encounter sufficient cases of particular tumor types to be able to constitute a sizable training set to develop robust software-based tumor classifiers capable of providing reliable diagnoses and prognoses when presented with non invasive imaging and spectroscopic data. A key aim of the HEALTHAGENTS system is that, through data sharing between hospitals across Europe, more powerful diagnostic and prognostic support can be facilitated. Not only will it be possible to build local classifiers based solely on a hospital's own cases, but also global classifiers based on aggregated appropriate cases in the distributed system. Hospitals and countries vary in their approach to restricting the mobility of data and the system design anticipates this variability. To build global classifiers, classifier builder agents will typically gather appropriate cases from across the network, but will be able to work locally within a hospital node if the hospital restricts the movement of data.

Another relatively new set of technologies, on which we draw, is the set called "semantic web technologies", in which ontologies are used firstly to structure the knowledge implicit in the data of the application, secondly as a vehicle for interoperability between software components such as agents and finally to provide a platform for reasoning over that knowledge [25].

Although there are moves towards standardization, different hospitals often use different schema for their tumor case data and, in order to support interoperability between the data from different hospitals and between agents utilizing that data, we have developed several ontologies in a modular fashion. These cover the brain tumor domain and include the relevant medical imaging modalities, clinical information and histopathological classes involved in tumor diagnosis and prognosis. We are including in the ontology relevant knowledge from medical experts, such as any established relationships between anatomical location and tumor type and between clinical data and tumor type. Using this knowledge from the ontology and information from Yellow Pages (YP) agents about classifier agents available in the system, their functionality, performance characteristics and reputation, agents will be able to reason about and recommend appropriate classifiers to be used for a particular case.

In addition to the domain ontology, which describes what sorts of objects are referred to by components of the system, we have developed a separate ontology, which defines the terms to be included in the communication language used by the agents. This means the messaging vocabulary used by agents can be expanded without modification to the individual agents in the system.

The use of agent technology and ontologies is not new. Several authors have described systems in the medical and bio-informatics domains and elsewhere [12, 22, 31–34, 38, 51]. However, there are several novel aspects to the approach taken here, including the use of the communication language ontology, the implementation of agent functionality through the use of a Lightweight Coordination Calculus (LCC) [43], innovations we are making to handle classifier agent performance and reputation ranking and the integration of an evidence-based search service. Some of these issues are discussed more fully in the following sections.

3 Architectural specification

Before describing the architectural specification it is instructive to consider a simplified high level overview of the functionality to be achieved.

First, to begin the process, hospitals need patient cases for which the tumor diagnosis is known from biopsy analysis (histopathology, etc.) and for which potentially predictive MRI and MRS data is available. These cases are link anonymized and copied to the hospital's local HEALTHAGENTS datamart.

The MRS data is typically in a format dependent on the MRS machine manufacturer and is first preprocessed to a canonical form. At the request of a medical user, and when sufficient cases are available within the datamart, classifiers are developed to answer specific diagnostic questions. Once trained and tested using the appropriate cases from the distributed datamarts, the classifier is added to the system and its existence, its initial performance and reputation, and the profile of its training and test data are published in the HEALTHAGENTS YP. The ontologies for the system encompass these descriptive labels.

A medical user, attempting to diagnose a patient for whom MRS data is available, uses a local web based Graphical User Interface (GUI) to initiate entry of the case information into HEALTHAGENTS, once again in link anonymized and canonical form. The system, via the GUI, may be able to suggest appropriate classifiers based on the clinical data, tumor location etc or the user may ask, via the GUI, whether appropriate classifiers are available. The GUI consults nearby YP to establish the availability of appropriate classifiers. This is not a straightforward process. Classifiers may be appropriate on the basis of the tumor types between which they can discriminate but may be less obviously suitable when comparing the patient profile of the case to be classified with the profile of the training set used to build a particular classifier.

When performance and reputation of a classifier are taken into account the problem of classifier selection may become a substantial reasoning and negotiation process and several classifiers may be capable of satisfying the request of the user.

In HEALTHAGENTS all potentially suitable classifiers are invoked to classify the current case and the various factors influencing classifier choice are used to rank the results unless the user makes a specific over-riding choice. The classifiers may be located at classifier nodes anywhere on the HEALTHAGENTS network, in which case the data to be classified may be sent from the hospital to the remote classifier nodes for classification. If the hospital does not allow data to leave the local node, classifiers may be run locally. Results from the different classifiers are gathered, ranked and returned to the user via the GUI to support the user's decision making processes. Classifier results are also recorded in the system so that, if and when a confirmed diagnosis is available for a case, an estimate of the "dynamic" performance and reputation of classifiers can be updated.

In addition to the classification processes described above, the HEALTHAGENTS system provides an Evidence-based Search Service (EbSS) which seeks, in a context sensitive way, papers from the medical literature to assist the medical user in the current task. The search service has a manual mode in which the users indicate the topics for which supporting material is required but an automatic search mode may also be triggered by the classification processes being undertaken and the resulting literature made available to the user if desired.

This simplified overview of functionality suggests the need for at least the following agents:

- Database agents to handle input and output of cases to and from the hospital datamarts
- Preprocessing agents to convert imaging data to canonical form
- GUI interface agents to handle interaction with medical users at hospital nodes
- YP agents to keep track of resources in the system including the location of case data, classifiers and their profiles, performance and reputations.
- Classifier builder agents to (help to) gather appropriate cases and build, train and test classifier agents
- Classifier agents to provide tumor classifications based on case data
- Petitioner agents to invoke appropriate classifiers and gather and rank results
- EbSS agents to provide the context sensitive information searching

A multi-layer agent framework has been built in order to provide seamless integration of the new functionalities into HEALTHAGENTS with minimum programming effort, as well as to support information extraction and analysis in a timely fashion. By deliberately abstracting all specific agent functionality from the interface, this framework enables platform independence. The framework, as depicted in Fig. 1, is composed of the following layers:

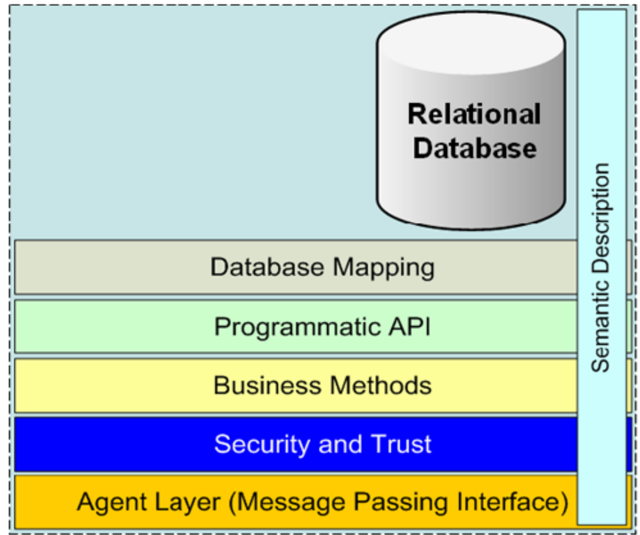


Fig. 1 The HEALTHAGENTS multi-layer framework

Database Mapping The database-mapping layer is used to map relational database schemes to the HEALTHAGENTS ontological schema.

Application Programming Interface (API) The programmatic API layer abstracts the underlying database interaction from the agent architecture.

Business Methods The business methods layer contributes the main functionality of the agent such as new case classification, data retrieval from a datamart etc.

Security and Trust The security and trust layer is a crucial system component due to the sensitivity of the data. Its functionalities are access control, data marshalling, tracking of on-going data, and the evaluation of reputation and trust of agents.

Agent The agent layer is in charge of all the communications and allows their abstraction from the rest of the system to allow flexibility in the underlying framework. Thus, we can use any agent development platform by modifying this layer only.

Semantic The semantic description contains the description of what the agent holds and what it is able to do.

The API at the agent layer consists of the basic messaging interface that queues incoming messages and currently takes them off the queue one-by-one to process them. The messages are automatically tagged with conversation identifiers to relate outgoing messages with their responses. What constitutes a conflicting message very much depends on the agent's functionality and such situations are not explicitly handled in the messaging interface.

```
// Here YPID is a yellowpages identifier
// and AID is an agent identifier

a(yellowpages,YPID) ::
(
 (
  // Check if someone is registering with us
 registerRequest(Abilities) <= a(registrant,AID)
  <- register(AID,Abilities) // then
  )
  or
 (
  // Check if someone is searching us
  searchRequest(Abilities) <= a(searcher,AID)
   <- search(Abilities,Results) then
  searchResponse(Results) => a(searcher,AID)
  )
 // ...
)
```

Listing 1 The Interaction Model for the YP Agent

That said, formal agent messaging definitions can be used to specify precisely what messages an agent should be expecting in the course of its execution. By providing an executable workflow definition we can simply invoke a workflow and the agent will behave in a determined way, allowing the agent's behavior to be easily altered or updated by those with the necessary authorization. Listing 1 shows part of the interaction model for the YP agent, encoded in LCC:

Communications within the HEALTHAGENTS network are governed by two complementary ontologies:

1. The *communication ontology* defines an agent language, the HEALTHAGENTS LANGUAGE (HAL), containing message primitives that support the HEALTHAGENTS architecture; for example, there are definitions for registration and deregistration messages received by YP agents that specify what data is required in that message. This language has been defined using the Protégé ontology editor [17] as a Web Ontology Language (OWL) [37] ontology. In the agents, a Turtle [5] representation is used for conciseness.

The ontology has been mapped to Foundation of Intelligent Physical Agents (FIPA) performatives [27] should the underlying agent layer support such messages.

2. The *domain ontology* defines concepts and relations relating to brain tumor diagnosis. The ontology is used to facilitate interoperability between agents and disparate data resources, and also to provide support for agent based learning and reasoning processes.

Listing 2 shows an example of the use of HAL for the process of YP Registration for a classifier agent.

In summary, whilst focusing on a specific knowledge domain—brain tumor diagnosis and prognosis—, HEALTHAGENTS is creating a generic intelligent agent communication architecture to securely connect user sites with a distributed database and provide appropriate support for applications built thereon.

```
@prefix hal: <http://www.healthagents.net/
  HAAgentCommunicationLanguage.owl#>.

@prefix rdf: <http://www.w3.org/1999/02/22-rdf-
  syntax-ns#>.

hal:messageContent
  rdf:type hal:YellowPages_Register_Request;
  hal:has-agent-to-register hal:object1;
  hal:has-abilities hal:object2.

hal:object2
  hal:has-class-name "net.healthagents.agent.
    RDFCollection";
  hal:has-collection-item hal:object1455484972;
  hal:has-collection-item hal:object1638383633.

hal:object1638383633
  hal:has-ability hal:has-name;
  hal:has-class-name "net.healthagents.agent.
    SpecificAgentAbility";
  hal:has-ability-specification "5
    _agmmas_mrs_lese_lda_001".

hal:object1455484972
  hal:has-class-name "net.healthagents.agent.
    SpecificAgentAbility";
  hal:has-ability-specification hal:Classifier;
  hal:has-ability hal:has-type.

hal:object1
  hal:has-class-name "net.healthagents.agent.
    jade.JadeAgentIdentifier";
  hal:has-jade-agent-platform-address <http://
    pasiphae:1633/acc>;
  hal:has-jade-agent-id-name "Classifier@192
    .168.2.11:1099/JADE";
  hal:has-jade-agent-platform-address <http://
    pasiphae:7778/acc>;
  hal:has-jade-agent-platform-address <http://
    pasiphae:1632/acc>.
```

Listing 2 YP Registration for a Classifier Agent

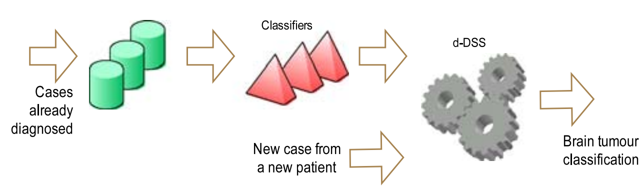


Fig. 2 Overview of the data flow in HEALTHAGENTS

Moreover, the architecture specification is intended to support the building of a completely distributed repository of local databases. An overview of the data flow is shown in Fig 2.

4 Implementation

Conceived as an open-source platform, the HEALTHAGENTS DSS is implemented using the Jade agent development environment [6], Java, Ant and D2RQ [8], and supported under Windows and Linux platforms, and intended to be distributed into four different types of computing nodes with at least one active agent, as depicted in Fig. 3.

Pre-processing node. Involves not only the conversion of time-domain MRS data into frequency-domain data but also the increase of its signal/noise ratio. It requires the application of both a Lorentzian apodization and a Fast Fourier Transform on the metabolic profile.

Classifier node. Implements classification functions and data projection based on the LDA latent space, implemented as classification agents in the HEALTHAGENTS network. These agents provide not only support to the decision-making process during the diagnosis of new patients, but also seamless access to the results at the GUI to the classification model.

Database node. Includes an ontological mapping between the relational database and the HEALTHAGENTS ontology. By designing the agent system to utilize semantic web querying mechanisms via D2RQ, we assure the maximum flexibility for integration of different functionality as the network gets larger, as well as providing the ability to run more advanced reasoning over the data.

EbSS node. Provides contextualized searches, classification oriented searches, and generates an on-line literature search.

Client node. Furnishes the HEALTHAGENTS GUI to upload the raw data and visualize the result of the classification. This agent manages the user interaction with the MRS raw data, and is crucial to assure patient confidentiality through its anonymization capabilities.

Currently, the HEALTHAGENTS DSS furnishes classifiers for aggressive tumors (glioblastomas and metastasis), benign meningiomas and a low-glial mixture (astrocytomas grade II, oligodendrogliomas and oligoastrocytoma), and its functionality is primarily based on the Interpret DSS system [49].

The system will also ensure that new versions of the classifiers and their models are made available. These updates are based on any newly validated data entering the system, used to adapt and improve the behavior of the classifiers with respect to the constantly changing evidence in the field. In addition, updates incorporate any feedback from clinical users of the system. This type of feedback is considered the most useful information for the improvement of the DSS. A reputation subsystem using contextual evidence such as user choice of classifiers, clinician feedback and background evaluations of the classifiers will eventually provide quality information and statistics on the classifiers.

4.1 DSS operation

Firstly, in the HEALTHAGENTS DSS operation to upload the MRS raw data to the system, is in situ anonymization employing the HEALTHAGENTS GUI. This is a critical process, because HEALTHAGENTS ensures that no personal patient information leaves a clinical center. This applies to both clinical data records and data files such as MRI and MRS signals (raw data). Patient identifiable information is removed from these data files within the collecting hospital by a process of anonymization. This user interaction is illustrated in Fig. 4(a).

Secondly, once the data is completely anonymized, the MRS raw data is sent from the client to the pre-processing agent. The pre-processing agent transforms the raw MRS data file from the scanner into the HEALTHAGENTS data format, invokes the classifiers and sends the results back to the client.

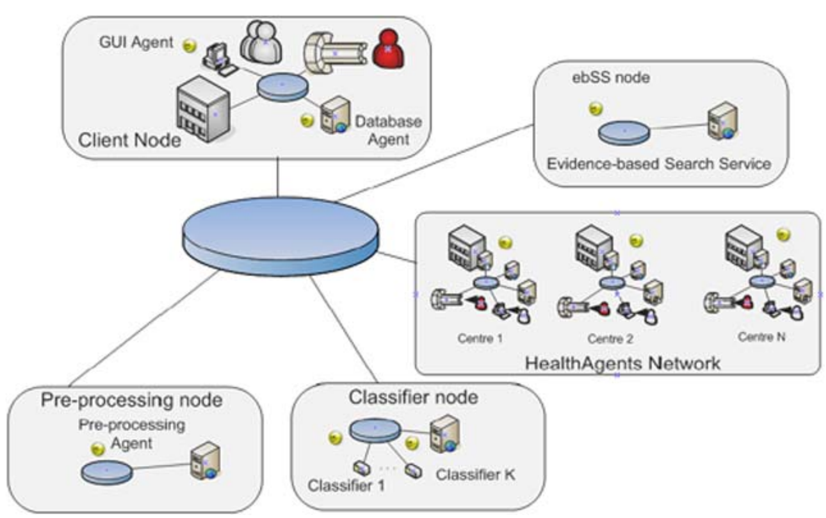
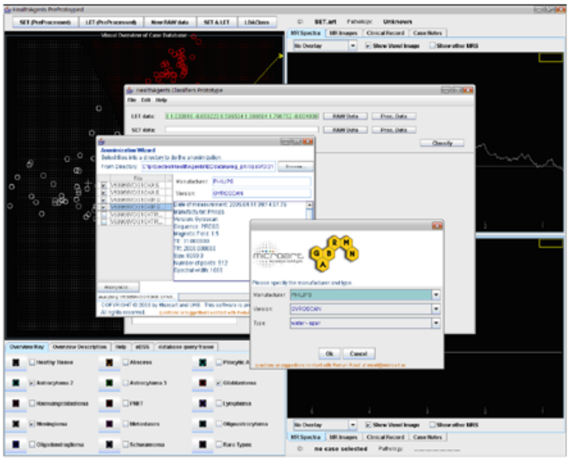
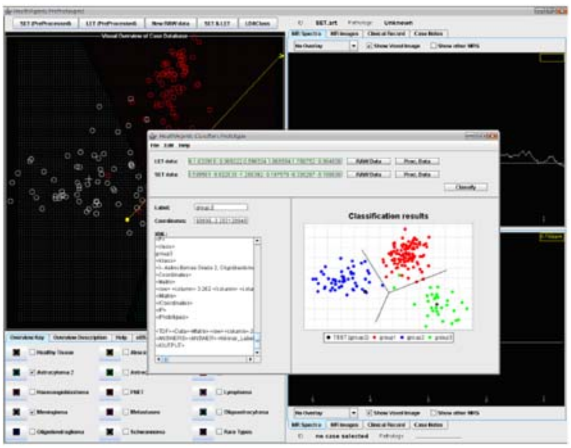


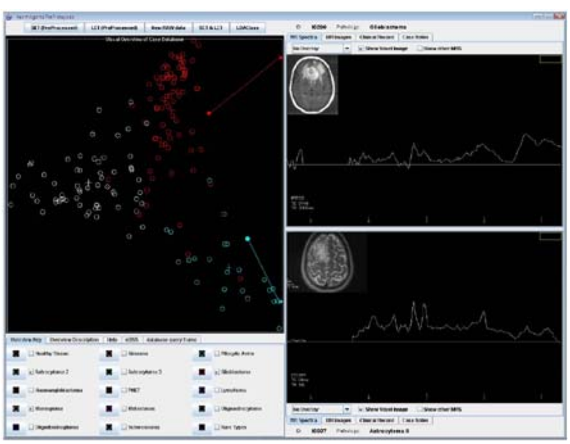
Fig. 3 The multi-node HEALTHAGENTS architectural implementation



(a) Anonymization



(b) Classification



(c) Visualization

Fig. 4 The HEALTHAGENTS graphical user interface (GUI). **a** Anonymization process of MRS data. **b** Classification. The classification results and their communication messages are combined into a single view. **c** Visualization. The case classification within the latent space is presented in the upper left part of the screen. Different types of tumors are presented as tick-in boxes in the bottom left portion of the screen. The MRS is presented on the right hand panel along with the MRI of the case. General informative fields on the cases are enlisted in the bottom and top left lines

The classification of a case is done in a specialized node (or nodes) where the trained classifiers reside. This classification is undoubtedly the cornerstone in the HEALTHAGENTS functionality as the basic database agent manages the interactions with the HEALTHAGENTS network which groups the different clinical centers (data marts) where classifiers are trained. This is depicted in Fig. 4(b). It is important to note that the accuracy of the classifiers depends heavily on the number of cases and therefore on the size of the HEALTHAGENTS network. The prototype currently contains a few hundred cases, and new cases will be acquired and incorporated from clinical centers in Spain and the United Kingdom within the following months.

Thirdly, the GUI agent collects the result of the pre-processing module in order to plot the spectra, the MRI (if any) and the classification of the current case in the latent space as shown in Fig. 4(c). While the visualization is essentially based on previous experiences [45], the agent and web-based capabilities will enable the GUI a seamless operation across networks.

Fourthly, the suggested case classification along with the MRI raw data is presented as local visualization queries, since personal data never goes out of a clinical center in order to meticulously preserve the patient identity.

The overall functioning is presented in Fig. 5.

5 Evaluation

The goal of this initial empirical evaluation is twofold: to evaluate the distributed agent infrastructure and to obtain the estimation of the true accuracy (or true error) of an inferred classifier by applying it to real data.

In order to evaluate HEALTHAGENTS and its aforementioned functionalities, we have been deployed the system using the following software:

- Java 1.4.2
  - Java 2 Runtime Environment, Standard Edition (build 1.4.2_06-b03)
  - Java HotSpot Client VM (build 1.4.2_06-b03, mixed mode)
- Ant 1.7.0
- Jade 3.4
- D2RQ 0.5

The agent architecture has been deployed into the following nodes:

Pre-processing node
 Server Dell SC1425
 Xeon 3.2 GHz/2 MB 300 MHz FSB processor
 1 GB Single Rank DDR2 Memory (2 × 512 MB)
 OS: Red Hat Enterprise Linux, x86_64 GNU/Linux

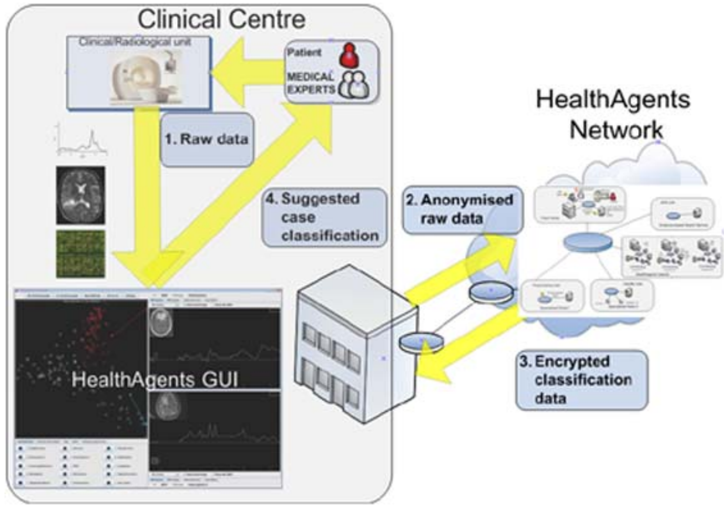
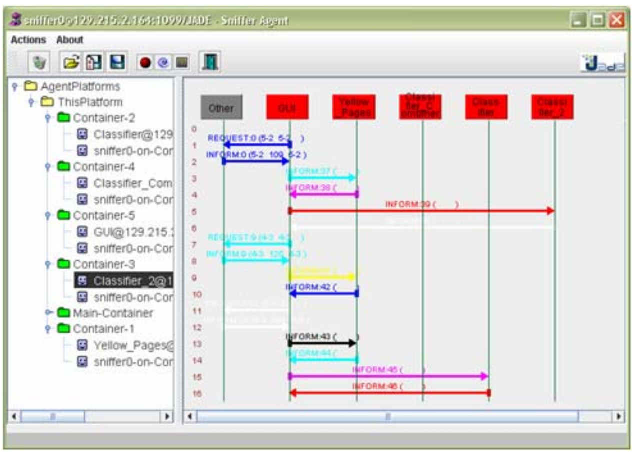


Fig. 5 The operation of the HEALTHAGENTS DSS (functional view)



(a) GUI classifier connection

(b) The HealthAgents process manager

Fig. 6 System monitoring in HEALTHAGENTS. **a** Sequence of service requests for the connection between the GUI and the classifier agents using the YP agents. **b** The operation of the system can be monitored with the HEALTHAGENTS process manager

Classifier node
  Server Dell PowerEdge 1850
  2x Xeon 3.2 GHz/2 MB 300 MHz FSB processors
  2 GB Single Rank DDR2 Memory (2 × 1 GB)
  OS: Red Hat Enterprise Linux, x86_64 GNU/Linux
GUI Agent
  Workstation, Dell Latitude D610
  Intel Pentium M 2 GHz processor
  1 GB Single Rank memory
  OS: Microsoft Windows XP Professional [v 5.1]

From a systems infrastructure standpoint, Fig. 6 illustrates the system monitoring in HEALTHAGENTS. Figure 6(a) presents a time chart with the message sequence for the connection between the GUI agent and two classifier agents, using a series of service requests through YP agent. Figure 6(b) shows the monitoring of the system using the HEALTHAGENTS Process Manager. Finally, the Listing 3 presents the HEALTHAGENTS initialization log for the overall platform.

As far as the classification is concerned, we have deployed a LDA classifier to perform a high-level discrimination comprising three tumor superclasses: *gmme* containing the glioblastoma multiforme (*gm*) and metastasis (*me*) aggressive tumor classes; *mm* for meningiomas; and *a*2*odoa* comprising a low-glial mixture of astrocytomas grade II (*a*2), oligodendrogliomas (*od*), and oligoastrocytoma (*oa*).

We have employed single-voxel MRS data on the Interpret database [29], executed on a single node instance, to perform descriptive discrimination of the aforementioned three tumor types. We have employed a discriminative model adjusted using terms from Short Time Echo (STE) and Long Time Echo (LTE) MRS data, and the terms in the three types were matched to single spectral points in the $[0.5..4.1]\,ppm$ range. A stepwise procedure based on the leaving-one-out evaluation of an LDA classifier was used to obtain the subset of points more discriminant for the multiclass task. A summary of the sampling is presented in Table 1 with further details described in [48].

```
[java] 28-may-2007 12:46:32 jade.core.Runtime
    beginContainer
[java] INFO: ________________________________
[java] This is JADE3.4 - revision 5874 of
    2006/03/09 14:13:11
[java] downloaded in Open Source, under LGPL
    restrictions,
[java] at http://jade.tilab.com/
[java] ______________________________________
[java] 28-may-2007 12:46:33 jade.core.BaseService
     init
[java] INFO: Service jade.core.management.
    AgentManagement initialized
[java] 28-may-2007 12:46:33 jade.core.BaseService
     init
[java] INFO: Service jade.core.messaging.
    Messaging initialized
[java] 28-may-2007 12:46:33 jade.core.BaseService
     init
[java] INFO: Service jade.core.mobility.
    AgentMobility initialized
[java] 28-may-2007 12:46:33 jade.core.BaseService
     init
[java] INFO: Service jade.core.event.Notification
     initialized
[java] 28-may-2007 12:46:33 jade.core.messaging.
    MessagingService boot
[java] INFO: MTP addresses:
[java] http://devel:7778/acc
[java] 28-may-2007 12:46:33 jade.core.
    AgentContainerImpl joinPlatform
[java] INFO: ________________________________
[java] Agent container Main-Container@JADE-IMTP:
    //devel is ready.
[java] ______________________________________
[java] - Welcome to HealthAgents
[java] - Initial Action called.
[java] - Register with Directory Facilitator ...
[java] - Register with Directory Facilitator ...
[java] - Messaging Service Initialised with agent
     rpHAJMSA
[java] - Agent set to net.healthagents.agent.jade
    .JadeMessagingServiceAgent@7c138c63
```

Listing 3 Log for the HealthAgents Platform Initialization (28-may-2007)

We have observed that the combined model, LTE and STE, has obtained a good accuracy (> 90%) in the leaving-one-out evaluation, and a marginal improvement compared with models based on STE or LTE alone.

6 Related work

Machine learning surveys have summarized tumor classification techniques based on pattern recognition and clustering methods [20]. Eight of these studies were applied to brain tumor discrimination from normal tissue and other central nervous system diseases. All of them were based on LDA or artificial neural networks and were applied over relative metabolites and principal component transformations.

Table 1 Brain tumor sampling

Superclass	Classes	Nsamples	Total samples
gmme	*gm*	74	102
	me	28	
mm	*mm*	51	51
a2odoa	*a2*	20	29
	od	5	
	oa	4	
TOTAL		182	182

Furthermore, automatic brain tumor grading and image segmentation techniques, based on computational intelligence techniques, have successfully been applied to different case sets in the past five years [16, 18, 35].

There are a handful of projects which implement computer-assisted evidence-based brain tumor diagnosis using MRS. The Interpret project produced a centralized decision support system for single centers with classification based on histopathological diagnosis [45]. Interpret has successfully been used to discriminate among low-grade meningiomas, high-grade tumors (glioblastomas and metastases), and low-grade glial tumors. The eTUMOUR project incorporates MRS biochemical profiles from single voxel and metabolic spatial distribution by chemical shift imaging [46].

While the functionality of the first prototype is based on the single-voxel version of Interpret [45], HealthAgents expands the original Interpret capabilities with a distributed multi-center agent architecture, an in-vivo classification method with negotiation, an additional number of cases located in different centers across Europe, and a web-based user interface.

7 Concluding remarks

In vivo MRS combined with ex vivo/in vitro HR-MAS and gene expression promises to improve the classification of brain tumors and yield novel biomarkers for prognosis. Considerable amounts of highly complex data are required to build reliable specific tumour classifiers and it is a challenge to collect and manage this data. HealthAgents has started to address this problem by building a distributed system of databases centered on the users and managed by agents. As a result, HealthAgents proposes a unique blend of state-of-the-art technologies to develop novel clinical tools for the diagnosis, management and understanding of brain tumors.

HealthAgents extends the traditional scope of machine learning classification by providing a distributed agent-based approach, which enables the system to be retrained using aggregated sources while preserving security and patient privacy. Future work will include the application of LS-SVM to improve the combined approach and to characterize its behavior in pairwise classifications. Indeed, HEALTHAGENTS is also developing probabilistic mixture models and hierarchical agglomerative clustering for density estimation of heterogeneous brain tumour types and gene co-expression profiles.

The most promising and ambitious development in machine learning for the project is to provide a retraining system for the classifiers deployed in the network. It is expected to enhance the accuracy of the classifiers; to assist wisely in the compilation of additional biomedical data from affiliated clinical centers; and, above all, to improve the data sets leading to a more comprehensive and accurate tumour discrimination.

We argue that the HEALTHAGENTS DSS furnishes a completely new approach to brain tumour diagnosis. Since inferences from local predictions are based on limited amounts of data, they may well conflict with one another. Reasoned argument among intelligent agents, in a multi-agent system, will produce a consensus based on data available from a large range of databases hence improving reliability and accuracy. Additionally, HEALTHAGENTS aims to provide new concepts relating to the brain tumour domain, while introducing additional elements relating to analytic techniques, such as MRS, in the context of the project.

HEALTHAGENTS intends not only to apply agent technology to the biomedical field in a multi-disciplinary fashion, but also to develop the first distributed repository for brain tumour diagnosis, leading eventually to the formation of a special interest data grid, the HEALTHAGENTS network.

In this work we have presented the first release of the HEALTHAGENTS decision support system. Although still in development, the experience gained from production of an initial prototype strongly suggests that a system based on distributed intelligent agents can produce an innovative software system to help in the fight against one of the most pernicious diseases of our time: cancer.

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