Universidade de Aveiro
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Departamento de Eletrónica, Telecomunicações e Informática

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NEArBy: pesquisa em imagens cerebrais suportada em Atlas

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Engenharia de Computadores e Telemática, realizada sob a orientação científica do Professor Doutor José Maria Amaral Fernandes (orientador), Professor Auxiliar e do Professor Doutor Augusto Marques Ferreira da Silva (coorientador), Professor Auxiliar, do Departamento de Electrónica, Telecomunicações e Informática da Universidade de Aveiro

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Palavras-chave

Neuroimagem, Repositórios de Imagem, Anotação semântica, Atlas Cerebrais, Pesquisa de Imagem baseada em etiquetas, DICOM, Dicoogle

Resumo

Os atlas cerebrais têm vindo a ser utilizados como referência na classificação e identificação de informação topológica, tanto estrutural como funcional, de imagens do cérebro. Com recurso ao atlas, a análise que daí surge permite a extração de informação semântica a partir dos dados existentes na imagem.

Contudo, o processo de classificação e catalogação de imagens cerebrais com recurso ao atlas é frequentemente entediante e maioritariamente depende da observação e validação humana. Simultaneamente, mesmo quando disponível, é frequentemente de difícil utilização, nomeadamente quando se faz uso de serviços de consulta e recuperação de informação em repositórios de imagens médicas atuais. (e.g. PACS com base DICOM).

Neste trabalho, propomos a NEArBy, a solução que disponibiliza serviços de consulta e recuperação de informação com base na semântica de atlas cerebrais, facilmente integrado em repositórios de imagens médicas DICOM existentes. Recorrendo a uma interface web, a NEArBy suporta, não apenas as típicas buscas de consulta e recuperação, mas também chaves de consulta correspondendo ao dicionário de atlas cerebral. Para automatizar a catalogação semântica das imagens cerebrais, recorremos a métodos externos na identificação de características espaciais relevantes que são posteriormente rotulados usando um atlas cerebral standard. Sendo o DICOM um standard baseado em *tags*, estas relacionadas com o atlas são, assim, discretamente embebidas em ficheiros DICOM como descritores XML NEArBy. Estes descritores codificam o mapeamento entre o tipo de característica, localização espacial no atlas e a respetiva *tag* do atlas. As *tags* codificadas do XLM são também adequadas para a indexação através de uma ferramenta de imagens médicas Q/R, como Dicoogle, permitindo consultas com base, ambos em *tags* standard de DICOM e em chaves relacionadas com o atlas incluídas no *middleware* NEArBy.

NEArBy permite fazer consultas num repositório de imagens médicas, recorrendo a informação técnica e topológica com base em atlas.

Ilustramos a potencial utilização da NEArBy num conjunto de imagens por ressonância magnética funcional (IRMf), utilizando a interface web do utilizador para formular as consultas em critérios relacionados com o atlas e aceder aos resultados daí recuperados. Foram levadas a cabo várias experiências com sucesso, demonstrando a eficácia na recuperação de sujeitos com ativações em áreas similares e em locais específicos.

Keywords

Neuroimaging, Image Repositories, semantic annotation, Brain Atlas, Tag-based Image Query-Retrieve, DICOM, Dicoogle

Abstract

Brain atlases have been used as reference to classify and tag topological information either structural or functional from brain images. Using atlases, the resulting analysis allows the extraction of semantic information from the existing image data.

However the process of classifying and tagging brain images using an atlas is often tedious and mostly dependent on human observation and validation. At the same time, even when available is often difficult to use, namely when using typical query retrieve services in modern imaging repositories (e.g. DICOM based PACS).

In this work we propose NEArBy, a solution that provides query and retrieve services based on brain atlas semantics that can be easily integrated in existing DICOM based imaging repositories. Using a web interface, NEArBy supports not only typical DICOM query retrieve searches but also query tokens matching the brain atlas dictionary. To automate the semantic tagging of the brain images we rely on external methods to identify relevant spatial features that are later labelled using standard brain atlas. Being DICOM a tag based standard, atlases related tags are then privately embedded into DICOM files as NEArBy XML descriptors. These descriptors encode the mapping between feature type, spatial location in the atlas and the respective atlas tag. XML encoded tags are also suitable for indexation by a medical imaging Q/R tool such as Dicoogle allowing queries based both on standard DICOM tags and specifically on atlases related tokens included by NEArBy middleware.

NEArBy provides a way to perform queries over a medical imaging repository using technical and atlas based topological information.

We illustrate the NEArBy potential usage over a set of functional magnetic resonance imaging (fMRI) datasets using the web user interface to formulate the queries with atlas related criteria and access the retrieved results. Several experiments were successfully performed demonstrating the effectiveness in retrieving subjects with activations in similar areas and in specific locations.

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List of abbreviations and acronyms

AAL	Automated Anatomical Labelling
ACR	American College of Radiology
BOLD	Blood Oxygen Level Dependent
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CSF	Cerebrospinal fluid
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
dMRI	Diffusion Magnetic Resonance Imaging
EEG	Electroencephalography
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
GLM	Generalized Linear Model
IOD	Information Object Definition
MEG	Magneto encephalogram
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NEArBy	NEuroimaging Atlas Based
NEMA	National Electrical Manufactures Association
NMR	Nuclear Magnetic Resonance
P2P	Peer-to-Peer
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
QR	Query Retrieval
rfMRI	Resting-state Functional Magnetic Resonance Imaging
SPM	Statistical Parametric Mapping
TLV	Tag-Length-Value
VR	Value Representation

1 Introduction

The analysis of a brain image from the neuroscientist requires the knowledge of the brain structure in order to classify the regions of interest and consequently extract useful information within the neuroscience context. This implies the previous knowledge of the brain structure and/or often the support of a brain atlas when performing the analysis. This way, when addressing the field of neuroimaging two perspectives are possible:

1. the first perspective is concerned on extracting information from neuroimaging datasets to support the characterization of brain "function" in a specific task performed which adds even support to relate brain structures with brain functions;
2. the second perspective is technical and is concerned with technical and processing details that lead to the extraction of relevant/meaningful information to support neuroscience reasoning. This can include low-level access to the data (e.g. handling formats) to extract features (e.g. image processing and pattern recognition).

From a technological perspective, as noted before, a crucial point is the processing of image data to extract relevant information that lead to a meaningful feature subset that can support a feature labelling. To succeed in the development of an architecture and implementation of a software solution that will provide the feature space enabling of the Query-Retrieve process, it is important to consider four key issues in the business logic of the solution proposed, as shown in Figure 1.

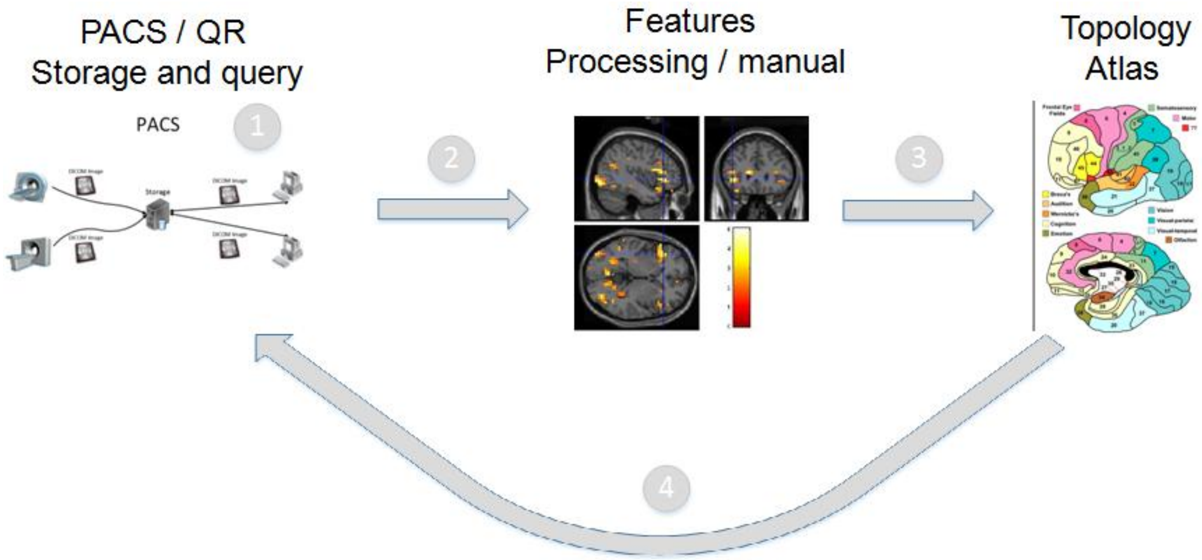


Figure 1 – Four key issues to address in the solution of our system
1) access to data, 2) extract relevant dataset features, 3)map those features into brain structures and 4) add such semantic information to the original datasets

1. The original dataset must allow the access to the data for processing or visualization through a primary and Picture Archiving and Communication System (PACS) oriented Query Retrieval (QR) mechanism (1);
2. Be able to, depending of the nature of data, extract relevant topological neuroscience information from the original dataset (2);
3. Support the processing steps that allow feature extraction from existing data (3);
4. Integrate the atlas tagged information into the PACS in order to supply a transformed dataset with topological/anatomical information (4).

We envisaged an autonomous system that is able of merging two common approaches in the field of neuroimaging to support neuroscience research:

1. Tag based Image Retrieval – nowadays the technical support for QR of datasets namely in Digital Imaging and Communications in Medicine (DICOM) based PACS ensure good options to quickly retrieve classified/tagged information;
2. Atlas based Neuroimaging - using reference maps/atlases to classify and extract topological information is popular in Neuroimaging and, in most of the times, is the quickest way of relating findings in data to topological related information either structural and/or functional.

The main driving idea of this work consisted on combining the two approaches by looking at the atlas not only as feature mapping tool but also as source of tags that could readily be embedded into a

QR system. More concretely, our approach proposes a tag-based structure to code topological information that will be inserted afterwards in the medical image repository.

Given the fact that the atlas provides a way to map a particular brain structure it can be used to relate the information extracted from the image data with the structural or functional information. This relationship is commonly done manually when a neuroscientist surveys the brain image and often uses an atlas to map the different areas of the brain. The information existing in the image data is merely information provided by the scanner. However, the digital repository contains more information than the image data itself from the scan. This information, usually related with the acquisition process, has been proven to be extremely useful to provide solutions for tag based image retrieval. Unfortunately, this type of existing meta-information most of the times has no neuroscience domain related tags.

Medical imaging datasets usually aggregate a large number of image files. One of the better-known and most commonly used format/standard to aggregate this information is DICOM. DICOM is the ubiquitous standard that governs all the image acquisition, storage and communication transactions within picture archiving and communication systems (PACS). The DICOM file format is based on sequences of Tag-Length-Value (TLV) triplets. DICOM tags stem from a rather large and rich data dictionary, which is part of the object-oriented architecture of a standard, designed to accommodate each and every medical imaging modality. DICOM image files are thus natural candidates to undergo some sort of indexing procedures once there is a DICOM compliant indexing engine. Unfortunately the vast majority of the tags conveys only technical information related with the instantiation of a particular imaging procedure. There is by default no tag oriented mechanism to embody the resulting files with image related semantic content.

At the same time, a typical neuroscience study relies heavily on mapping topological features extracted from image datasets to one or multiple atlases.

Atlases are multi-dimensional data structures that provide accurate spatial references within an anatomical domain such as the brain. A volumetric segmentation defines the structural organization of the brain where each identified region might be denominated with an ontological term. Although atlases are already valid references for brain image segmentation/classification there are still several drawbacks to fully automated processes:

- atlases are not specific for each subject – there is the need to map the brain info into the atlas space;
- atlas information may not be fully reliable - in some situations the atlas information may not have the required precision.

One of issues of using atlases is that they are not specific for each subject so there is the need to register all information to the same spatial referential – both the atlases information and the subject specific brain imaging data. There are several brain spatial references namely MNI and Talairach (B.

Matthew, 2002). The combination of an atlas and a common brain spatial referential provides a good option for associating topological semantics to individual datasets where actually there is, to our knowledge, no universal solution. There are already several reliable options to map brain imaging data to a common referential (a.k.a. registration) (Kostelec & Periaswamy, 2003) their accuracy may not be enough for a neuroscientist when performing fine analysis

Consider, for example, the Automated Anatomical Labelling (AAL) MNI and the Brodmann Area. Regardless of their lack of precision, the atlases labels enable a quick and comparable categorization between studies and subject, relating ontological terms commonly used in studies and papers (B. C. Matthew, Rorden, 2013; Turner et al., 2010). In proper contexts, although with some flaws, the atlas provides a common reference and a set of ontological terms that can be used as a quick a way to identify and relate brain anatomy with relevant imaging features.

However the process of relating both sources of information remains highly human dependent and there are no automatic methods to easily perform this mapping and generate easily searchable information.

The availability of topologically tagged features which can be semantically aggregated provides the basis to enable innovative ways of query and retrieval over neuroimaging repositories.

1.1 The conceptual approach

Given the existence of the two major components in the analytical process in the analysis of medical images and their great contributions in their respective areas it is legitimate to foresee a software workflow that aims at the integration of both approaches. In fact, the possibility to query and retrieve classified/tag information from a medical imaging repository provides a way to perform queries at the level of medical knowledge using for that the semantics existing in topology neurological beyond the existing technical information in the image data. Unfortunately, such information is limited to the standard information about the characteristics of the scan performed.

So, why don’t use the ability of information tokens and create specific information about the ultimate results from the imaging scan? But for this, there must be an analysis of the medical image dataset. It is infeasible to conduct a manual analysis and consequently describe the information resulting from the analysis. As can be inferred, the problem becomes even more complex by the inherent 3D nature of the imaging data represented by extensive image stacks. The amount of human resources to carry out the task in time would be extremely high. Currently there are sophisticated software tools that enable quite elaborated image analysis tasks. These tools can be a solution for an automated way to extract information from the brain imaging datasets. The extracted information may consist on structural or functional information providing, eventually a semantic content about the subject(s) under analysis. The acquisition of semantic content would enrich the existing information in a raw image dataset supplementing it with processed information about the relevant imaging study findings that go well beyond the common parameters associated with the scan procedure and patient data.

Why don't we extend the process of feature extraction and generate tagged information tokens suitable to be somehow integrated within the DICOM file? Can we envisage to associate semantic content and DICOM objects? In the case of brain imaging it is at least intuitive to acknowledge that an atlas is a data structure that provides a rich set of spatially referred tags that end-up to be used mostly in any processing workflow that depends on proper localization.

In this context, the atlas labels can be extremely important to provide a basis for semantic content, which appears as a connection between the extracted features and their topological and/or functional attributes. This is important because it provides the means to make the image repository effectively searchable by user defined high-level queries.

It was the practical possibility of making the connection between atlas semantics and the tag based QR solutions on DICOM/PACS, that drove the ambition of creating a system that extends the process of feature extraction, and then uses a tokenized feature space to introduce semantic content in a tag-based format, suitable to be included within a DICOM file and ready for indexation.

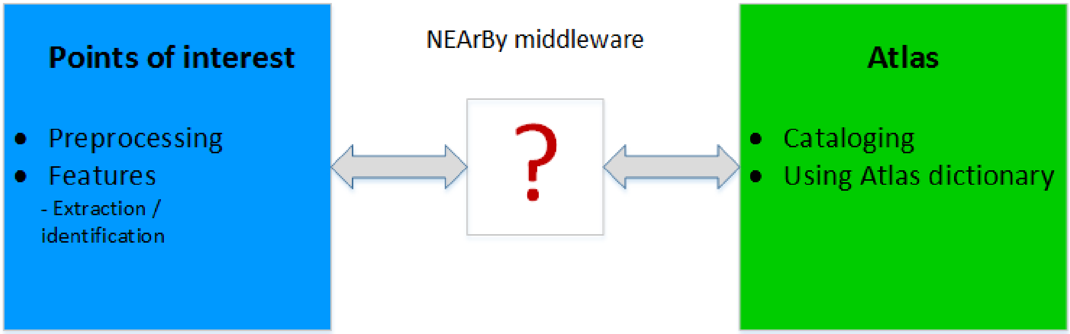


Figure 2 – NEArBy objective is to map relevant image features to structural labels.

In the context of Figure 2, an atlas may be understood as an information component that will bridge the analytical and the PACS tiers. NEArBy (Neuroimaging Atlas Based) middleware component is the core of the system to automate the process of creating tokens and adding them as semantic content into a DICOM file. This conceptual intersection of both parts is necessary to allow the user to use a pre-defined atlas tag set to perform searches in the image repository. As mentioned before, the semantic content resulting from the mapping with an atlas template must be inserted as tagged information tokens in order to allow the indexation of the information as required by currently available indexing engines. In this way as we will explain in forthcoming sections, the meta-data associated with image files is semantically enriched keeping the storage overload of the imaging repositories at rather low levels. Furthermore, the QR system can be used without any prior specification to handle the semantic information which, can be handled as normal text in the indexation and consequently in the retrieval process.

The developed software core consists in middleware tools that will provide a user-friendly QR platform for neuroimaging taking into account the components described in Figure 2. As already stated, the core system is responsible to automate the process of creating tokens taking into account inputs from both frameworks. This automated process consists in using the features extraction to get a set of activations/points of interest in order to map each one onto the atlas space and consequently obtain semantic information from this mapping. The structural atlas is used as a volumetric segmentation tool and consequently provides an anatomical reference of the brain enabling topological identification of the features extracted. The tag-based encoding of this atlas driven information into the image files provides the basis for the build-up of semantic enabled repositories.

1.2 Objectives

The purpose of this system is to allow a user to be able to query an image database using topological information about structural or functional features. Thus the system should be able to answer questions such as “What is here?”, “Which areas are involved?” and “What have we in this brain region?”. The answer provided by the system is a medical image or a set of images.

In order to answer these types of questions a proper connection between the semantics conveyed by the query tokens and the tagged image repository must be established. To accomplish this it is necessary to rely upon common references. These common references here in use will be the brain atlases templates AAL MNI and the Brodmann Area.

The implemented system is mainly focused in medical imaging resulting from fMRI scans. In this type of scan the goal is to map the neuronal activity of a subject while performing a given task, which may be a motor activity, cognitive or sensorial. Specifically, we want to find activations in which the value of intensity is an abnormal value, i.e., an extreme value. We intend to map this extreme value in the corresponding brain region. To perform this mapping between points of interest and the region of interest is used an atlas to support the relation. With an atlas we have a template with a volumetric segmentation of the brain providing a set of different labelled brain regions.

In this way, we use a template with semantic information to support the analysis of a brain imaging and it features extracted (points of interest) to mapping with the atlas according with the location of each point of interest in the brain region provided. The resulting mapping provides semantic information to support the analysis of Neuroimaging enriching the medical image to provide more resources to the neuroscientist in his reasoning.

1.3 Organization

In order to describe the organization of this document is described the context of the whole document which is divided into four chapters:

- **Chapter 1 – Introduction** – In this chapter, we introduce the motivation of the present work and the conceptual approach in the two different fields of neuroimaging. We also describe the goals established to the success of this work.
- **Chapter 2 – State-of-the-art –** In this chapter, we present the concepts behind the acquisition of medical images, as well as a survey of the concepts of the various key elements for the realization of this work.
- **Chapter 3 – NEArBy –** In this chapter, we present the concepts of our solution that lead to the accomplishment of the established goals. We describe the rationale behind the implementation of a solution able to integrate the various essential components in the approach to the neuroimaging features but with enough abstraction to create an extensible and modular framework.
- **Chapter 4 – Results and discussion –** In this chapter, we present and discuss the major results obtained from the developed system.
- **Chapter 5 – Conclusions and future work** – In this final chapter, we present a brief overview of the work as well as the main conclusions. We also discuss a possible framework extension for future developments.

2 State-of-the-art

In this chapter, we describe the fundamental elements in MR Neuroimaging and the elements to support a neuroscience research. The order in which the various elements are described has to do with the fact that it is necessary to first know the basics of medical image formation and acquisition and then understand how an atlas can support the neuroscientist when performing data analysis. To understand a networked imaging context we need to introduce some key concepts connected with medical image formats, archival processes and Q/R.

2.1 Imaging as the major localization tools

2.1.1 MRI – Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is one of the most powerful imaging modalities that provide detailed visual assessment of the human body. Initially known as Nuclear Magnetic Resonance (NMR) but with the bad connotation of the term “Nuclear” and the progressive computerization of the whole scanning process the actual designation was readily replaced by MRI (Rajan, 1998; Reddy, 2008).

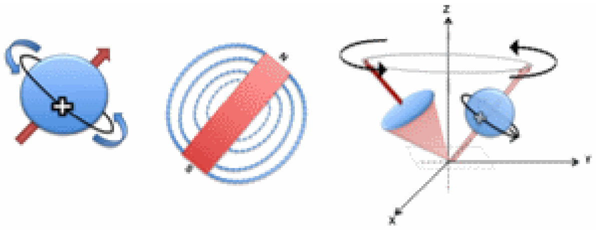


Figure 3 - Protons possess a positive charge and are constantly spinning around their own axes. When exposed to an external magnetic field, protons precess.
Adapted from Currie S et al. Postgrad Med J 2013;89:209-223

A MRI scan makes use of a magnetic field and pulses of radio wave energy to create structural or functional images of the brain. Images from a MRI scan end up as digital files that can be stored for future uses and consequently made accessible for local or even remote visualization (Healthwise, 2011; Rajan, 1998).

Since the human body is mainly composed by water, i.e., hydrogen atoms become the main “target” of the magnetic field. When applying the magnetic field on the atoms, these atoms tend to align with or against the field thus producing a magnetic moment (Rajan, 1998; Vagal, 2013) behaving like small dipole magnets (Brady, 2004). As suggested in Figure 3, hydrogen atoms when submitted to static magnetic fields exhibit measurable spin properties and magnet dipole like behaviour with their magnetic moment vectors aligned with the driving static field. The spin effect is better understood by its precessional nature about the external magnetic field direction. The precession’s angular frequency is well in the radio frequency range (66.7 MHz eg.) and is known as the Larmor frequency being directly proportional to the magnetic field intensity. A long and non-trivial technological pathway has been taken to produce an instrument that builds upon the physical phenomenon of magnetic resonance and is capable of producing high quality medical images that excel in spatial and contrast resolution. Structural anatomy and even physiological imaging is thus possible.

Figure 4 presents a simplified schematic view of a MRI scanner. The main magnet coils are part of the static magnetic field subsystem. The gradient coils deliver spatially encoded magnetization offsets that ultimately determine the voxels localization. The integral and external RF coils are responsible for the emission and reception of transitory RF signals that actually convey image data.

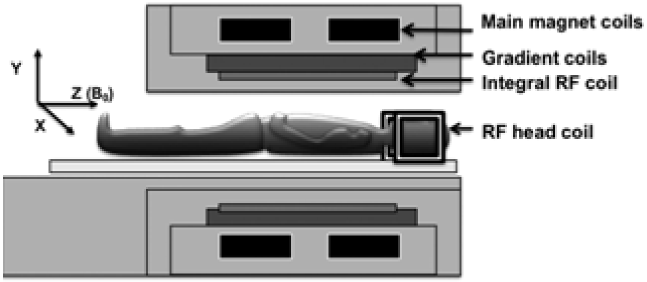


Figure 4 - MR machine and relative positions of the different magnet coils.
Adapted from Currie S et al. Postgrad Med J 2013;89:209-223

A MRI scan starts by submitting the human body to an intense static field (1.5T to 3T for example) so the hydrogen rich tissues contribute to a steady net magnetization aligned with the static field. Actual image data is obtained by selectively inducing transient magnetization changes in the spin population and measuring parameters related with the return to steady-state. These transient stimulations are somehow spatially encoded through the gradient coils and are accomplished by steering energy to the body in the form of sequences of radio-frequency pulses as close as possible of the target Larmor frequencies in order to fully exploit the resonance effect and therefore obtain maximum energy transfer.

The steady-state net magnetization can be altered in a controlled manner by external short radio-frequency pulses. These pulses affect the spin's magnetic moment orientation for a transitory period. The actual measurement takes place during the return to steady-state of the spin population. This is called the relaxation process where radio frequency signals are thus freely emitted by the hydrogen rich tissues and collected by appropriate antennas. These signals are intensity modulated by temporal parameters that are tissue dependent ensuring therefore the remarkable contrast capabilities for soft tissue visualization. In order to obtain images the radio-frequency pulses explore the resonance effect using spatially encoded frequency and phase modulation schemes. The gradient coil system provides both slice selection and intra-slice localization by frequency modulation and successive phase modulation. Figure 5 depicts the establishment of a steady-state longitudinal net magnetization and the transient changes induced by external RF pulses.

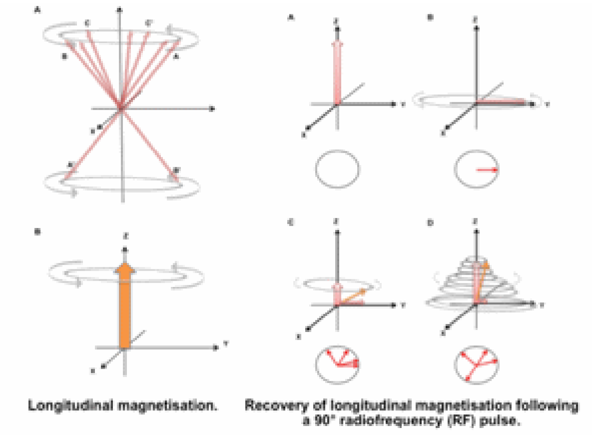


Figure 5 - Switching between steady-state longitudinal magnetization and transient transversal magnetization is governed by relaxation time constants which are tissue dependent.
Adapted from Currie S et al. Postgrad Med J 2013;89:209-223

The collected signal by the receiving antennas is thus influenced by the so-called relaxation times that are better perceived with the help of Figure 6. T1 is associated with the recovery of longitudinal magnetisation over time following the switching off of tilting radiofrequency (RF) pulse. Since decay is too fast for appropriate data collection there is need to replicate free induction decay signals. This is accomplished by 180º refocusing pulses separated by another temporal parameter known as echo time TE. However the exponential decreasing trend with time constant T2 continues as the net transversal magnetization vanishes. This effect is still deepened by the lack of echo pulses resulting in an effective decay ruled by the T2* parameter. This Spin-Echo pulse sequence is elementary to the MRI signal generation and is repeated as long as the pre-defined field of view (FOV) is scanned. Many other pulse sequences exist to match the large variety of image acquisition protocols taking into account the body part and the specific clinical or research context.

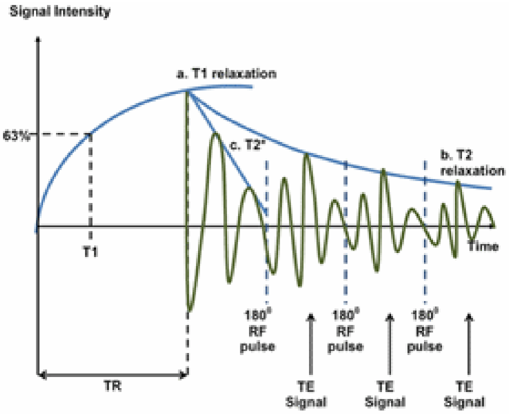


Figure 6 - Relaxation times definitions for a common MRI intensity signal.
Adapted from Currie S et al. Postgrad Med J 2013;89:209-223

In order to understand the variety of MR images that can be produced by the scanner, it is instructive to consider a voxel as an elementary emitter and that the intensity of the received signal has the form of (Liang and Lauterbur 2000)

$$f(x,y,z,t) \propto P_D\left(1 - e^{-\frac{TR}{T1(x,y,z)}}\right)e^{-\frac{TE}{T2*(x,y,z)}}$$

So, according to a particular choice of external timing parameters it is possible to have different weighting schemes. Images may be proton density (P_D) weighted, T1 or T2* weighted depending on the relative magnitude of the exponential factors. Image contrast is thus strongly determined by the PD, T1 or T2* values that are tissue specific. Comparing for example with X-ray computed tomography (CT), MRI provides much more contrast within soft tissue regions. Without entering into details about the actual spatial encoding of signals and the mathematics behind the image reconstruction process for the purposes of this thesis it suffices to present the paradigmatic MRI image set in Figure 7.

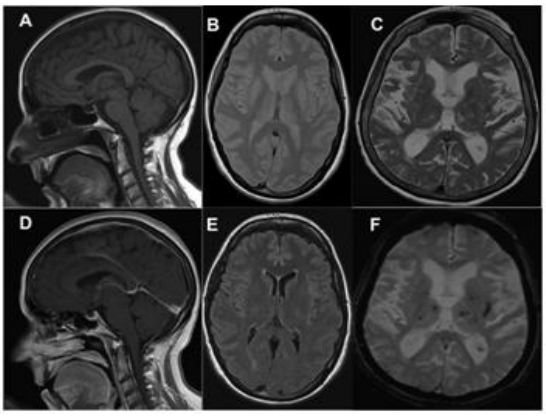


Figure 7 - Examples of typical clinical MRI.
Adapted from Currie S et al. Postgrad Med J 2013;89:209-223

(A). Sagittal T1-weighted image. Note that fat (around scalp and neck) is bright and cerebrospinal fluid (CSF) is dark. (B) Axial proton density image. Note the minimal contrast between grey matter and CSF. (C) Axial T2-weighted image. Note that CSF is bright. (D) Same image as (A) but following contrast agent (gadolinium) administration. Note the dural venous sinuses appear bright due to T1 shortening. (E) Axial fluid attenuated inversion recovery image. Note suppression of the CSF signal. (F) Axial gradient echo T2* image. Same patient as in (C). Note the increase conspicuity of multiple dark foci due to magnetic susceptibility of haemosiderin deposition in a patient with amyloid angiopathy. (Adapted from (Currie, Hoggard, Craven, Hadjivassiliou, & Wilkinson, 2013; Liang, 2000)**)**.

2.1.2 fMRI - Functional Magnetic Resonance Imaging

The performance of any task causes an increased neuronal metabolism, which in itself implies an increase in blood flood (CBF) and increased blood volume (CBV). CBF is the blood volume per minute passing though the vessels and CBV is the volume occupied by the vessels. The neuronal activity requires a continuous supply of oxygen (O_2) and glucose that is carried in the blood flow. The brain areas with more activity will receive a greater quantity of blood, which implies that they are in a greater neuronal effort requiring a greater flow of O_2 and glucose. In these areas the protons emit a stronger signal.

The fMRI measure the changes of blood flow in the brain indirectly by means of the Blood Oxygen Level Dependent –the BOLD effect (Ogawa, Lee, Kay, & Tank, 1990; Seong-Gi & Seiji, 2012). When neuronal activity increases, there is a temporary, slight decrease in the level of blood oxygenation followed by a large increase in oxygen concentration in order to compensate the demand made by the neuronal activity (Rombouts, Barkhof, & Scheltens, 2007; Seong-Gi & Seiji, 2012).

Well-known examples are the use of fMRI to study motor, sensory or cognitive activities (Rombouts et al., 2007; Wallis, 2012; Watson, 2008). In contrast to other MRI modalities, fMRI can be seen as the non-invasive way to explore the brain at a functional level (i.e. brain function vs. tasks along time) with some coarse structure/anatomy information allowing mapping the different areas of activation involved in a given task.

The most common information extracted from fMRI datasets is based on statistical parametric mapping, where using Generalized Linear Models (GLM) based analysis (Ashburner, 2012; Karl J Friston et al., 1995; K. J. Friston et al., 1994). Given know conditions (e.g. motion vs. non–motion) one looks for areas in the brain that exhibits BOLD activations statistically related to those conditions – these are usually presented as clusters of voxels related (activation) or negative related (non-activation) as illustrated in Figure 8.

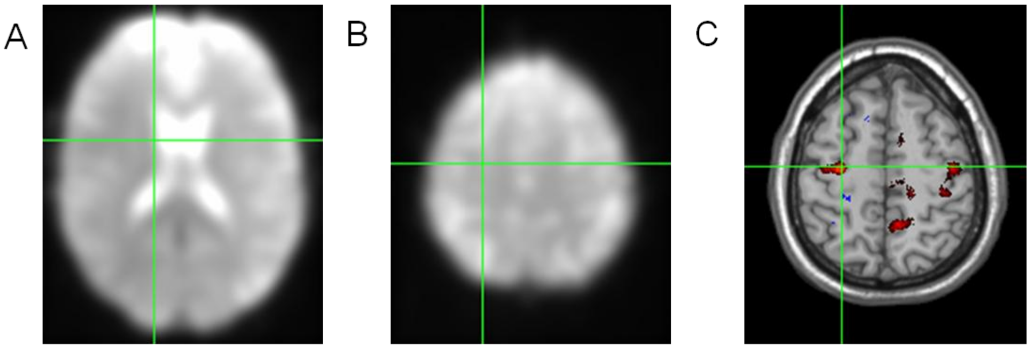


Figure 8 – Extracting activations from a fMRI sequence

From a fMRI sequence (a slice in A), after pre-processing (B normalized fMRI slice in the MNI space) is possible to apply SPM method to obtain a statistical map of the image dataset with activations (warm colour) and deactivation (cold colours). These activations and deactivations can them be interpreted by neuroscientist to support a given reasoning that lead to the fMRI acquisition in the first place.

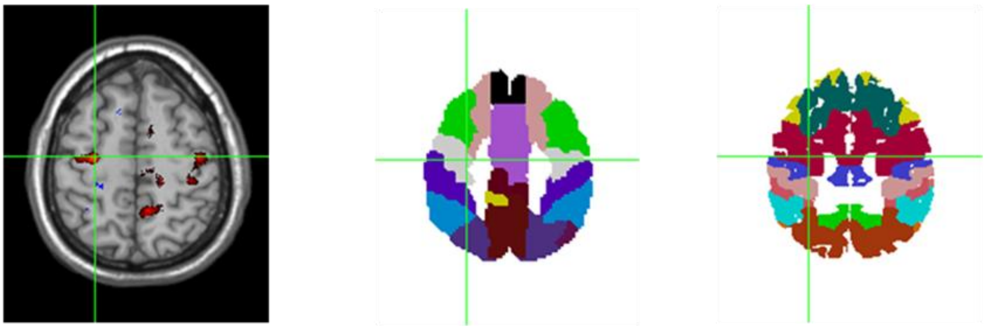
2.2 Atlas

Within its proper spatial context an atlas provides a volumetric segmentation of anatomical structures. The many different brain regions are properly labelled and can be useful as a reference source for feature annotation providing the basis for better assessment of brain structure and or function (Devlin & Poldrack, 2007). In practice an atlas leads to a brain spatial reference – a template – for alignment and interpretation of the brain scans allowing not only a quicker labelling of image datasets but also allow a (sometimes coarse) spatial inter and intra subject comparison between different datasets and features extracted from brain imaging data. In broad sense, an atlas may be both a spatial reference allowing a common reference space and also an “annotated” feature space – i.e. named structurally segmented areas of interest associated with a given function.

Brain atlases, regardless of the several existing ones, present a “physical” segmentation of the brain structure – a natural physical reference for a kind of brain related information. Thus, atlases can be used as an element for localization of topological structures and interpretation of results. (Heckemann, Hajnal, Aljabar, Rueckert, & Hammers, 2006; Poldrack, Mumford, & Nichols, 2011; Thompson et al., 2000; Toga, 1998). The Anatomical Automated Labelling (AAL) (Tzourio-Mazoyer et al., 2002) and Brodmann Area are provided as part of MRIcro (Rorden, 2013) that are among the most popular atlases.

However selecting an atlas depends on the purpose of the anatomical analysis mainly the level of detail in specific areas like the basal ganglia (Abbas et al., 2011; Bardinet et al.) and the expected functional reasoning behind each of the different atlas areas (Shirer, Ryali, Rykhlevskaia, Menon, & Greicius, 2011).

A simple example presented in Figure 9 shows that the same brain location may be labelled differently, it is the *Precentral_L* in the atlas AAL and area *6* in the Brodmann atlas.



Voxel: (63, 114,127),
MNI: (-27,-12,55)mm

AAL:precentral_L

Brodmann: BA6

Figure 9 - The same coordinate can have different labels in different atlases.
In this case the MNI coordinate (-27.-12, 55) mm is labelled as *precentral_L* in AAL and as *BA6* in Brodmann atlases.

2.3 Pre-processing

The use of an atlas for structural image segmentation or for labelling functional active regions in the brain is of primary interest. Prominent tools for neuroimaging processing do rely on atlases in order to provide reliable analysis workflows. See for example SPM (Ashburner, 2012) or FSL (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012).

The studies acquired during the scan are susceptible to have noisy data, which interfere with the quality of the image. Some acquisition protocols may be error prone. Head movements, cardio-respiratory dynamics and even the slowly varying magnetic field may induce noise and artefacts that may impair the final image quality.

We may rely on a set of pre-processing tasks that provide image enhancement for subsequent statistical analysis. These enhancement procedures are almost mandatory in order to minimize the influence of data acquisition noise, physiological artefacts and afterwards to standardize the segmentation of the brain regions.

For this reason the whole analysis process requires pre-processing to ensure the quality of the analysis input image data. Pre-processing stage is typically organized in several steps that may vary but often include noise minimization, non-uniformity compensation, movement compensation, artefact removal and spatial registration. For in-depth overviews of pre-processing techniques that are often used in neuroimaging see for example (Ashby, 2011; Clare, 2006; Faro & Mohamed, 2010; Lindquist, 2008; Poldrack et al., 2011; Vink, 2007).

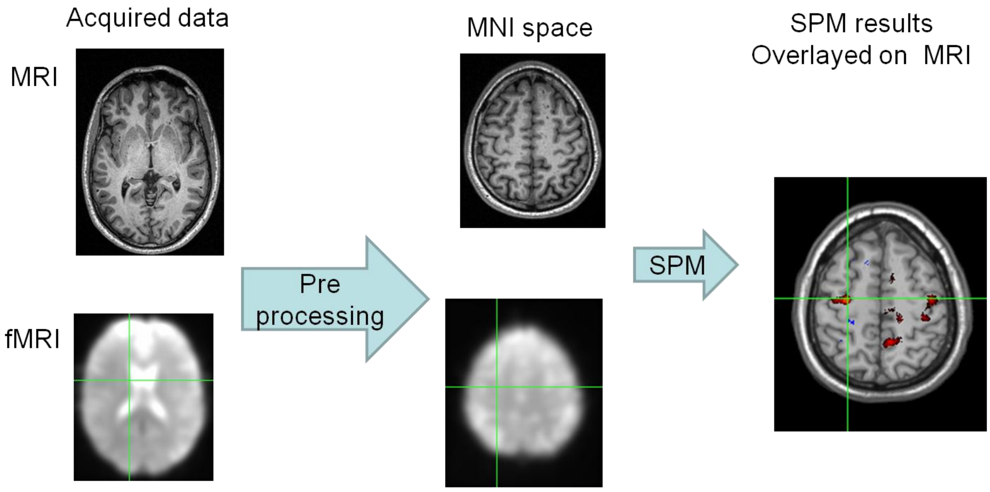


Figure 10 – Typical fMRI analysis workflow.

From original acquired data through pre-processing (including normalization into the MNI space) it is possible to perform processing (e.g. SPM of fMRI) and visual overlay the results (in this case SPM results over an fMRI sequence registered visually with a structural brain image).

In the context of pre-processing, one of the most important steps that should be mentioned and that it is of our interest to understand and detail, is the registration process that have a relevant role in the future analysis process of a study. Image registration consists in performing the alignment of two images allowing the overlapping of them in order to identify the common features and differences, emphasizing them for a more robust analysis.

In order to map an image data and brain locations, it is necessary the co-registration of the image datasets with atlas to have both with the same spatial reference. This is especially true in inter-subject comparison or in comparison with atlas information. Given the fact that the brain shape of each subject is unique, the spatial registration is necessary to transform it according to the spatial reference defined usually as standard space. The most popular spatial references are the MNI (Montreal Neurological Institute) (Evans et al., 1993) and the Talairach atlases (Talairach & Tournoux, 1988).

These spatial references provide a standard spatial reference that allows the labelling of brain areas based on an atlas. Frequent examples are the AAL and Brodmann atlases that are registered on the MNI space.

In the specific case of fMRI, the process of labelling activation areas binds structurally annotated areas with specific brain functions It is possible to understand the typical fMRI workflow in Figure 10.

Using the very popular MRI visualization package MRIcro (Rorden, 2013) we show the possibilities of atlas labelling of an fMRI study after spatial normalization. As shown in the last example multi-atlases labelling are also possible, provided there is a common spatial reference.

After completing the normalization process it is possible to overlap the target imaging study with the brain atlas template. It is possible to see in Figure 11, the mapping between a given voxel in the image and the brain atlas is done manually using the MRIcro. When selecting a voxel in the image or in the brain atlas template, the viewer automatically repositions the crossbar at the selected voxel on both images. Thus is possible to manually identify the areas of the brain of the selected voxels.

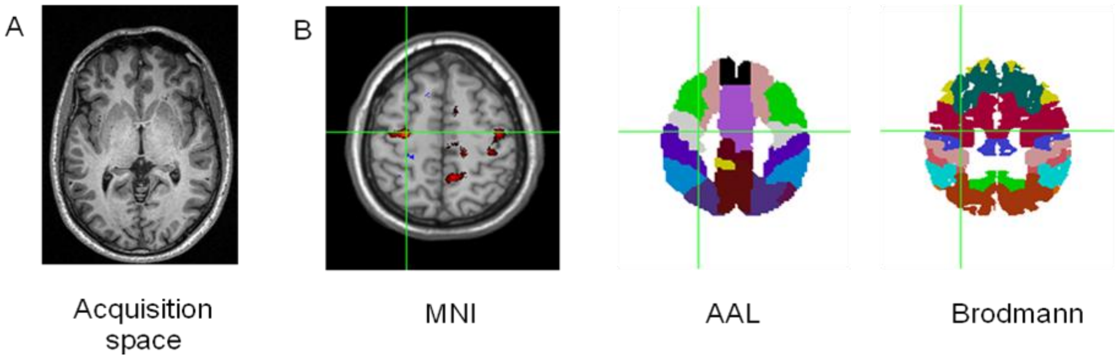


Figure 11 – Normalization allows mapping the acquisition space (A) to MNI space (B).
–This allows the comparison with other normalized datasets and/or MNI space based atlas like AAL and Brodmann like presented here.

As mentioned before, a processing chain driven by multi-atlases provides a larger mapping with multi-topological classifications associated with the same brain region, thus obtaining a more complete tag classification from the extracted information from the medical imaging.

Registration methods depends on the accuracy imposed by the application and can range from fast linear rigid body transformations with several degrees of freedom (up to 12) to non-linear transformations (Ashburner & Friston, 1999; Toga, 1998). The 12-parameter registration is also known as affine transformation. Such transformation consists in 4 groups of 3 operations, i.e., 3 translations, 3 rotations (rigid-body), 3 zooms and 3 shears. This registration approach is often sufficient to spatially match the MRI study with an atlas. Neuronal activity can thus be appropriately mapped to several anatomical regions within the spatial context embedded by the atlas (Lindquist, 2008; Poldrack et al., 2011).

2.4 Digital Image Handling

The signals from the scan are processed into three-dimensional stack image slices of the brain. An MR image consists of a matrix of pixels. Each position of the matrix is a pixel and each pixel is assigned a number representing tissue dependent signal intensity. These pixels define a point in a two-dimensional space and in fact contain information about a volume element, called voxel. A voxel defines a point in three-dimensional space. The dimension of a voxel is given by the pixel together with the thickness of the slice bringing dimension to the z-coordinate. The size of the voxels is closely related to the spatial resolution of MRI image (Weishaupt, Köchli, Marincek, Pruessmann, & Froehlich, 2006).

2.4.1 DICOM

Digital Imaging and Communications in Medicine (DICOM) is a standard for digital medical imaging (Pianykh, 2008) which had its first publication in 1993 and was developed by groups from the ACR (American College of Radiology) and the NEMA (National Electrical Manufactures Association). The groups ACR/NEMA formed a committee in 1983 and since then have been developing a medical image management standard. Only in 1993 they reached the third version of the standard giving it the name of DICOM (Gibaud, 2008; Kagadis & Langer, 2011).

The DICOM is a standard that enables not only to store the image itself but also associated meta-information. This format was designed with the goal of universal interoperability of medical imaging equipment (Bidgood Jr, Horii, Prior, & Van Syckle; NEMA, 2011a) to exchange data with the required quality for clinical use (NEMA). This image format is used in various medical procedures, such as, Magnetic Resonance (MR), Computed Tomography (CT) and Positron Emission Tomography (PET) (NEMA, 2011b). It is a specification of the information content, structure, coding and communication protocols to exchange medical imaging from medical scans and information related with the image (Bidgood Jr et al.). One of the goals is to aggregate the imaging studies of a patient, resulting from the scan of one of the modalities, and associate information about the patient. This information is in a format that allows an easy interconnection and interaction of the equipment with the imaging data.

The DICOM file format consists of two parts: the header and the pixel data. The header contains information about the many features of the study acquisition procedure, including the characteristics of the modality and the imaging equipment that performed the scan. It also contains information about the patient, such as its name, its position in time of the scan, and other elements. The DICOM file consists essentially of Data Elements that we can broadly classify into meta-information elements and pixel data. The pixel data only contains the data that actually embody the images. The sequence of bits forming the image is then stored in this file segment and it is the last element of the DICOM file ("DICOM Research, 2013,").

In fact, the DICOM file is processed as an object with properties and attributes. The definition of these objects and their attributes are standardized according to the DICOM Information Object Definition (IOD) (Pianykh, 2008). The creation of each and every medical image means instantiating a new object (NEMA, 2011a). Initially all the fields of the file are empty until information is entered. As the file is being filled values are being associated with its attributes. The attributes will represent a particular instance of the IOD. The IOD define the different types of imaging studies that DICOM supports (Kagadis & Langer, 2011). It can be stated that the IODs are like a set of attributes of class that is designed to describe an object (Deserno, 2011; Pianykh, 2008). Each of these attributes follows a well-defined and organized structure. In practice it consists of a tagged based structure in which each tag is formed by two hexadecimal numbers. The first number represents the group to which the attribute belongs. The second is a sequential number within that group. This pair is presented, for instance as, (0010,0010) which identifies the group 0010 and the element 0010 representing the "Patient Name" (Deserno, 2011). As previously stated, the pixel data is in the last element of the DICOM file, it is identified by the tag (7FE0 0010) ("DICOM Research, 2013,").

In order to guarantee a uniform and correct use, there is the DICOM Data Dictionary, which ensures the consistency of the attributes names. The Data Dictionary provides a list of all standard data items (attributes) used in digital medical imaging. These items are divided into groups where each group has a set of elements. In this way each item is represented by a combination (group, element) thus forming the tag that represents an attribute, i.e., a DICOM Data Element. All existing groups in the standard are even numbers (Clunie, 2000; Deserno, 2011). Furthermore, all the attributes must be formatted with one of 27 possible values – Value Representation (VR) (Deserno, 2011; Pianykh, 2008). However, it is not mandatory the presence of this field. If any, it will be located between the tag field and the length field (Kagadis & Langer, 2011). A VR allows to represent the type of data contained in a tag ("DICOM Research, 2013,"). In its majority, VRs imposes a maximum size limit for the content of the tag (Pianykh, 2008). The VRs supported by DICOM are listed in the Data Dictionary (Kagadis & Langer, 2011).

We have been considering so far the existing tags in the DICOM Data Dictionary and are therefore referred as public tags. These are essentially identified with a unique property, given that in a standard tag regardless the group number its value is even (Clunie, 2000; Deserno, 2011). Beyond these public tags the DICOM standard provided the possibility of creating nonstandard tags, i.e., private tags (Kagadis & Langer, 2011). The private tags are structured in the same way as the tags so far described, but instead of an even number they will have an odd value to identify the group. The parity of the group number allows thus to differentiate between these two types of tags (Clunie, 2000; Deserno, 2011).

The private tags are used with the intention to support the manufacturers needs to convey specific information about their systems and are often used for maintenance purposes (Kagadis & Langer, 2011). Formally, they can be used as common standard attributes but containing all kinds of manufacturer specific. Although the existence of these tags is acknowledged by general image viewing software tools they are ignored for the matter of the most common visualization tasks. Thus, in accordance with the DICOM standard, unrecognizable tags should simply be ignored. However, in practice this can be quite undesirable given the fact that the private tag can have distinct meaning for different DICOM manufacturers. This can lead to a misinterpretation of the tag information by the DICOM viewer application. Thus, DICOM tries to prevent this occurrence and to such reserve some private tags as private creator tags enabling the creation of private dictionaries (Pianykh, 2008).

The DICOM format is organized according to the initials TLV (Tag-Length-Value) and this means that each element of the DICOM file in the first field has the tag value – consisting of two hexadecimal numbers – then the length of the content associated to the tag, and finally the content itself to be stored in the tag. All the information to be put in the Value field for each tag can be text or binary. The text format is reserved for elements such as the patient's name, dates, among others. All numeric content is converted to binary values.

The existing information in the DICOM has to be handled by a parser that decodes the TLV triplet - Figure 12 - so that the information is presented in a readable form (Gibaud, 2008).

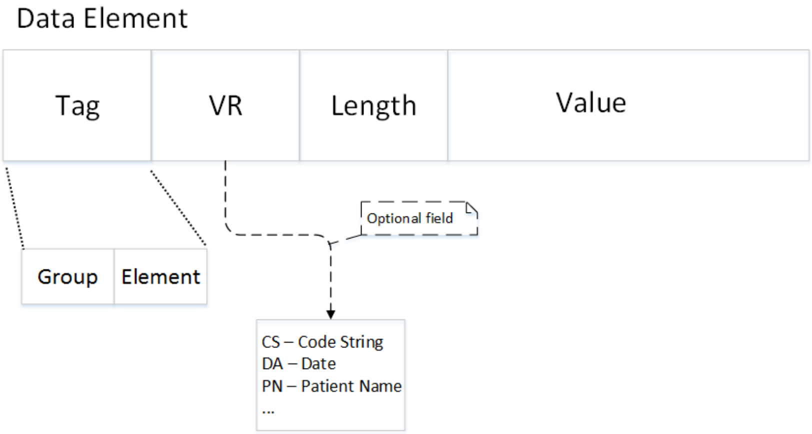


Figure 12 – Structure of a Data Element in a DICOM file.

2.5 Repositories and Q/R tools

Repositories of digital medical imaging allow the creation of a dataset with DICOM files. In order to take full advantage of the information within such repository we need proper Q/R tools. These tools must be able to perform queries over the DICOM repository that extend the rather limited and confined query and retrieve services defined by the DICOM standard.

2.5.1 PACS

Picture Archiving and Communication System (PACS) is a designation for a computer system consisting of the combination of hardware and software components capable of executing medical imaging (Pianykh, 2008) – see for instance a PACS architecture in Figure 13. This system is responsible for the acquisition, storage, retrieval management, communication, distribution and presentation of medical imaging (Association; Hood & Scott, 2006; Rouse, June 2010). The PACS dissemination over imaging departments is leading the trend to fully filmless imaging environments. It is clear the advantage of not demanding physical space for the storage of ever growing imaging datasets (Hovenga & Kidd, 2010).

With the existence of a digital system able to transfer images, display the images across multiple workstations and a more organized management information retrieval is potentially facilitated. This system makes the entire process of medical imaging analysis and reporting more efficient (Hood & Scott, 2006)..

Although a PACS is quite expensive to deploy, the advantage of making more efficient the process of delivery of medical imaging can reduce the delivery time of medical results and reduce the underlying costs to transport them (Feng, 2011; Hood & Scott, 2006). But for this system to be able to support all the features it is necessary to assemble a set of costly hardware and software components. The hardware components of the PACS are mainly three:

- Acquisition devices of different types of medical scans (1);
- Digital repository for medical imaging, i.e., database to store all medical imaging acquired (2);
- Workstation for viewing the medical imaging stored (3).

. All these components are interconnected by a data network (Hovenga & Kidd, 2010; Pianykh, 2008). Naturally a PACS is meant to be governed by the DICOM standard. It ensures the interoperability between the different system components. Imaging studies resulting from the medical scan are stored and transferred in DICOM format and can be handled whenever and wherever the networked client software is required to operate.

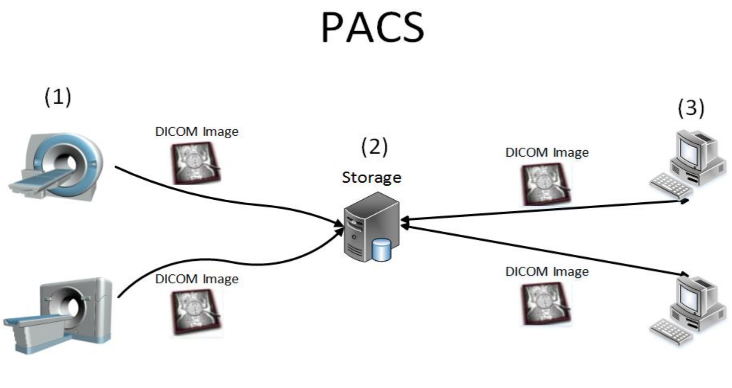


Figure 13 – PACS example architecture.

Typical architecture includes the acquisition equipment (1), the storage (2) and viewing/processing workstations (3).

2.5.2 XNAT

The Extensible Neuroimaging Archive Toolkit (XNAT) is an open source software platform with the goal to facilitate common management and productivity tasks for neuroimaging. XNAT can handle DICOM images, providing an online viewer to display not only DICOM files but also neuroimaging formats as Analyze. This platform supports several modalities as MRI, CT and PET. XNAT also provides a web interface to store, retrieve, navigate and to perform queries over the data (Health, 2013; Marcus, Olsen, Ramaratnam, & Buckner, 2007).

Currently the Neuroinformatics Research Group is working on the exploration and research of large data sets. The goal behind this project intends to enables users to store, retrieve and query data using for that data structures. ConnectomeDB is a tool in progress to support data gathered as part of the Human Connectome Project. This project aims to understand the functional relationships of the of different regions of the human brain. In this study four imaging modalities are considered: resting-state functional MRI (rfMRI), diffusion imaging (dMRI) task-evoked fMRI (MEG/EEG) and Structural MRI.

It is a fact that XNAT provides storage and a Q/R environment for neuroimaging studies. However our approach is rather distinct in the sense that we rely on atlas data structures to build the specific and flexible query tokens with which direct “interrogations” to the DICOM based repositories will be feasible. The forthcoming chapters will enlighten this approach

2.5.3 Dicoogle

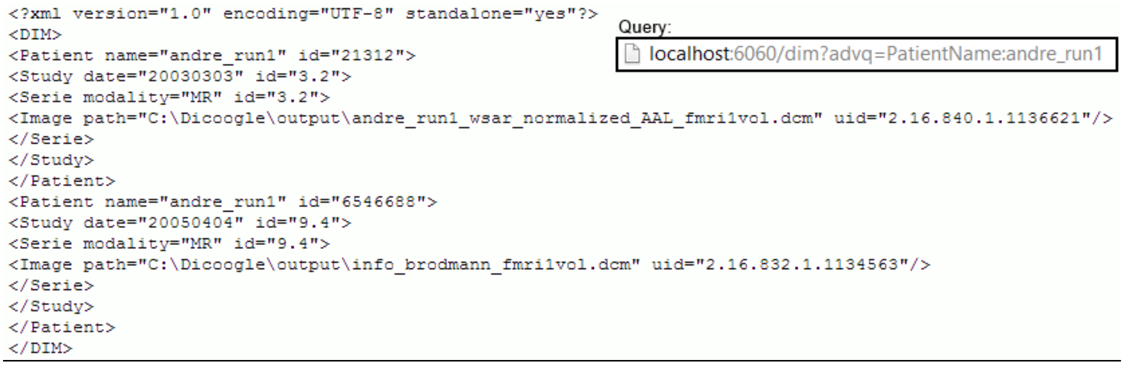
Dicoogle is an open-source project to handle medical imaging repositories using Indexing System and P2P mechanisms (C. B. Costa, Luís; Campos, Samuel, 2012). This solution allows the indexing of medical images stored as standard DICOM persistent objects. Using this tool is possible to extract, store and index all the metadata that are in the DICOM header.

Dicoogle allows all tags to be manipulated regardless of being public or private.. To manipulate private tags it is only required to provide the indexing engine, with the private tag subset to index – indicating the group number and subgroup as well as the name that will identify the tag. In this way, after indexing a new DICOM file the private tags will be also available for Q/R purposes.

Dicoogle itself also provides a DICOM Query/Retrieve service to perform queries on the stored information and consequently the extraction of desired information. The system returns the path to access to the DICOM files found, as well as all the pertinent information associated with them (C. Costa et al., 2011). This feature is extremely important to allow research on the information that is stored in the file content. Associating a name to a tag facilitates the realization of an advanced query, where the query may contain as a prefix the name of the tag indicating to the system to search only the contents of the specified tag.

Besides these characteristics, Dicoogle provides a range of services including a Web Service REST allowing through the URL http://www.dicoogle.com/services/dws/dim?advq= to create an advanced query. As mentioned, the query will have a prefix indicating the tag name on which we want to search.

See the example, where we want to search for the patient named “André”. The search by patient name implies that the content of the attribute PATIENT NAME in the DICOM file must be André. This attribute is then the prefix on which we intent to search. The prefix is aggregated to the URL provided by the Web Service resulting in the following URL: http://www.dicoogle.com/services/dws/dim?advq=PATIENTNAME:André. This service allows any client, whether human or machine to use its features remotely without the necessity of having the deployment of the system or files on the local machine. Regardless of the query performed, the Dicoogle response is given in XML as the Figure 14 shows.



Query:

localhost:6060/dim?advq=PatientName:andre_run1

```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<DIM>
<Patient name="andre_run1" id="21312">
<Study date="20030303" id="3.2">
<Serie modality="MR" id="3.2">
<Image path="C:\Dicoogle\output\andre_run1_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1136621"/>
</Serie>
</Study>
</Patient>
<Patient name="andre_run1" id="6546688">
<Study date="20050404" id="9.4">
<Serie modality="MR" id="9.4">
<Image path="C:\Dicoogle\output\info_brodmann_fmri1vol.dcm" uid="2.16.832.1.1134563"/>
</Serie>
</Study>
</Patient>
</DIM>
```

Figure 14 – Dicoogle XML response for a patient name search.

3 NEArBy

In this chapter, we describe NEArBy a software solution to automate a process of mapping features extracted from neuroimaging studies to morphological information contained in brain atlas.

In order to support this implementation, we rely upon a set of pre-processing and analysis tools to obtain a set of features extracted after normalizing the target imaging study with a chosen atlas. In this chapter we present the developed solution designed as a middleware component that ensures the seamless integration between the feature space and the tag space that comprises a brain atlas template.

3.1 The rationale

The process of mapping locations where there may be image findings such as lesions or activations into specific brain areas remains highly dependent on human intervention. Typically an atlas is used as reference to label such findings in order to associate them with specific areas or functions implicit on the atlas genesis.

In this context the atlas has a dual functionality both as a tagged spatial reference and as brain volumetric segmentation tool of relevant structures.

A major NEArBy consists of providing an automated way to catalogue points of interest to further allow query and image datasets retrieval from imaging repositories based on atlas topological information - Figure 15. In order to achieve this goal, NEArBy exploits the atlas dual role:

1. By using the atlas spatial reference as a common spatial reference it allows direct spatial comparison between different normalized datasets features;
2. By using atlas as a dictionary to support automated labelling of brain multimodal feature set it allows proper label cataloguing and subsequent query and retrieve of datasets using textual criteria.

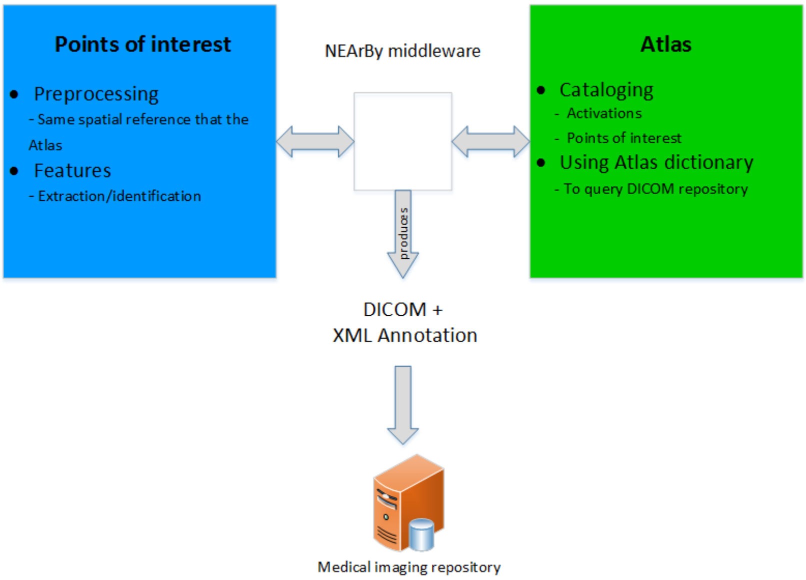


Figure 15 – NEArBy solution overview.

The role of NEArBy is to integrate in the same medical imaging repository both the image dataset and labels containing semantic information namely features and points of interest relevant in a given image dataset

3.2 NEArBy - The architecture

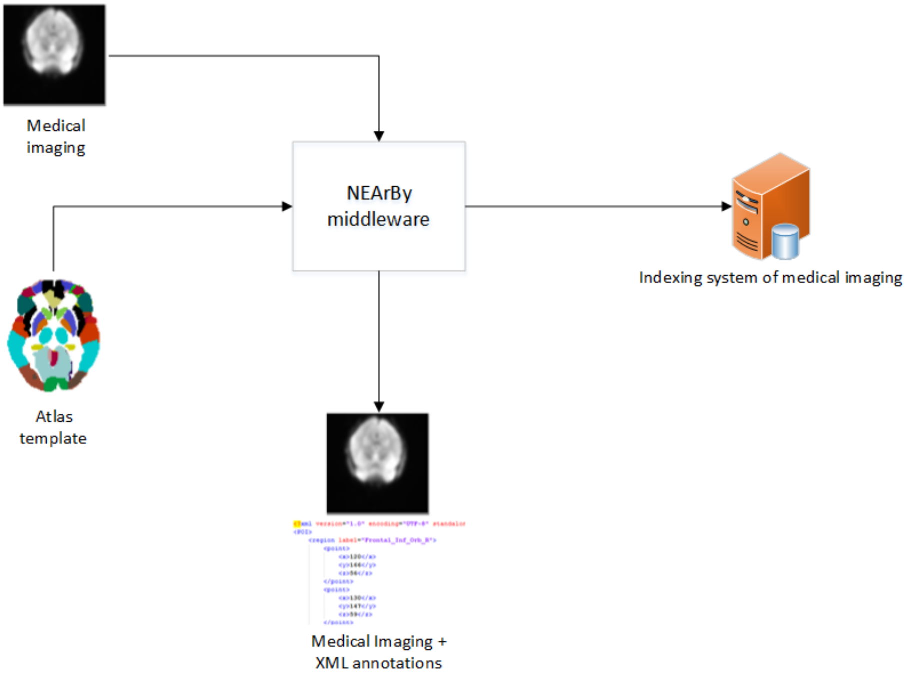


Figure 16 – NEArBy High-level conceptual model.

The NEArBy high-level architecture (Figure 16) is composed by several key components, each with a very specific function. Our architecture has a middleware component, with the primary role of interconnecting those key components. Two of them are critical data sources – medical imaging and atlas template – on obtaining the image data, where points of interest can be extracted, and the topological information, that provide cataloguing labels from the several regions of interest. Extracted information that derive from these two sources are major contributors to supply the middleware solution. The autonomous system proposed in the middleware solution consists on the integration of this information to produce a DICOM file containing the XML annotations. Figure 17 shows NEArBy middleware disassembled illustrating the integration of the several components

In order to ensure the right application process, NEArBy architecture reflects two major concerns in distinct perspectives.

From a brain imaging perspective, the objective is to ensure that all relevant features in input images are in the same spatial reference prior to any labelling process. From the labelling perspective, the concern is to map the features into atlas labels and catalogue them for future queries.

The ultimate goal of NEArBy is to enable queries on a medical imaging repository using atlas topological/anatomical information rather than image/modality specific information.

In order to accomplish this goal, it is necessary to process the input target imaging study in order to obtain relevant features. To perform the extraction of relevant information an analysis workflow has to be accomplished according to each imaging modality specifics.

The original dataset may not be fully able to perform data process in our context, mainly because the features locations may not be according to the standard spatial reference. If a case study is not in the same spatial reference it is necessary to perform a mandatory pre-processing step, the co-registration to normalize the dataset into the atlas space. Thus, the atlas tagged spatial reference is essential as a reference by providing the standard to perform the co-registration.

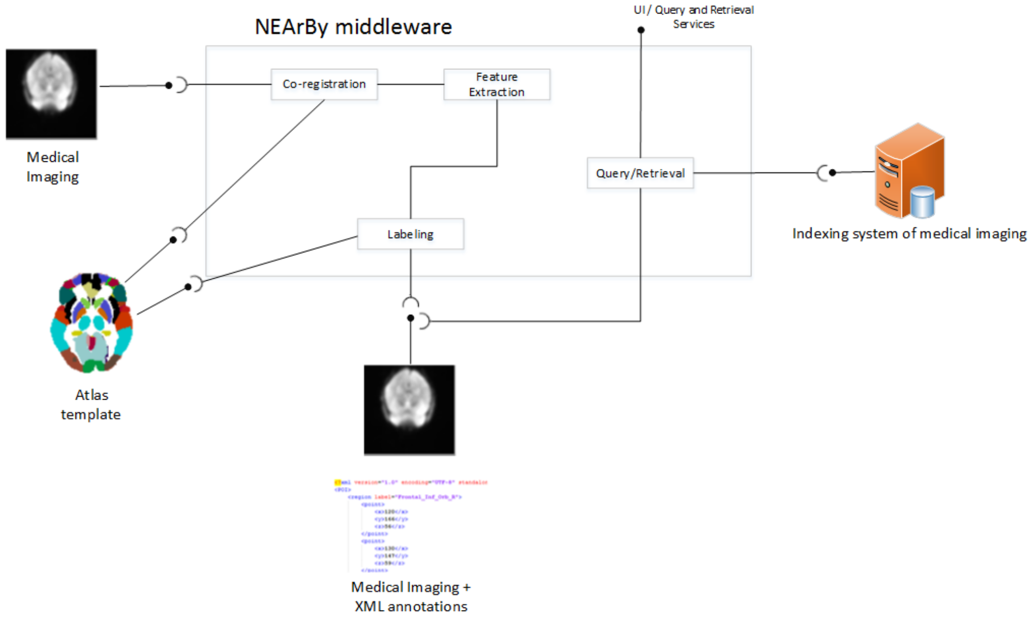


Figure 17 – NEArBy: an architectural overview from medical imaging Q/R.

3.2.1 Atlas as a spatial reference

Brain imaging datasets relevance, regardless of the modality, comes from specific identifiable features (e.g. visually, using modality specific analysis process) that within a clinical or research context may represent valuable information.

Although NEArBy concepts are modality agnostic, it relies on the assumption that a method to identify those features exists and that is possible to apply a normalization process from the original dataset into a reference – the atlas. If these premises are met it is possible to map relevant features of a given imaging study into the atlas space using the atlas's intrinsic label set.

The features extraction is dependent on the modality, the analytical techniques and the interpretation of these data. Well-established analysis tools exist so our approach was focused on creating within NEArBy workflow an instance of these tools. Feature extraction remains a matter of user expertise taking full advantage of each tool capabilities but without having necessarily to understand the business logic behind this analysis process. There are analysis tools as SPM and FSL that are extensively used in imaging datasets coming out of modalities such as, for instance, PET, fMRI and MRI, fMRI, respectively.

Before proceeding to the analysis, each imaging dataset should be normalized allowing the alignment of the imaging to a stereotaxic space. Different approaches can be taken, using as standard spatial reference the MNI or the Talairach space. The result of the feature extraction after this normalization returns the volume of interest according to the spatial normalisation. Thus, we also have the data consistent with the spatial reference of the brain atlas.

3.2.2 Atlas as a semantic enabler

An atlas provides a volumetric segmentation of brain anatomy and subsequent and immediate labelling for the different areas of the brain. The fact that provides a set of annotated representations of brain anatomy facilitates the understanding of the brain structure allowing a better analysis and more reliability when relating brain areas with brain functions. The labelling process is primary oriented to the features location - Figure 18. However, aggregate labelling and higher level functional relations may be also feasible to encode in a tagged environment. Content retrieval will be therefore attainable since, as it will soon be described, complex querying will be able to embody some sort of semantics.

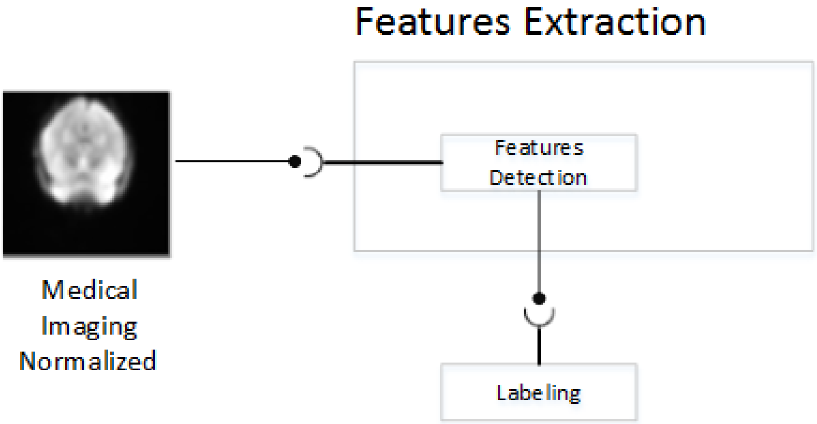


Figure 18 – Feature extraction in detail.

Figure 19 describes a typical application where normalized studies are directly mapped onto one or more atlases. Each previously elected VOI's in the image dataset is thus readily labelled by each atlas tag set. NEArBy uses this information to seamless encodes the tagged information as XML annotations within each image file.

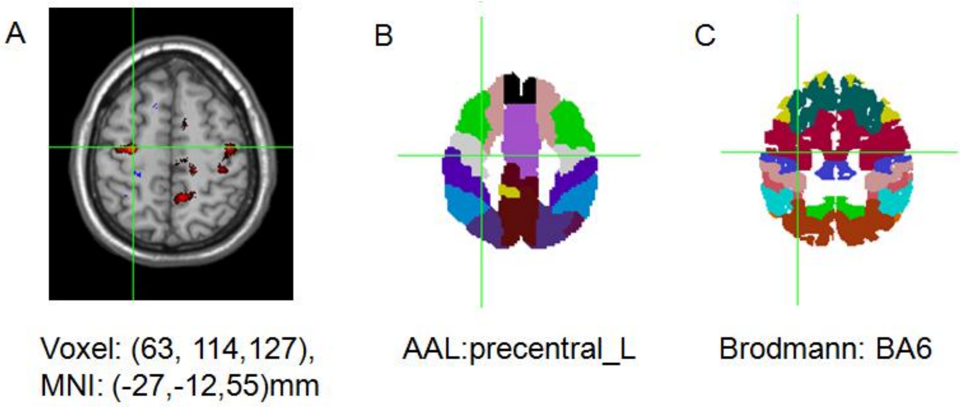


Figure 19 – Using common spatial reference system.

On a common spatial reference system (MNI in this case) is possible to map specific voxels to standard coordinates and used them to label using atlases such as – AAL and Brodmann Area.

3.2.3 Atlas tags as query tokens

From a set of features of a given brain image dataset, already labelled according to an atlas, we have valuable semantic textual information in a standard spatial reference and coded using atlas normalized labels – an atlas based dictionary. NEArBy query mechanism uses this semantic textual information to build a catalogue, using an indexing system, of both the features and the original brain image metadata. A generic query mechanism is thus feasible over a medical imaging repository.

The transformation of the original dataset and the coexistence of original information resulting from the acquisition process with a set of annotations from the labelling process, allows the creation of a repository of medical imaging semantically enriched.

The integration of these annotations enables to perform queries on the medical imaging dataset using the topological information provided by the chosen reference brain atlas. However, the provision of this feature depends mainly on the indexing of this information. Therefore one needs an indexing system able to index not only the technical imaging metadata but also the semantic information. In order to make this information useful in the retrieve process it is necessary to integrate a QR mechanism that will enable querying the imaging repository. This mechanism will provide the means for a user to make use of a topological/anatomical dictionary to query the imaging dataset through a web interface enabling the user to build their potentially semantically rich queries and retrieve the corresponding data.

The UI supported by the NEArBy middleware establishes a bridge between the user and the transformed dataset.

3.3 NEArBy: our proof of concept based on DICOM and Dicoogle

Our proof of concept implementation of NEArBy uses DICOM to support the coupling between image and atlas based tags and Dicoogle as the indexing solution.

The DICOM file format has a tag-based organization. In this case study, we extend the tag availability to insert the information tokens resulting from the labelling process.

With this integration the embedded information becomes an additional element for the indexing process. Our option was to rely upon an external indexing system such as the Dicoogle, conceived to deal with the DICOM tag universe.

This system needs to configure the subset of tags that should be indexed. In addition, this tool has its own QR mechanisms that allow performing queries over the indexed repositories. When performing a query, the Dicoogle engine does the search over the indexed content, more specifically, over information tokens contained in the labelled tags. So, indexing the atlas related tags that contain the xml annotations makes that content a target to perform queries. Thus, queries may be performed by using the atlas dictionary in “google” like style. Logical associations may lead to enriched semantic queries that go well beyond the simple tag-value pair.

This entire technical component should be transparent to the user and thus disregard the requirements of HW and SW, the implementation of a web interface is required to ensure proper interaction between the user and the medical imaging repository. A web interface should then provide the possibility of performing queries and using the Dicoogle system to perform the search and return the matching response to the query.

3.3.1 DICOM integration

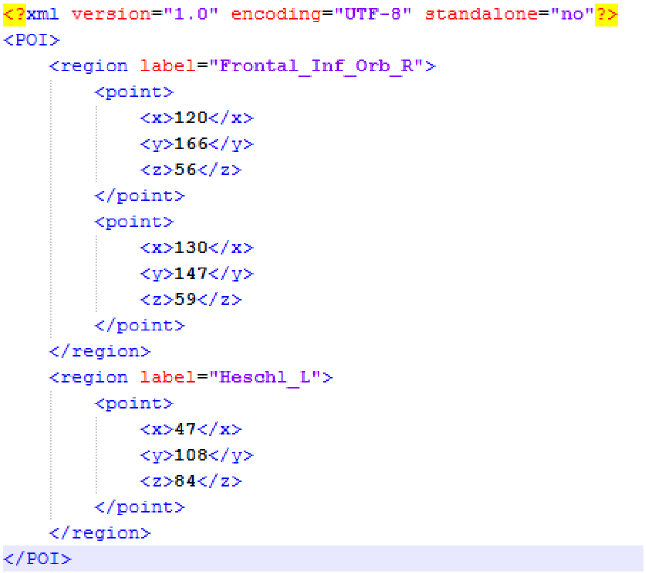
As DICOM files are tag-based, all the existing embedded information is organized into tags. This is appealing given the fact that it is easily extendable to integrate information. In this way we solve the persistence problem of the semantic information using for that the DICOM file to integrate the tagged information tokens. Given that this type of semantic content is not standard DICOM information we cannot use the standard tags to insert the information into DICOM files. To do this, we have to make use of the private tags defining a group number and an element to keep the semantic information that we intend to integrate.

In this way we can use a well structured and standard file format to embody the resulting semantic information from the medical imaging analysis going beyond the technical information related with the instantiation of a particular imaging procedure. The DICOM file as we already know do not possess a tag oriented mechanism to embody semantic information resulting from a functional analysis. However using the private tagging it is possible to store in the DICOM files relevant information enriching their use. Thus, it is possible to merge the tag based image retrieval provided by the DICOM standard tags with retrieval based on private tags encoding atlas based topological information.

With this process we can encode non standard information within DICOM file to integrate semantic information resulting from the labelling of the imaging features extracted.

3.4 NEArBy: encoding imaging features in DICOM

In the tagging process, the Points of Interest (POI) of a given dataset are tagged with the atlas label and used to produce a XML output (Figure 20) that is later embedded to the DICOM dataset pushed into the medical imaging repository.



```xml
<?xml version="1.0" encoding="UTF-8" standalone="no"?>
<POI>
    <region label="Frontal_Inf_Orb_R">
        <point>
            <x>120</x>
            <y>166</y>
            <z>56</z>
        </point>
        <point>
            <x>130</x>
            <y>147</y>
            <z>59</z>
        </point>
    </region>
    <region label="Heschl_L">
        <point>
            <x>47</x>
            <y>108</y>
            <z>84</z>
        </point>
    </region>
</POI>
```

Figure 20 - Example of XML semantic annotation.

In this example the atlas used is the AAL. The section "POI" contains the brain regions (frontal_Inf_Orb_R and Heschl_L in the example) where the locations are encoded – in the example with coordinates (120, 166,56) , (130,147,59) and (47,108,84).

As can be seen in Figure 20, the element 'region' includes an attribute that contains the name of the brain region with POIs. This element can have one POI or a set of POIs. These POIS are the points mapped in the region of interest. The POI is defined by the values of each coordinate: x,y and z. This semantic content existing in XML format is handled as if it were a string when indexing.

The final step is indexing the new/altered DICOM file. The name of the region according to a specific atlas can then be used to build a "neuro-query" and, for instance, used to retrieve the POIs with that area or to retrieve datasets with POIs in that area. It is also possible to perform specific search of POIs in a given position, using initially the associated atlas tag to retrieve the datasets and then compare each the retrieved POIs within that same area in the original position.

In short, in a query by atlas region, the indexing system seeks in the private tag the element 'region' with the 'label' attribute with the same identifier. A trickier search consists in a query with a given POI, where the query is handled by the middleware layer translating into the correspondent atlas region, in order to use the search method by atlas region. After seeking for that region and with the set of POIs obtained, the system looks for the given POI to retrieve the matching dataset.

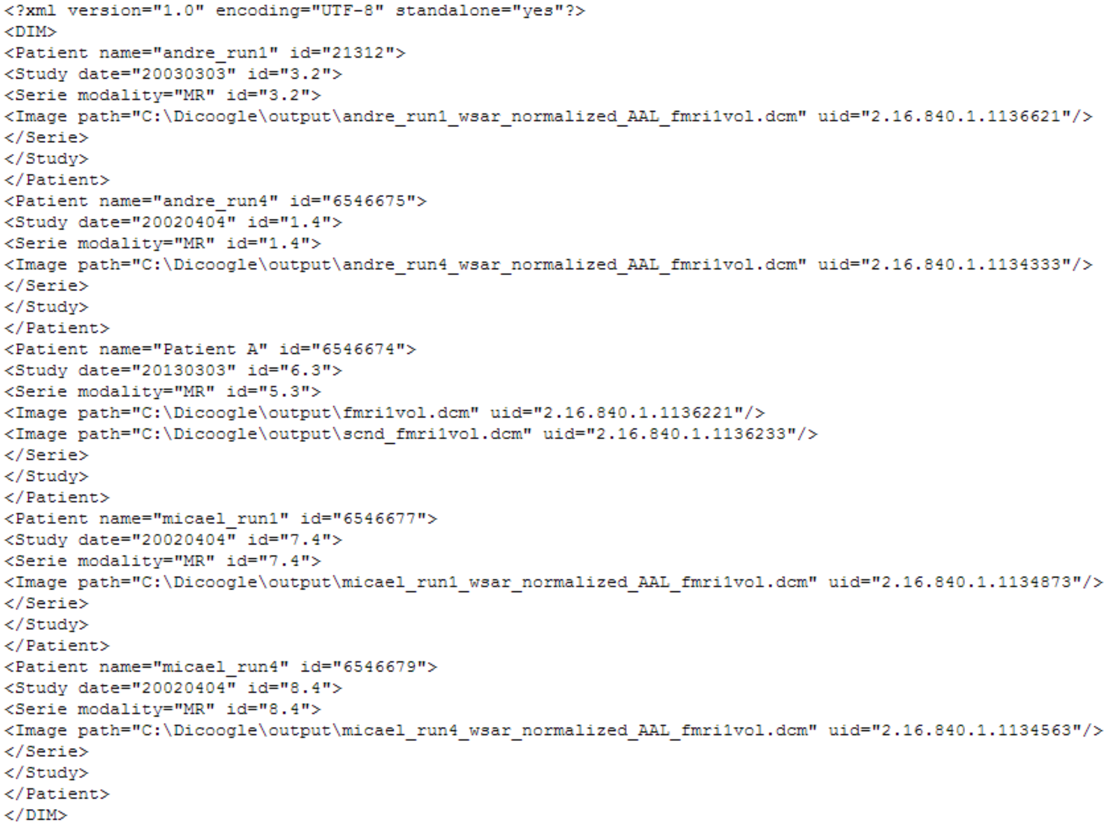
3.4.1 Q/R Dicoogle

Dicoogle (C. Costa et al., 2011; C. B. Costa, Luís; Campos, Samuel, 2012) is the indexing system for medical imaging behind NEArBy that indexes the DICOM files namely the NEArBy XML annotation atlas and POI information. Using this system is possible to retrieve, store and index all the metadata existing in the DICOM header. The key advantage of Dicoogle is that there is no formal distinction between indexing standard DICOM tags and private tags namely those from NEArBy. However some configuration is needed to configure Dicoogle to index NEArBy tags, i.e. providing the group number and the respective name to identify them. The use of the NEArBy DICOM private tag, allows including non-normalized DICOM information as semantic content in text based, e.g. the atlas labels that can also be used as part of the query strings.

Dicoogle provides its own Query/Retrieval mechanism on DICOM datasets to perform queries on the stored information and also a http-based query interface (REST services). These interfaces allow different query methods depending on the specific query parameters in the URL address:

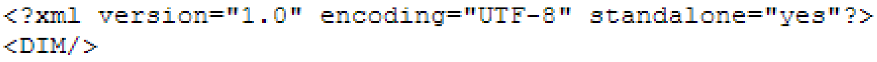
- Query for a specific brain region within NEArBy DICOM private tag defined by the name "region" <http_address>/dim?advq=region:
- Query for a specific patient name within DICOM standard patient name tag <http_address>/dim?PatientName:

The queries to Dicoogle are based on the tags used to index the image content in the repository, i.e., each DICOM tag existent in the metadata becomes available to be queried. Thus, the XML annotation formerly integrated in DICOM private tag enables the use of the atlas dictionary to support the queries. In a given search, Dicoogle seeks all the DICOM files in the repository searching a brain region atlas denomination in the private tag equal to the query token. Successful queries return an XML response with the patient name and the path for the image study which contains the searched information, among other information –Figure 21. If the system does not find any matching image study it returns an empty XML response -Figure 22.



```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<DIM>
<Patient name="andre_run1" id="21312">
<Study date="20030303" id="3.2">
<Serie modality="MR" id="3.2">
<Image path="C:\Dicoogle\output\andre_run1_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1136621"/>
</Serie>
</Study>
</Patient>
<Patient name="andre_run4" id="6546675">
<Study date="20020404" id="1.4">
<Serie modality="MR" id="1.4">
<Image path="C:\Dicoogle\output\andre_run4_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134333"/>
</Serie>
</Study>
</Patient>
<Patient name="Patient A" id="6546674">
<Study date="20130303" id="6.3">
<Serie modality="MR" id="5.3">
<Image path="C:\Dicoogle\output\fmri1vol.dcm" uid="2.16.840.1.1136221"/>
<Image path="C:\Dicoogle\output\scnd_fmri1vol.dcm" uid="2.16.840.1.1136233"/>
</Serie>
</Study>
</Patient>
<Patient name="micael_run1" id="6546677">
<Study date="20020404" id="7.4">
<Serie modality="MR" id="7.4">
<Image path="C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134873"/>
</Serie>
</Study>
</Patient>
<Patient name="micael_run4" id="6546679">
<Study date="20020404" id="8.4">
<Serie modality="MR" id="8.4">
<Image path="C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134563"/>
</Serie>
</Study>
</Patient>
</DIM>
```

Figure 21 – Dicoogle XML response searching case studies with POI in the Frontal area.



```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<DIM/>
```

Figure 22 – Dicoogle XML response – no results founded.

In NEArBy system (Figure 23), the search process is completely transparent for the user since he only knows where the search begins (Client terminal) and what it is about (DICOM repository). In order to access the system the user only needs a device with Internet connection. The user just connects to the URL web interface and accesses the available features. The process of search and the results obtained are handled by the web application, as described in the following figure, which acts as bridge between the client and the medical image repository.

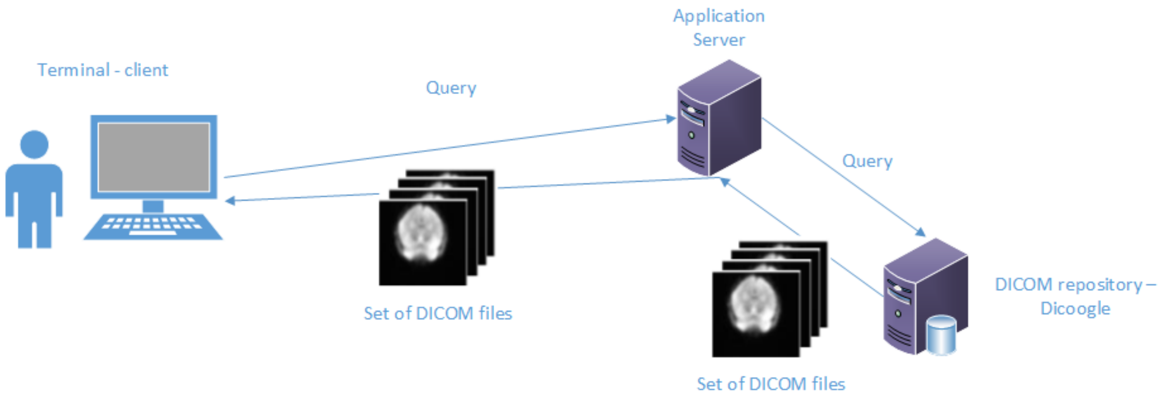


Figure 23 - Generic overview of the system.

3.5 Implementation Details

As our main focus was to prove the NEArBy concept, it should be noted that assumptions were made namely on the fMRI pre-processing to decrease its complexity, i.e., we assume that datasets used were already normalized in the MNI referential. This allowed us to focus only in the cataloguing implementation and not in pre-processing (not the focus of the current work).

NEArBy software system is mostly an integration of existing modules as illustrated in Figure 17 and implied the implementation of two modules: a set of pre-processing and labelling applications and a web interface with Neuroscience semantic wrapping the calls to Dicoogle – an external system for the imaging indexation solution.

The pre-processing and labelling application were implemented in java to implement the steps of features extraction and to generate a DICOM labelled image dataset from the initial dataset. As described, the feature extraction consisted, in the specific case of the fMRI, in the local extrema identification over a 3D image volume using an existing solution based on ImageJ {Schneider, 2012 #237}. The labelling and creation of DICOM semantically tagged dataset was based using the API dcm4chee (Zeilinger, 2011). During this process the application generated the XML labels for the detected image features (POIs) using the atlas labels.

The web interface was implemented with Play! Framework (Leroux, 2012) which provides a web framework written in Scala but with a Java API, following the Model-View-Controller pattern. The web interface provides access to a simple business logic to interact with Dicoogle through http requests and display the results retrieved from Dicoogle.

4 NEArBy Web interface

NEArBy provides a web interface as the main end-user interface allowing the user to perform queries over the medical image repository. The web interface only acts as a mediator to perform queries to Dicoogle, i.e., image repository which contains the indexed images can supply a web service that allows performing the search queries using parameterized URL addresses. The web application also provides an easy interface to use the atlas nomenclature in the queries.

4.1 Query by free text

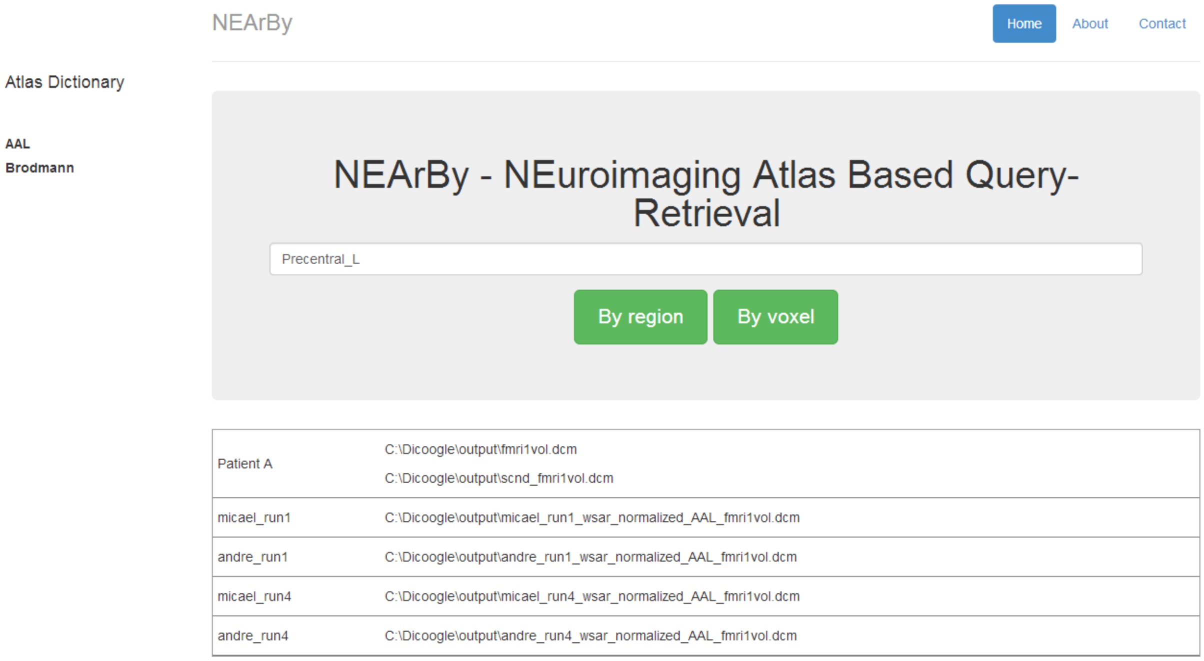
When performing queries, the user can use the name/identifier of the region according to the atlases - AAL or Brodmann - or a free input field where the user can use unconstrained text. Through the web interface the answer to queries sent to Dicoogle (Figure 24) are processed and presented in a more human readable format (Figure 25). Note that the syntax in this type of query is the inherent syntax of the Dicoogle.

Such processing allows abstracting the user of any technological knowledge and provides the necessary tools in a simple and oriented way when performing queries. Thus, there is no need for any knowledge of the Q/R mechanism behaviour, e.g., there is no need to understand the parameters necessary to build the URL address delegating these tasks to the middleware solution. This has the duty to understand the query to then perform the Http request in accordance with the required parameters.

http://localhost:6060/dim?advq=region:Precentral_L

```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<DIM>
<Patient name="andre_run1" id="21312">
<Study date="20030303" id="3.2">
<Serie modality="MR" id="3.2">
<Image path="C:\Dicoogle\output\andre_run1_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1136621"/>
</Serie>
</Study>
</Patient>
<Patient name="andre_run4" id="6546675">
<Study date="20020404" id="1.4">
<Serie modality="MR" id="1.4">
<Image path="C:\Dicoogle\output\andre_run4_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134333"/>
</Serie>
</Study>
</Patient>
<Patient name="Patient A" id="6546674">
<Study date="20130303" id="6.3">
<Serie modality="MR" id="5.3">
<Image path="C:\Dicoogle\output\fmri1vol.dcm" uid="2.16.840.1.1136221"/>
<Image path="C:\Dicoogle\output\scnd_fmri1vol.dcm" uid="2.16.840.1.1136233"/>
</Serie>
</Study>
</Patient>
<Patient name="micael_run1" id="6546677">
<Study date="20020404" id="7.4">
<Serie modality="MR" id="7.4">
<Image path="C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134873"/>
</Serie>
</Study>
</Patient>
<Patient name="micael_run4" id="6546679">
<Study date="20020404" id="8.4">
<Serie modality="MR" id="8.4">
<Image path="C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134563"/>
</Serie>
</Study>
</Patient>
</DIM>
```

Figure 24 – Dicoogle response in the web browser with the query Precentral_L.



NEArBy - NEuroimaging Atlas Based Query-Retrieval

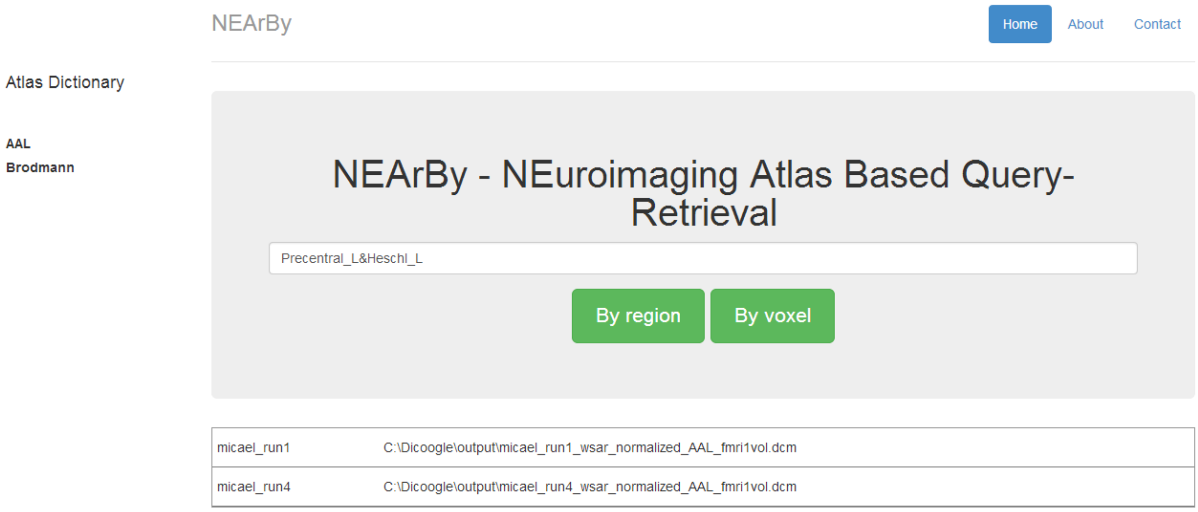
Precentral_L

Patient A	C:\Dicoogle\output\fmri1vol.dcm C:\Dicoogle\output\scnd_fmri1vol.dcm
micael_run1	C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm
andre_run1	C:\Dicoogle\output\andre_run1_wsar_normalized_AAL_fmri1vol.dcm
micael_run4	C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm
andre_run4	C:\Dicoogle\output\andre_run4_wsar_normalized_AAL_fmri1vol.dcm

Figure 25 – Response in the NEArBy web application with the query Precentral_L.

This type of query also enables the performance of queries combined, with an unlimited number of regions. A query combined in the middleware solution behaves like an AND search, i.e., only retrieve the datasets which contains points of interest in the set of regions given as query. In the following example - Figure 26, both datasets are the only that contains points of interest in both regions of the query.

In reality, a combined query implies two Http request to Dicoogle, where, in this case, the middleware keeps the first dataset retrieved matching with the second dataset obtained in order to retrieve to the user interface the datasets that are commons to both responses. Matching these two sets allows getting the response datasets which results to the query performed.



NEArBy - NEuroimaging Atlas Based Query-Retrieval

Precentral_L&Heschl_L

micael_run1	C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm
micael_run4	C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm

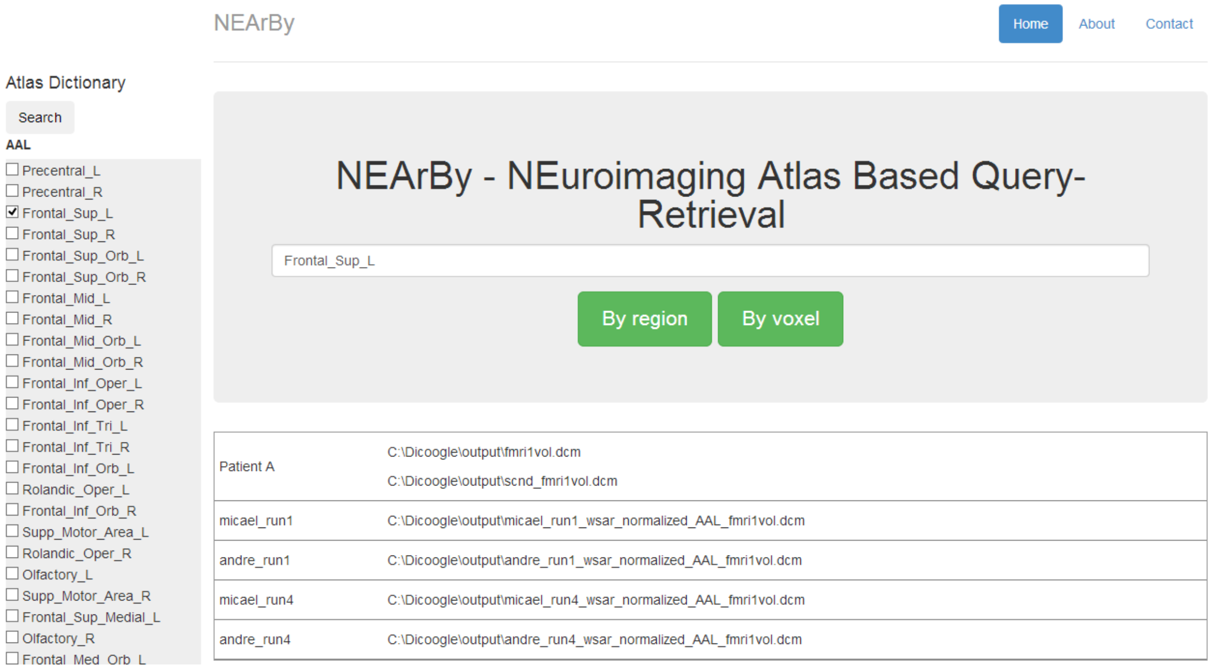
Figure 26 – Combined query

4.2 Query by Atlas

By using an atlas based checklist, the user does not need to be able to fully or partially understand atlas labels from segmented regions, and is also able to avoid unwanted syntax errors in the search query. For example, the selection of *Frontal_Sup_L* and submission of the query results in a XML (Figure 27) that is later displayed in the web interface (Figure 28).

```
<?xml version="1.0" encoding="UTF-8" standalone="yes"?>
<DIM>
<Patient name="andre_run1" id="21312">
<Study date="20030303" id="3.2">
<Serie modality="MR" id="3.2">
<Image path="C:\Dicoogle\output\andre_run1_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1136621"/>
</Serie>
</Study>
</Patient>
<Patient name="andre_run4" id="6546675">
<Study date="20020404" id="1.4">
<Serie modality="MR" id="1.4">
<Image path="C:\Dicoogle\output\andre_run4_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134333"/>
</Serie>
</Study>
</Patient>
<Patient name="Patient A" id="6546674">
<Study date="20130303" id="6.3">
<Serie modality="MR" id="5.3">
<Image path="C:\Dicoogle\output\fmri1vol.dcm" uid="2.16.840.1.1136221"/>
<Image path="C:\Dicoogle\output\scnd_fmri1vol.dcm" uid="2.16.840.1.1136233"/>
</Serie>
</Study>
</Patient>
<Patient name="micael_run1" id="6546677">
<Study date="20020404" id="7.4">
<Serie modality="MR" id="7.4">
<Image path="C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134873"/>
</Serie>
</Study>
</Patient>
<Patient name="micael_run4" id="6546679">
<Study date="20020404" id="8.4">
<Serie modality="MR" id="8.4">
<Image path="C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm" uid="2.16.840.1.1134563"/>
</Serie>
</Study>
</Patient>
</DIM>
```

Figure 27 - Dicoogle response in the web browser with the query *Frontal_Sup_L*.



NEArBy - NEuroimaging Atlas Based Query-Retrieval

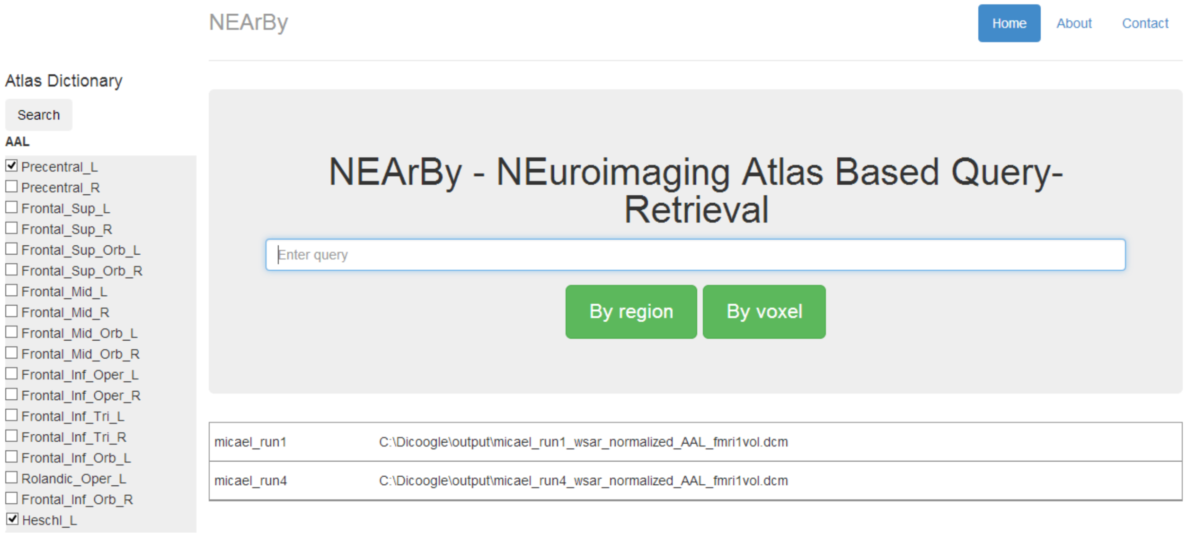
Frontal_Sup_L

☐ Precentral_L
☐ Precentral_R
☑ Frontal_Sup_L
☐ Frontal_Sup_R
☐ Frontal_Sup_Orb_L
☐ Frontal_Sup_Orb_R
☐ Frontal_Mid_L
☐ Frontal_Mid_R
☐ Frontal_Mid_Orb_L
☐ Frontal_Mid_Orb_R
☐ Frontal_Inf_Oper_L
☐ Frontal_Inf_Oper_R
☐ Frontal_Inf_Tri_L
☐ Frontal_Inf_Tri_R
☐ Frontal_Inf_Orb_L
☐ Rolandic_Oper_L
☐ Frontal_Inf_Orb_R
☐ Supp_Motor_Area_L
☐ Rolandic_Oper_R
☐ Olfactory_L
☐ Supp_Motor_Area_R
☐ Frontal_Sup_Medial_L
☐ Olfactory_R
☐ Frontal_Med_Orb_L

Patient A	C:\Dicoogle\output\fmri1vol.dcm C:\Dicoogle\output\scnd_fmri1vol.dcm
micael_run1	C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm
andre_run1	C:\Dicoogle\output\andre_run1_wsar_normalized_AAL_fmri1vol.dcm
micael_run4	C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm
andre_run4	C:\Dicoogle\output\andre_run4_wsar_normalized_AAL_fmri1vol.dcm

Figure 28 - Dicoogle response in the web browser with the query Frontal_Sup_L.

As it happens in free-text combined query, the same feature can be used through the checklist, where the user can select two or more brain regions (Figure 29)



☑ Precentral_L
☐ Precentral_R
☐ Frontal_Sup_L
☐ Frontal_Sup_R
☐ Frontal_Sup_Orb_L
☐ Frontal_Sup_Orb_R
☐ Frontal_Mid_L
☐ Frontal_Mid_R
☐ Frontal_Mid_Orb_L
☐ Frontal_Mid_Orb_R
☐ Frontal_Inf_Oper_L
☐ Frontal_Inf_Oper_R
☐ Frontal_Inf_Tri_L
☐ Frontal_Inf_Tri_R
☐ Frontal_Inf_Orb_L
☐ Rolandic_Oper_L
☐ Frontal_Inf_Orb_R
☑ Heschl_L

NEArBy - NEuroimaging Atlas Based Query-Retrieval

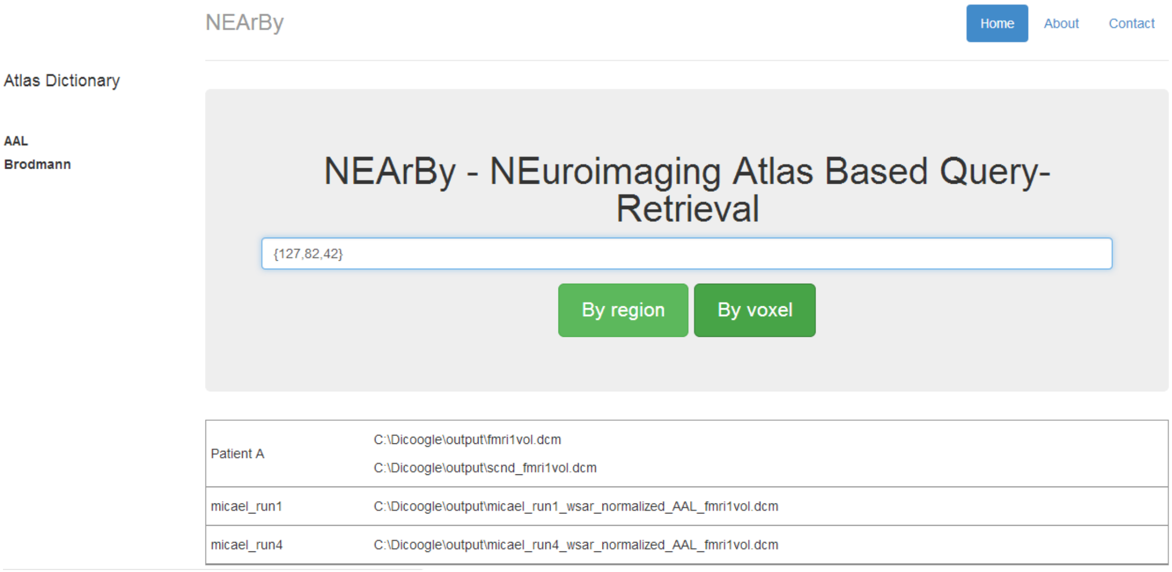
Enter query

micael_run1	C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm
micael_run4	C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm

Figure 29 – A combined query using the checklist.

4.3 Query by MNI location

It is also possible to execute query using the MNI coordinate system (Figure 30). In such queries the MNI coordinate is translated into the corresponding atlas region. The query by MNI location reuses the atlas based query mechanism already described. If, in a given dataset, features coordinates are found in the same brain region, then all the associated POIs are retrieved. After getting those POIs, the system seeks if the voxel entered by the user exists in that set of POIs. If there is no matching the response to the user through the web browser is a empty response without results. We chose this method for its efficiency since the number of “region” elements is smaller than the number of POIs.



NEArBy - NEuroimaging Atlas Based Query-Retrieval

{127,82,42}

Patient A	C:\Dicoogle\output\fmri1vol.dcm C:\Dicoogle\output\scnd_fmri1vol.dcm
micael_run1	C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm
micael_run4	C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm

Figure 30 – Query by a voxel for position (127,82,42).

The web interface also allows searching for specific subject based on personal information, i.e., subject name. In this search, NEArBy retrieves each brain region which contains activations/POIs in the subject dataset. The query by name is performed on DICOM standard tag “Patient Name”.

Given the fact that Dicoogle retrieves the imaging paths of each subject dataset, an extra step must be performed – filtering the results based on the DICOM private tag in order to read the XML annotation created by NEArBy. As XML annotation contains the semantic information, specifically, a set of brain regions resulting from a previous feature mapping, the attribute “label” of the element “region” (Figure 20) is used to obtain the list of regions in the subject dataset. Thus, the list of all the brain regions of interest of the subject with activations/POIs is displayed as query result.

4.4 fMRI case study

We illustrate the NEArBy potential usage over a set of functional magnetic resonance imaging (fMRI) (Figure 32) datasets using the web user interface to retrieve datasets on DICOM and atlas based criteria namely to retrieve subjects with activations in similar areas, in specific location and/or values under a given range.

In functional brain analysis using MRI we are mostly interested in finding activation and deactivation areas. These are obtained using Statistical Parametric Mapping (SPM) images (Karl J Friston et al., 1995; K. J. Friston et al., 1994) analysis over a sequence of fMRI for fMRI studies, as illustrated in Figure 31. The SPM output is a set of statistical 3D datasets where each brain position (voxel) has a value that indicates the statistical association of that voxel time course with specific protocol/condition.

The activation and deactivations are often represented using the local 3D extreme (3D coordinate). Using simple threshold criteria it is possible to discriminate points of statistical interest that can be interpreted according to their anatomical location and specific condition used in the SPM analysis.

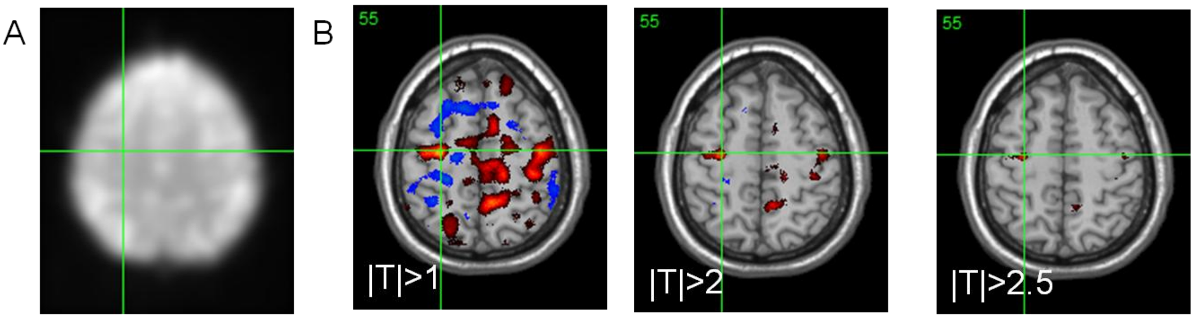


Figure 31 – Processing fMRI using SPM to find activations and deactivations.

From a fMRI sequence of images – as example of in A –usually SPM method is used to obtain a image data with statistical significance (B) using warm colour for activation and cold colour for deactivation when analysed within a given protocol context. By using different thresholds (it is possible to filter the most relevant activation).

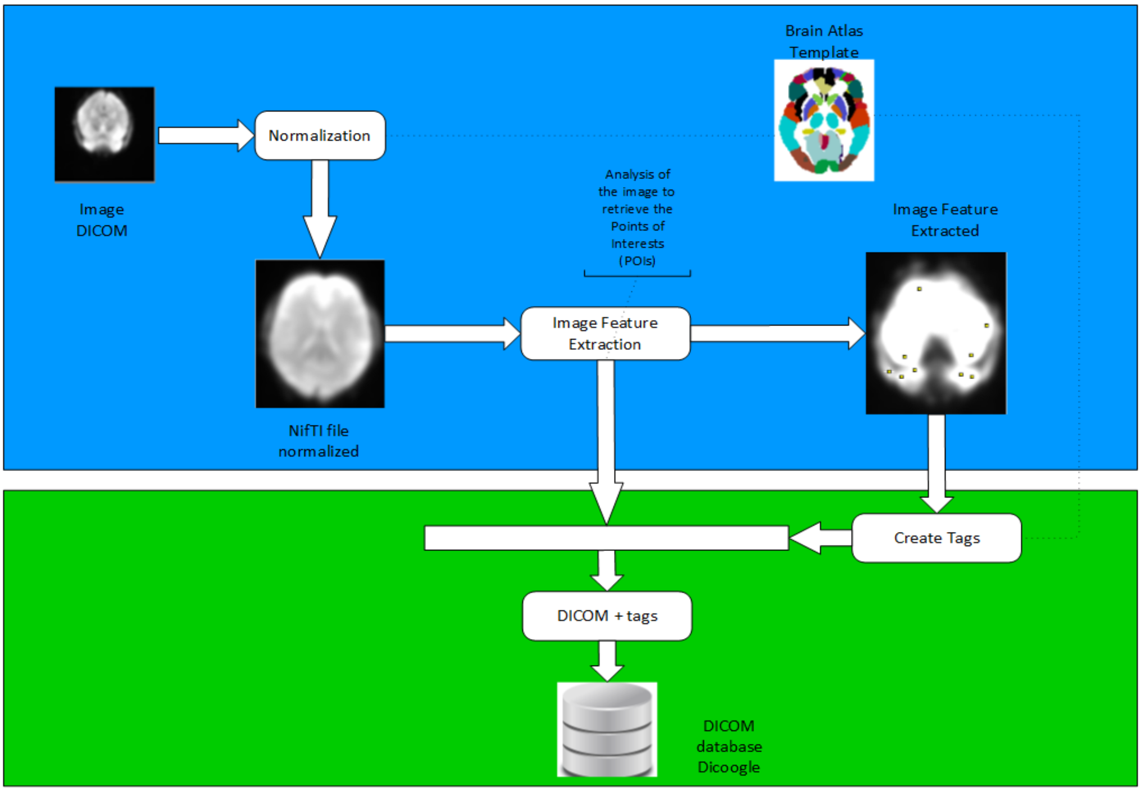


Figure 32 – fMRI NEArBy Workflow

In our fMRI scenario for NEArBy, the SPM extrema (activation and deactivation) will be our POIs and the datasets will be our 3D imaging datasets.

We tested NEArBy over a set of 5 datasets Table 1– results of SPM analysis over a set of fMRI sequences. Given the protocol used in the fMRI acquisition (self paced finger tapping and sound cued finger tapping) and SPM results clear local extrema existed within known brain locations.

Dataset	**Precentral_L**	**Frontal_Sup_L**	**Cerebelum_3_L**
Andre_run_1	x	x	
Andre_run_4	x	x	x
Micael_run_1	x	x	x
Micael_run_4	x	x	x
Patient A	x	x	

Table 1 – Sample datasets have different features – in our examples the focus was on three specific areas in the AAL atlas (Precentral_L, Frontal_Sup_L, Cerebelum_3_L).

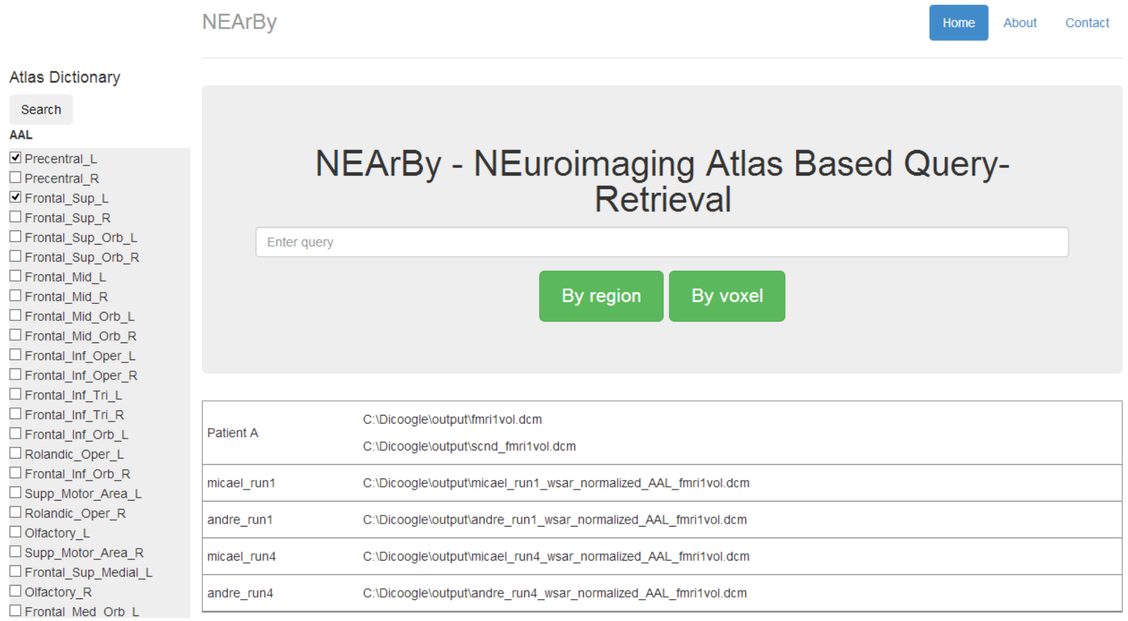
The “x” in a given column indicates if a given dataset has a POI in that region. For instance all datasets have POI in the Precentral_L, but Patient A and Andre_run_1 does not have a POI in Cerebelum_3_L.

To illustrate NEArBy usage we will describe a session where several NEArBy features will be presented from a perspective of the end-user – refer to previous chapter for technical details. We will consider the Table 1 with some example queries in order to guide the use cases in NEArBy usage, where the ‘x’ indicates that the dataset has activations/deactivations in the region.

To achieve this, we intend to cover some samples which allow illustrating the main features of our system, retrieving different case studies for different queries performed.

As stated, NEArBy supports simple queries and composed queries. In the simple format, the query consists in just one atlas region, which can be set using the input free-text or selecting an atlas region from the checklist. The composed queries are a combination of different atlas regions, that can also be set using the input free-text but with the constraint that it is necessary the use of & to “connect” the several atlas regions or selecting two or more atlas regions from the checklist.

NEArBy currently supports AAL and the Brodmann atlases to catalogue the datasets - the web interface reflects this by presenting from the start AAL and Brodmann labels for quick selection (checklist in Figure 33).



AAL

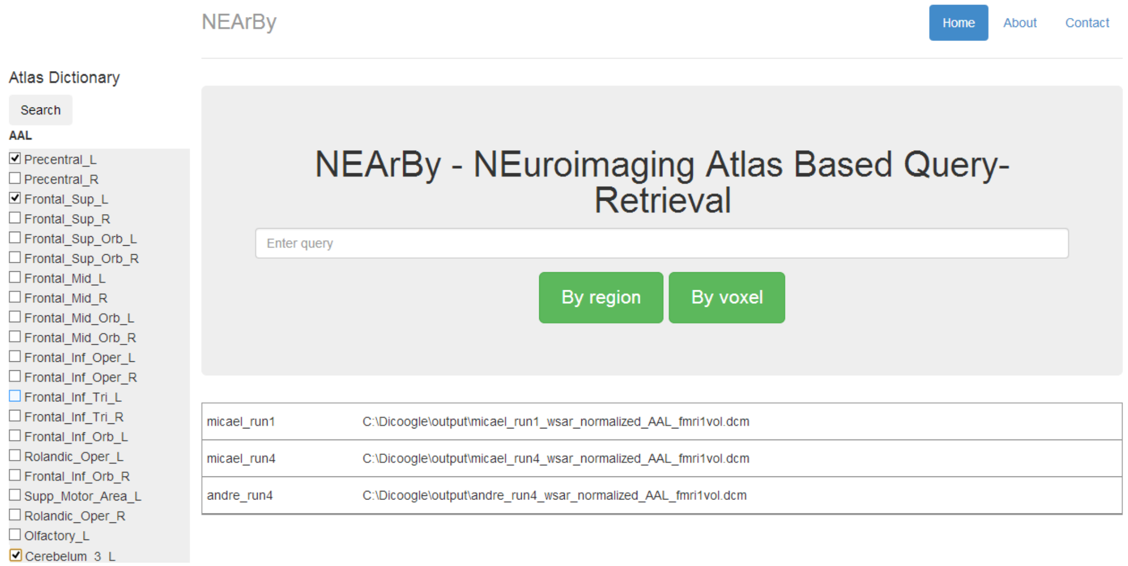
☑ Precentral_L
☐ Precentral_R
☑ Frontal_Sup_L
☐ Frontal_Sup_R
☐ Frontal_Sup_Orb_L
☐ Frontal_Sup_Orb_R
☐ Frontal_Mid_L
☐ Frontal_Mid_R
☐ Frontal_Mid_Orb_L
☐ Frontal_Mid_Orb_R
☐ Frontal_Inf_Oper_L
☐ Frontal_Inf_Oper_R
☐ Frontal_Inf_Tri_L
☐ Frontal_Inf_Tri_R
☐ Frontal_Inf_Orb_L
☐ Rolandic_Oper_L
☐ Frontal_Inf_Orb_R
☐ Supp_Motor_Area_L
☐ Rolandic_Oper_R
☐ Olfactory_L
☐ Supp_Motor_Area_R
☐ Frontal_Sup_Medial_L
☐ Olfactory_R
☐ Frontal_Med_Orb_L

Patient A	C:\Dicoogle\output\fmri1vol.dcm C:\Dicoogle\output\scnd_fmri1vol.dcm
micael_run1	C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm
andre_run1	C:\Dicoogle\output\andre_run1_wsar_normalized_AAL_fmri1vol.dcm
micael_run4	C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm
andre_run4	C:\Dicoogle\output\andre_run4_wsar_normalized_AAL_fmri1vol.dcm

Figure 33 – NEArBy combined query for *Precentral_L* and *Frontal_Sup_L*.

In the example of Figure 33, a combined query for *Precentral_L* and *Frontal_Sup_L* (checklist on left) is shown. Note that these topological annotations are defined according to the AAL atlas. After submitting the query, only the patient name and the imaging paths of the results are returned. The paths indicate the files where exist POIs within the area in the query. This query retrieves 5 datasets (central textbox).

It is possible to narrow the query by introducing new brain regions, for instance the brain region *Cerebelum_3_L*, as shown in Figure 34.



AAL

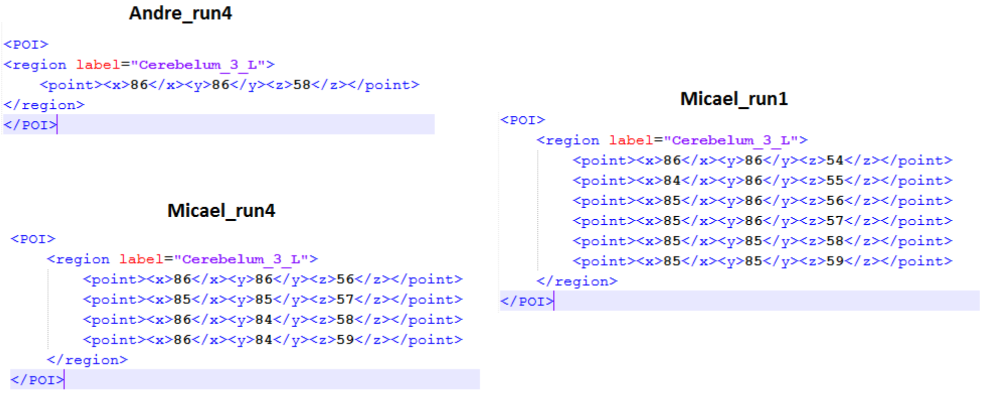
☑ Precentral_L
☐ Precentral_R
☑ Frontal_Sup_L
☐ Frontal_Sup_R
☐ Frontal_Sup_Orb_L
☐ Frontal_Sup_Orb_R
☐ Frontal_Mid_L
☐ Frontal_Mid_R
☐ Frontal_Mid_Orb_L
☐ Frontal_Mid_Orb_R
☐ Frontal_Inf_Oper_L
☐ Frontal_Inf_Oper_R
☐ Frontal_Inf_Tri_L
☐ Frontal_Inf_Tri_R
☐ Frontal_Inf_Orb_L
☐ Rolandic_Oper_L
☐ Frontal_Inf_Orb_R
☐ Supp_Motor_Area_L
☐ Rolandic_Oper_R
☐ Olfactory_L
☑ Cerebelum_3_L

micael_run1	C:\Dicoogle\output\micael_run1_wsar_normalized_AAL_fmri1vol.dcm
micael_run4	C:\Dicoogle\output\micael_run4_wsar_normalized_AAL_fmri1vol.dcm
andre_run4	C:\Dicoogle\output\andre_run4_wsar_normalized_AAL_fmri1vol.dcm

Figure 34 - NEArBy web application composed query with three brain regions.

The answer retrieved by NEArBy (using Dicoogle) now only retrieves 3 out of the 5 initial. This indicates that only three cases have activations in the three brain regions selected.

However it is important to note that having POIs within the same brain regions does not mean these POIs are the same. For example, selecting the region *Cerebelum_3_L* will produce 3 datasets as results, however the POIs in the 3 datasets may not be equal (Figure 35) but have in common the activations in the same brain region.



Andre_run4

```xml
<POI>
<region label="Cerebelum_3_L">
    <point><x>86</x><y>86</y><z>58</z></point>
</region>
</POI>
```

Micael_run1

```xml
<POI>
    <region label="Cerebelum_3_L">
        <point><x>86</x><y>86</y><z>54</z></point>
        <point><x>84</x><y>86</y><z>55</z></point>
        <point><x>85</x><y>86</y><z>56</z></point>
        <point><x>85</x><y>86</y><z>57</z></point>
        <point><x>85</x><y>85</y><z>58</z></point>
        <point><x>85</x><y>85</y><z>59</z></point>
    </region>
</POI>
```

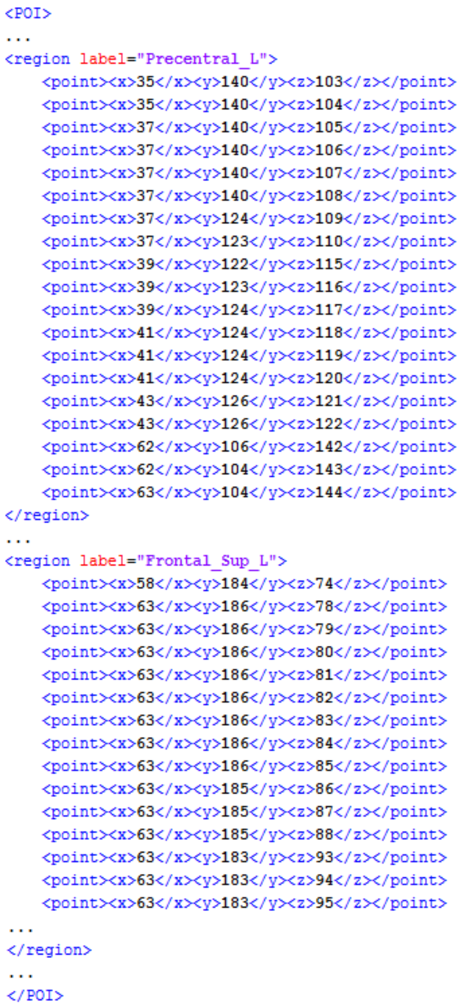
Micael_run4

```xml
<POI>
    <region label="Cerebelum_3_L">
        <point><x>86</x><y>86</y><z>56</z></point>
        <point><x>85</x><y>85</y><z>57</z></point>
        <point><x>86</x><y>84</y><z>58</z></point>
        <point><x>86</x><y>84</y><z>59</z></point>
    </region>
</POI>
```

Figure 35 – XML annotations from 3 different users for the same brain region.

Let's see how this information is found, this requires knowing that information is the XML annotations created in the process pipeline to be integrated within the DICOM file. We only will consider the DICOM of the patient *micael_run1* and an excerpt of the XML annotation.

Using the example of Figure 33 where we combine a query with two brain regions (*Precentral_L* and *Frontal_Sup_L)* let us analyze in general how the results are retrieved. The first step consists in splitting the query into two. Since the Dicoogle does not allow performing combined queries, it is necessary to make a http request for each of the regions of the query. In fact, when this request is made and taking in mind that the URL is parameterised specifically to seek the private tag with the XML annotations, the Q/R mechanism seeks for the element which contains the label with the same value as the query given as parameter. As is shown in Figure 36, we have the two 'region' elements with activations in both areas. Internally, NEArBy middleware solution keeps in memory the datasets retrieved as response to the first query (*region: Precentral_L*) and then proceeds with the second request (*region: Frontal_Sup_L*). With the datasets retrieved in the second response, we merge those results with the dataset in memory to retrieve only the case studies which are common to both Dicoogle responses.



```
<POI>
...
<region label="Precentral_L">
    <point><x>35</x><y>140</y><z>103</z></point>
    <point><x>35</x><y>140</y><z>104</z></point>
    <point><x>37</x><y>140</y><z>105</z></point>
    <point><x>37</x><y>140</y><z>106</z></point>
    <point><x>37</x><y>140</y><z>107</z></point>
    <point><x>37</x><y>140</y><z>108</z></point>
    <point><x>37</x><y>124</y><z>109</z></point>
    <point><x>37</x><y>123</y><z>110</z></point>
    <point><x>39</x><y>122</y><z>115</z></point>
    <point><x>39</x><y>123</y><z>116</z></point>
    <point><x>39</x><y>124</y><z>117</z></point>
    <point><x>41</x><y>124</y><z>118</z></point>
    <point><x>41</x><y>124</y><z>119</z></point>
    <point><x>41</x><y>124</y><z>120</z></point>
    <point><x>43</x><y>126</y><z>121</z></point>
    <point><x>43</x><y>126</y><z>122</z></point>
    <point><x>62</x><y>106</y><z>142</z></point>
    <point><x>62</x><y>104</y><z>143</z></point>
    <point><x>63</x><y>104</y><z>144</z></point>
</region>
...
<region label="Frontal_Sup_L">
    <point><x>58</x><y>184</y><z>74</z></point>
    <point><x>63</x><y>186</y><z>78</z></point>
    <point><x>63</x><y>186</y><z>79</z></point>
    <point><x>63</x><y>186</y><z>80</z></point>
    <point><x>63</x><y>186</y><z>81</z></point>
    <point><x>63</x><y>186</y><z>82</z></point>
    <point><x>63</x><y>186</y><z>83</z></point>
    <point><x>63</x><y>186</y><z>84</z></point>
    <point><x>63</x><y>186</y><z>85</z></point>
    <point><x>63</x><y>185</y><z>86</z></point>
    <point><x>63</x><y>185</y><z>87</z></point>
    <point><x>63</x><y>185</y><z>88</z></point>
    <point><x>63</x><y>183</y><z>93</z></point>
    <point><x>63</x><y>183</y><z>94</z></point>
    <point><x>63</x><y>183</y><z>95</z></point>
...
</region>
...
</POI>
```

Figure 36 – XML integrated into the DICOM file.

The easy combination of different brain areas in the composed queries is an extremely useful tool that hides the specificities of the QR mechanisms and NEArBy solution from the user – leaving the user only with the familiar nomenclature of the atlas (AAL in the examples) to perform more complex data queries.

5 Conclusions and future work

In this work we propose a software solution, NEArBy, to automate a process of mapping features extracted from a medical imaging with topological/anatomical information obtained from a brain atlas.

The NEArBy system has two main parts:

- the tool which catalogues the relevant features of a given dataset using brain atlas based tags and encodes such information in XML that is merged into DICOM dataset;
- the user-friendly WEB QR platform that performs QR and retrieve actions over a medical imaging repository using atlas specific semantic. The implemented system results in a lightweight deployment due to the fact that it is an implementation comprised in modules.

We believe that the option for XML encoding of atlas based tags was a novelty and optimal in the sense of integration with the DICOM tag set and also in the sense of increased flexibility of the queries.

This solution is not specific for any field of neuroscience and only assumes that relevant features of a given dataset have a MNI coordinate and the original dataset is available. Fulfilling these assumptions is possible to perform a fully automatic labelling of the features, integrate a new dataset containing both the original dataset information plus atlas-based labels.

NEArBy integration only assumes that there is an indexing system able to cope with user specific DICOM tags and a QR solution. We illustrated NEArBy with an external and agnostic indexing solution – Dicoogle – also used to support the QR services. NEArBy web delegated to Dicoogle all QR procedures and acted as a facilitator to a human end-user to query a dataset repository and review the results.

By using the atlas tags and the MNI referential during the semantic labelling NEArBy established a standard syntax and nomenclature (the atlas) and brain spatial reference (MNI). In this way, the topological information extracted from the brain atlas template was used as a semantic enabler to build-up semantic enabled repositories.

The selection of DICOM to support NEArBy was natural since DICOM allows user to store the imaging information (the dataset data), define specific textual tags (semantic) and has several efficient solution for efficient indexation and tag based image retrieval (Dicoogle was the solution used).

This highlights the extensibility of the NEArBy as a system that is totally independent of all semantic information (POIs and atlas) and does not imply any specific configuration, other that customized QR interface, to apply it to a different neuroscience context. It is only necessary to integrate the different mapping results in the same XML to afterwards be integrated in medical imaging and indexed in the data repository. In the examples using fMRI based datasets, although POIs where specific to fMRI, the web interface QR was context and modality agnostic and the only semantic information was those contained in AAL labels.

As NEArBy is a proof of concept, there is several opportunities to evolve it besides technical aspects.

The addition of an easy way to integrate new atlases to provide others brain volume segmentation with new topological/anatomical information. However such changes imply some business logic to deal with the new atlases and their nomenclature in order to label the brain imaging datasets and to generate the XML annotations. For instance, adding support to functional atlas like the one provided by the FIND lab at Stanford University (Shirer et al., 2011) could be useful to label automatically specific areas associated to relevant cognitive states.

Future work may also include a visual query tool most likely in the form of an atlas viewer to select, with the mouse, the atlas brain areas/locations. In this way, the user will not need any syntax knowledge on the atlas since the desired query will result from the visual exploration of the brain atlas volume. Although the current information retrieved from the searches performed is sufficiently indicative of the datasets, a well-integrated image viewer to explore the retrieved datasets will also be an added-value component to the whole system.

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