Segmentation techniques in Nuclear image

Research Techniques

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2016/2017
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Chapter 1

Introduction

Medical image is nowadays a continuously evolving means of disease diagnosis, staging, surgery planning and progression evaluation in healthcare. Physicians recur to different medical imaging techniques for the tasks of visualization of anomalies in shape and texture the human anatomy. More conventional medical image techniques recur to the ionization of body tissues though the use of electromagnetic radiation of different frequency spectrum. After capture of the releasing radiation from body tissues and upon adequate signal processing, the reconstruction and visualization of the in vivo anatomy is possible, with varying degrees of resolution and tissue penetration. The most common imaging techniques in this setting are Computed Tomography (CT), Magnetic Resonance Imaging (MRI), X-Rays and Ultrasound (US).

Nuclear image consists in a specific technique of medical imaging, which recurs to the actual internal injection of a radiolabelled molecule which will release radiation from the tissue it reaches, hence from inside the body. This technique uses gamma radiation, released upon the decay of the radionuclide injected intravenously. This radiation is, similarly to the abovementioned techniques, captured outside the body. However, nuclear image has the particularity of injecting the radiolabelled molecule, consisting in a functional molecule that is metabolically processed by a specific type of tissue that is intended to be imaged. This molecule is linked to the radionuclide, whose releasing energy will allow its tracing over the human tissues over time, and the visualization of their convergence, binding and concentration to specific organs. The most common imaging techniques in this setting are Single Positron Emission Tomography (SPECT) and Positron Emission Tomography (PET).

For several years, medical image has only recurred to the first group of techniques described, especially with the particular advancement of the tomographic techniques of CT and MRI. However, in recent years, the development of hybrid imaging techniques has emerged. Hybrid imaging, began with the experimental development of a joint imaging equipment, fusing both SPECT and CT, acquiring both simultaneously, by Hasegawa et al. [1], [2]. Later commercial equipment was released for healthcare usage, of PET-CT [3] and PET-MRI [3] imaging systems. The advantages that motivated this study were the superiority of data retrieval that is made possible when acquiring functional molecular data from the tissues and morphologic
visualization, in a simultaneous manner, and in a similar coordinate space. These advantages are exactly the reasons that justify the emerging usage of these techniques in recent years, in a varied range of medical scenarios, with specific relevance in oncology.

State-of-the-art Computer Vision techniques, are continuously developing, presenting novel techniques for the proper analysis of medical images. For this purpose, as in other medical diagnostic diseases, the need for software tools that would aid the clinical analysis of the information present in medical images, is of high importance.

The works presented in this document are intended to complement the basic knowledge necessary for the development of a PhD project in focused on the segmentation, diagnosis, and modelling tasks based on SPECT-CT images, in a clinical liver cancer scenario. The aim of this PhD project is to develop an integrated segmentation techniques to segment the liver and sub-regions of cancer masses, recurring to both individual segmentations on these structures on SPECT and CT images.

Different techniques with varying degrees of complexity have been applied to medical images, namely varying computer vision techniques and segmentation algorithms.

Computer Vision methods have been applied in medical images through image processing and pattern recognition approaches. Among these, different classes of image analysis and machine learning algorithms are used in the literature to extract meaningful information from medical images. As an overview, advanced machine learning techniques are the most state-of-the-art algorithms used for the tasks of organ detection, classification or segmentation in medical images. On its turn, image processing and analysis techniques have been developed for many years until present, for organ segmentation purposes.

In this report, the development of preliminary image analysis and segmentation algorithms is presented. Some of the algorithms used in the literature for the analysis of nuclear images were applied to a limited number of brain PET images. The results presented will consist in preliminary works, which allow the evaluation of the challenges presented upon the segmentation of structures in nuclear images. The development of techniques that have been used in the literature, to segment varied structures in nuclear images is studied, having hence, their potential application in the segmentation of the liver in the SPECT images that will be used in this PhD project. Moreover, more advanced techniques have been studied in the literature for the segmentation of the liver in CT images, but these have also in many works, been complemented with more simple segmentation techniques, such as the ones stated in this document. Hence, the final objective in the proposed PhD work includes the usage of the techniques developed in this document in both scenarios.

The current report is divided in six main sections, along with the current Chapter 1 of introduction, namely: 2) a review of the several techniques currently used in nuclear image; 3) a description of the methods used for the segmentation problem; 4) a description of the
experimental setup, i.e. the set of images used and the segmentation problem under study; 5) the results obtained; and 6) a discussion of the results and main conclusions.
Chapter 2

State of the art

Computational analysis of medical images is of high importance for the development systems capable of extracting relevant information from images which can be used by physicians to solve several clinical problems. Nuclear image has an important role in diagnosis, staging, surgical planning and chemotherapy tumor target volume delineation. In particular, nuclear image has emerged as an important tool for clinical evaluation in oncology, in the tasks of resective surgery planning and radiotherapy target volume delineation.

In a clinical setting, the medical evaluation protocol requires the answers of three main questions: What is the type of pathology?, What is the location of the tissue? and What is the degree of severity and extension?. Although the type of pathology and its location determine the type of treatment course to be taken, the degree of severity or extent of the lesion determine the moment intensity of the intervention.

2.1 Imaging technology towards cancer diagnosis

Cancer is primarily characterized by a change in the metabolic capacity of tumorous cells, which is combined with an associated nonstandard growth and multiplication of abnormal cells. The abnormal cells start to deposit and continue growing, forming lumps. Lumps on their turn, if not physiologically controlled, will develop into malignant masses which will continue to grow and affect the proper function of surrounding normal tissues, and possibly, latter additionally spreading to other organs. Clinical diagnosis of cancer disease is firstly accessed through morphological imaging. The deposited malignant masses appear as morphological alterations in CTs or MRIs. However, the metabolic changes that primarily occur in the tissue may in many cases, not be depicted as morphologically affected areas. Hence, the diagnosis and delineation of the affected area may not be adequately identified solely by a morphological imaging study. This is important for the proper definition of the tumour volume that needs to be excised, or the proper irradiation of the tumour volume with maximal effectiveness, in both cases to guarantee minimal percentage of tumor recurrence. The clinical protocols of identification of cancer disease include
several variations upon the stage of clinical intervention. Diagnosis is performed via biopsy and morphological imaging. Staging and surgery planning however, may require proper delineations of tumor volume. In specific cases where the tumor size justifies drastic clinical procedures, resective surgery is proven to be the most adequate course of action. Resection has proven to be most effective with preponderant tumor sizes, minimizing the risk of recession, i.e. of a tumour reappearance.

Computed tomography (CT) represents the primary modality to plan personalized radiation treatment, because it provides the basic electron density map for correct dose calculation. If PET scanning is also performed it is typically co-registered with the CT study. This operation can be executed automatically by a hybrid PET/CT scanner or, if the PET and CT imaging sets have been acquired through different equipment, by a dedicated module of the radiotherapy treatment planning system.

Nuclear image consists in PET and SPECT. In nuclear image radionuclides are combined with pharmaceutical compounds, which will be metabolized by tissues. The radiation that is releasing from inside the body, is registered by gamma chambers which are prepared to decode it, and reconstruct the tissue images. The distributions of radiopharmaceutical molecules on the tissue can be analysed quantitatively, allowing the extraction of bio-distribution concentrations and kinetic metabolization descriptors of the radiolabelled molecule. The different imaging techniques that recur to radiopharmaceuticals will be described in more detail in the following sub-sections. In a clinical oncology setting nuclear image allows the identification and characterization of tumors to be conducted based on their metabolic properties.

2.1.1 SPECT

SPECT, such as all nuclear imaging methods, is considered a diagnostic complementary method, minimally invasive. This imaging modality requires only the intravenous administration of a radiopharm. By revealing chemical activity of specially designed radiotracers, SPECT imaging is capable of detecting a wide range of abnormal activity in the human body, including tumor activity.

SPECT imaging uses a radionuclide characterized by a radioactive energy decay from a single photon, hence the name Single Photon Emission Tomography. A gamma chamber is incorporated in the imaging equipment, capable of capturing the gamma radiation that emanates from the tracer-labelled tissues. From this signal, the technique allows the reconstruction of tomographic images, i.e. co-adjacent and transversal sets of slice images depicting the radiotracer distributions along the tissues. Similarly to CT, from the image stacks generated other view planes
can be formatted, such as sagittal and coronal image planes, recurring to advanced signal processing algorithms.

It has been widely applied to cancer clinics as a tool for tumor detection and diagnosis. However, SPECT imaging has low spatial resolution in its nature, making it very difficult for precise localization of tissues and tumor boundaries. Precise localization is important for radiation therapy, a mainstream tumor treatment method, for treatment efficiency and avoiding side-effect. Therefore, in early clinical application, SPECT was often combined with CT, an imaging modality with limited functional information but higher anatomic spatial resolution. Shortly after, specially designed scanner combining SPECT and CT was developed, and SPECT-CT has become a mainstream imaging modality ever since. However, many challenges remain to be solved in precise tumor segmentation and localization using SPECT-CT imaging.

### 2.1.2 PET

PET is a similar technique to SPECT, differing on radionuclide type of decay. In PET the radionuclide molecule decays releasing multiple positrons. PET is widely established in nuclear image studies, because there have been developed radio pharms in this modality that are very well established in the literature for a great number of studies. Namely, the most used tracer in PET image consists in a Fluor radionuclide bonded to glycose. Glicose is metabolized by a number of different organs, and is a fundamental function for normal homeostasis of the human body. Hence, glycose metabolization is widely studied, for instance to evaluate normal metabolism in the brain, among other areas. Tissue organs with higher metabolic capacity imply higher tracer concentrations in those areas. Tomographic images are generated, in similar manner to SPECT. The advantage in this modality consists in a higher spatial resolution acquired due to the higher number of photons that complement the retrieved signal.

### 2.2 Quantitative evaluation of radiotracer uptake in nuclear image

A qualitative assessment of the PET image done by experts is often sufficient for tumor assessment and detection. However, accurate tumor diagnosis and assessment require quantitative evaluation of the PET scanner records, since such records vary with time and dose of radiotracer. Popular semi-quantitative and quantitative methods are standard uptake value (SUV), tumor-to-background ratio (TBR), nonlinear regression techniques, total lesion evaluation (TLE), and the Patlak-derived methods. Among them, SUV is the most popular technique, for it relates to physiological activity of cellular metabolism. SUV represents the tissue concentration of the radiotracer at a given time divided by a few normalization factors [4]. These factors include
injected dose, patient size in terms of weight, and a decay factor related to the radiotracer. It is defined as:

$$SUV = \frac{C_{\text{img}}(t)}{ID/BW}$$

where $C_{\text{img}}(t)$ stands for total radiotracer concentration in time $t$, ID represents injected dose (Bq) and BW is body weight (in g or kg). SUV is used in localization for normalization purposes. For details of the available different quantitative evaluation methods, the reader can refer to the review work.

2.3 Literature Review

Delineation of organs and lesions in images has been studied through several techniques. While manual delineations are highly time consuming and prone to intra- and inter-observer subjectivity, some semi-automatic delineation tools of tumor volume [5]. However, the need of developing computational methods for automatic analysis of nuclear images has been tackled in the literature, recurring to a wide range of algorithms. The implicit challenges faced in this setting are the highly noised retrieved images and in some equipment’s also the limited spatial resolution. In nuclear image, studies can be validated using phantoms, devices that simulated the tissues being images to which the tracer is applied and imaged, with known ground truths, or in turn, with real patient datasets. Moreover, manual tumor delineation has been for many years the solution for physicians, leading to very subjective Gross Tumor Volume (GTV) delineations.

To avoid these factors different image processing algorithms have been employed to solve segmentation tasks of varying complexity and via varying automaticity methods.

Pre-processing of nuclear images has gained relevance in this field in recent years, being a particularly challenging matter in this imaging modality. Pre-processing is tackled in some segmentation contexts described in the literature.

The segmentation step has been explored using: (i) image processing algorithms well established in the literature such as thresholding, active contours, statistical segmentation algorithms, clustering, among others; (ii) learning algorithms that require an adequate image database computationally modelled in a supervised manner.

2.3.1 Thresholding algorithms

Segmentation via thresholding algorithms is intuitively very easily implemented to nuclear image. The higher intensities in nuclear image translate into regions with the highest tracer uptake.
Hence, thresholding of important regions consists of defining specific range of SUV values which characterize the target object, and differentiate it from the background [6].

Thresholding methods have been primarily attempted in a fixed thresholding manner. Relationships between SUV values and peak target object uptakes can be established to derive for instance percental ratios of fixed threshold to detect lung lesions [7]. The authors expose the limitations of conducting threshold estimation using phantom studies, which may not entirely allow interpolations to real medical liver lesions, and loose accuracy when bigger lesion diameters appear, that the diameters tested in the phantom studies. Different fixed values have been proposed at 42 % and 50 % [8] of maximum intensity.

The thresholding may in many cases be estimated analytically, with the result being independent from the tumor to background ratio, and extracted adaptively. In a background subtraction framework, a relative-threshold level (RTL) cab be analytically extracted of the convolution result of the point-spread function, validated with a phantom characterized by varying diameter spheres, and with liver a liver PET scan [9].

Thresholding however, is implemented in this setting upon the assumption of several factors such as: the target object uptakes homogeneously the tracer, the correct boundaries are defined in uniform manner, there is a well-defined interval between the uniform intensities of the target object and the background and the resolution of the object boundaries remain constant.

2.3.2 Image intensity analysis and contour based algorithms

Intensity analysis of image data has been explored recurring several types of data descriptors of the nuclear images. This segment of methods recurs to image gradient computation or texture analysis. One gradient-based algorithm is the watershed algorithm. In this formulation, the gradient image is interpreted as a continuous surface or landscape, in which, mountains of higher gradient magnitude and chains of lower gradient magnitude exist. “Flooding” this surface iteratively, will originate different boundaries which will ignore the chains and delineate the mountains present. Hence, the segmentation process in this setting is originated by finding out the correct level of flooding that captures the boundaries of the target object. Superior performance of this algorithm, compared to standard threshold-based methods, was validated by Blaffert et al. [10].

Contour-based algorithms have also been applied in nuclear image. Among these, active contours, as in other segmentation problems, has been validated for the task of segmentation of nuclear images. Active contours, or “snakes” rely on gradient information to guide the segmentation contour towards boundaries represented in images, which correspond to higher gradient magnitudes. Active contours capability to segment phantom images with various contour
smoothness constraints has been validated extensively by Li et al., using a fixed percental thresholding to initialize the segmentation method followed by an active contour-based segmentation [11]. Although active contours are a well-established segmentation method, many complementary modifications are up until present continuously being proposed. Active contours, as will be detailed in the Methods chapter of this document, are dependant of an energy function which control properties of the moving contour towards image boundaries. Hence, modifications to this energy function, towards the specific challenges of object segmentation in nuclear image, have been proposed by Ballangan et al. [12]. The authors validate the performance of a localized region based active contour segmentation model for tumor delineation, more robust to leakages due to low image resolution.

2.3.3 Region based algorithms

Region growing algorithms have also been explored using its classical implementation or in an adaptive methodology. An adaptive region growing algorithm, locally tuned by mean of intensity values and norm of the intensity gradient was developed for the segmentation of bones in PET images [13].

Image thresholding and region growing methods are the most widely used algorithms due to their implementation simplicity but they lack in robustness on low contrast images and in non-homogenous lesions.

The random walk (RW) algorithm first appeared for computer vision applications and was used later for image segmentation [14]. RW is robust against noise and weak boundaries, a necessary trait due to the low resolution and high noise characteristics of PET images. Finally, Bagci et al. compared RW with two well-known threshold based segmentation methods, FLAB and FCM, and outperformed them [15].

2.3.4 Data learning algorithms

The more recent group of medical image analysis include algorithms derived from learning-based methods of the field of machine learning and data mining. In this setting clustering algorithms are one of the most widely used methods to analyse nuclear image in recent years.

Fuzzy locally adaptive Bayesian (FLAB) uses a Gaussian mixture models to locally adapt to target object. In an unsupervised fashion, this statistical method considers the image as having two hard tissue classes and a finite level of “fuzzy levels”, described by the gaussian distributed mixtures. This method has been validated for nuclear image segmentation [9]. The FLAB
algorithm based on statistical and fuzzy modelling was insensitive to noise and works well for low spatial resolution images. However, the robustness of this method is limited when heterogeneous or high uptake regions occur [5].

More recent methods use well established models such as graph cuts and Markov Random Fields for segmentation purposes. A fuzzy Markov Random Field model was proposed by Guo et al. for lung tumor segmentation [16].
Chapter 3

Methods

Due to the intensive research in this field and the evolution of computing resources, the introduction of 3D advanced computational simulations, 3D models have evolved to more complex and are currently used in other areas such as image segmentation, statistical modelling of medical structures anatomy or surgical planning. The usage of simple intensity based segmentation algorithms were used to iteratively segment and adapt a model into the structures boundaries, called active contours. Novel segmentation algorithms are continuously emerging, since the accurate modelling of these structures is still in development. This technique has proven effective in the segmentation of the heart, which in terms of characteristics of points of analysis of its muscular structure and acquisition qualities and dynamicity, needs to be characterized similarly.

Tumor segmentation through SPECT imaging can be subdivided into two parts: initial tumor recognition and its sequential delineation. Recognition determines the tumor location from other similar regions in the image. Traditionally, experienced clinicians identify the high uptake regions in SPECT images from other normal tissues with high uptake. In many modern algorithms, a rough area of tumor region defined by clinicians is still needed. Subsequently, delineation focuses on drawing a spatial extent of tumor in the area defined by recognition, in order to achieve a precise separation between tumor and background areas. Several difficulties can be encountered throughout the segmentation process. In recognition, whether a high-uptake area represents a tumor or normal tissue is also determined by a clinician’s subjective judgment, i.e., a decision that is dependent on both tumor appearance and clinician experience. On the other hand, in delineation, several factors affect segmentation. First, PET images typically suffer from low resolution and high smoothing factor. What is more, PET image may be further filtered in order to address factors like motion artifacts. Second, tumors have large variations in their shape and texture, and this makes generalizing PET segmentation rules more difficult. Last, the noise in PET is high because the nature of PET itself. As indicated by work [17], noise is considered as the most significant factor affecting segmentation performance. Given the challenges above, several algorithms have emerged to help clinicians in the process. A literature review details them in the following chapter.
3.1 Computational analysis of nuclear image

3.1.1 Active contours

Active contour models (ACM, or simply AC), also known as snakes, consist in curves that evolve towards the direction of certain image features, searched within the neighbour positions of the current position, in the image. The algorithm was firstly described by Kass et al., and have since been applied to multiple segmentation problems. An initial active contour in a given image representation of an object, evolves towards its interior normal direction, and stops when it theoretically finds the object’s boundaries. The snakes notation, considering an image $U$, the segmentation is performed using a contour $c$ that will be iteratively altered in position and conformation. Hence, describing the initial contour as a spline curve $c(s) = (x(s), y(s))$, described by a set of elements $x$ along the contour, and a set of corresponding real boundary edge positions $y$, that vary along the time $s$ between 0 and 1. At each iteration the curve evolves a position of minimization of external constraining forces and internal image force, as follows:

$$E(c) = \alpha \int_0^1 [E_{\text{internal}}(c(s)) + E_{\text{image}}(c(s)) + \lambda E_{\text{external}}(c(s))] \, ds$$

(1)

where $\alpha, \lambda$ and $\beta$ are weighting positive parameters.

The internal energy of the spline $E_{\text{internal}}$, controls and preserves the curve’s mechanical properties and smoothness, describing elasticity and rigidity properties that were incorporated as:

$$E_{\text{internal}} = \left( \frac{\alpha(s)}{2} |c'(s)|^2 + \frac{\beta(s)}{2} |c''(s)|^2 \right)$$

(2)

where the first-order term $c'(s)$, controls the snakes’ cohesion and second-order term $c''(s)$, that controls rigidity of all the points that constitute it.

The second term evaluates the whole image energy, and seeks for specific lines, edges and termination image features, as follows:

$$E_{\text{image}} = w_{\text{line}}E_{\text{line}} + w_{\text{edge}}E_{\text{edge}} + w_{\text{term}}E_{\text{term}}$$

(3)

where $w_{\text{line}}, w_{\text{edge}}, w_{\text{term}}$ control the weighting of the attractiveness of the snake to each of these features individually.

$$E_{\text{line}} = U(x, y)$$

(4)
$E_{\text{edge}} = -|\nabla U(x,y)|$ where $|\nabla U|$ is the gradient of the image $U$. The minimization problem formulated in (1) is minimized when $|\nabla U|$ is maximized, working as an edge-detector.

Line terminations are sought among the curvature of level lines of the contour found at each iteration, and requires Gaussian smoothing.

$$E_{\text{term}} = \frac{\partial \theta}{\partial n} = \frac{\partial^2 c}{\partial n^2} = \frac{c_{yy}c_{xx}^2 - 2c_{yy}c_{cx}c_{xy} + c_{xx}c_{yy}^2}{(c_{xx}^2 + c_{yy}^2)^{3/2}}$$  \hspace{1cm} (5)

The external energy $E_{\text{external}}$ may or may not be imposed in active contours. The third term, is the one that is dependant of image features. In the classical implementation of Kass et al. this term would consist on edge information extracted using image gradient calculation as follows:

$$E_{\text{external}} = E_{\text{distance}}(c(s)) + E_{\text{pressure}}(c(s))$$  \hspace{1cm} (6)

where $E_{\text{distance}}$ controls a distance energy of the current snake contour points to the centroid of the initial contour centroid, given by:

$$E_{\text{distance}}(c(s)) = \|x_g - c_k\|$$  \hspace{1cm} (7)

avoiding contour leakage.

On its turn, $E_{\text{pressure}}$ is given by:

$$E_{\text{pressure}}(c(s)) = -\frac{\rho}{2} \mathcal{P}(U(x,y))$$  \hspace{1cm} (8)

where a linear pressure $\mathcal{P}$ interferes with the spline linear stability:

$$\mathcal{P}(U(x,y)) = 1 - \frac{|U(x,y) - \mu|}{k\sigma}$$  \hspace{1cm} (9)

In this expression $k$ weights the image influence, and $\mu$ and $\sigma$ act statistical properties of the snake contour. In synthesis, active contours’ energy calculation consists in a combination $E_{\text{image}}$ and $E_{\text{internal}}$. $E_{\text{image}}$ infers the snake progression, a weighted energy balance between edge energy and other image feature, progressing to the minimization state that occurs upon the evolution to high gradient magnitude boundary features in the image.

Active contours have suffered further improvements of several authors, from which the most significant contributions will be described in the following subsections.
3.1.2 Edge-less active contours – Chan-Vese algorithm

Chan and Vese proposed in 2001, a major contribution to the image segmentation field [18]. The algorithm encompassed the level-set curve evolution and followed a fitting logic that did not take into account the edge image data. The main approach, similarly to the classical active contour algorithm, is based on an image energy function minimization. In turn, the energy function to be minimized analysis the mean intensities inside and outside the contour being fitted, hence, partitioning the image into two regions, assumed as foreground and background.

Chan-Vese algorithm is formulated as follows:

\[ E = F_1(c) + F_2(c) \]
\[ \Leftrightarrow \lambda_1 \int_{\text{inside}(C)} |U(x,y) - c_1|^2 \, dx \, dy + \lambda_2 \int_{\text{outside}(C)} |U(x,y) - c_2|^2 \, dx \, dy \]  \hspace{1cm} (10)

where \( c_1 \) and \( c_2 \) are the mean pixel intensities inside and outside of contour \( C \), on the image \( U \), and \( \lambda_1 \) and \( \lambda_2 \) are control weights of each energy functional.

To this, regularization of terms intended to be minimized were added by the authors, namely the contour \( C \) length and area inside the contour:

\[ E(C, c_1, c_2) = \mu \cdot \text{length}(C) + v \cdot \text{Area(inside}(C)) \]
\[ + \lambda_1 \int_{\text{inside}(C)} |U(x,y) - c_1|^2 \, dx \, dy + \lambda_2 \int_{\text{outside}(C)} |U(x,y) - c_2|^2 \, dx \, dy \]  \hspace{1cm} (11)

where \( \mu, v \) are control weights of each energy functional. Hence the minimization is performed towards \( c_1 \) and \( c_2 \), and considers the contour as a zero level-set Lipschitz function \( \phi \), whose zeros define the contour \( C \) mask. Hence, the solution to \( C \) is given by \( \phi \), making appropriate use of the known Heaviside function, and the Dirac measure:

\[ H(z) = \begin{cases} 1, \text{if } z \geq 0 \\ 0, \text{if } z < 0 \end{cases} \]
\[ \delta(z) = \frac{d}{dz} H(z) \]  \hspace{1cm} (12)

This notation is transposed and formulated as the level-set set curve \( \phi \) which evolves to the normal direction \( \vec{n} \) as:

\[ \frac{\partial \phi}{\partial t} = \delta \phi \left[ \mu \cdot \text{div} \left( \frac{\nabla \phi}{|\nabla \phi|} \right) - v - \lambda_1 (u_0(x,y) - c_1)^2 + \lambda_2 (u_0(x,y) - c_2)^2 \right], \frac{\partial \phi}{\partial \vec{n}} = 0 \]  \hspace{1cm} (13)

The dynamic mean intensities calculations in each image region \( \Omega \) inside and outside of the level-set:
\[
\begin{align*}
\text{c1} &= \int_{\Omega} u_0(x,y)H(\phi(x,y))dxdy \quad \text{if} \quad \int_{\Omega} H(\phi(x,y))dxdy > 0 \quad (14) \\
\text{c2} &= \int_{\Omega} u_0(x,y)(1-H(\phi(x,y)))dxdy \quad \text{if} \quad \int_{\Omega} 1-H(\phi(x,y))dxdy > 0 \quad (15)
\end{align*}
\]

Hence, the length \((C)\) and area \((C_{\text{inside}})\), are the computation of dirac measure of \(\phi = 0\) and the integral Heaviside function of \(\phi \geq 0\) of \(\Omega_{\text{inside}}\).

\[
E(C, c_1, c_2) = \mu \int_{\Omega}^{\phi=0} |\nabla H(\phi(x,y))|dxdy + \nu \int_{\Omega}^{\phi \geq 0} H(\phi(x,y))dxdy + \lambda_1 \int_{\text{inside}(C)} |U(x,y) - c_1|^2dxdy + \lambda_2 \int_{\text{outside}(C)} |U(x,y) - c_2|^2dxdy \quad (16)
\]

In this setting, it is intended to minimize the distance of the image intensities inside and outside the contour, to their corresponding mean intensities. Thus, curve evolution assumes that the background and foreground have two distinct mean values, where when \(F_1(c) > 0\) and \(F_2(c) \approx 0\), the contour is presumably outside of the object, and accordingly, when \(F_1(c) \approx 0\) and \(F_2(c) > 0\), the contour is presumably located inside the object. When both \(F_1(c) \approx 0\) and \(F_2(c) \approx 0\) the energy functional is minimized, and the distances to the mean are residual.

### 3.1.3 Markov Random Field clustering

The segmentation problem presented, consists in a statistical approach used for pixel labelling problems as an undirected graphical model, named Markov Random Field (MRF). In this problem’s setting, the initial labelling of the images needed to be carried out by a previous clustering step, namely a k-means clustering based on the grey-level intensities of pixels. The model MAP-MRF (Maximum a Posteriori – Markov Random Fields) to segment background, white and grey matter required thus, a \(k = 3\) clustering. The probabilistic problem can be formulated considering an image \(y\) of \(N\times M\) dimension, where each \(y_i\) represented the pixel intensity, and the inference target is the set of label configurations of \(x = (x_1 \ldots x_{NM})\), with \(x_i \in L\) and \(L\) being the set of possible labels, in this case, and all possible labelings are \(L_{NM}\). A probabilistic approach can optimize the parameters \(x\) given the set of observed features \(y\), which in this setting consists of an optimization using Expectation Maximization (EM). Thus, following a Maximum a Posterior criterion, the set of output \(x^*\) labels is found through:

\[
x^* = \arg\max_x \{P(x|y, \theta)\} \quad (17)
\]

This problem, formulated by Bayes Theorem is solved as:
\[ P(x|y, \theta) \propto P(y|x, \theta)P(x) \quad (18) \]

And the MAP problem is in fact formulated as:

\[ x^* = \arg\max_x \{ P(y|x, \theta)P(x) \} \quad (19) \]

The model is dependant of the parameter \( \theta = \{ \theta_l | l \} \) optimized by Expectation Maximization algorithm, whereas, the prior probability \( P(x) \) represented a Gibbs distribution and the point probability \( P(y|x, \theta) \) is given by:

\[ P(y|x, \theta) = \prod_i P(y_i|x, \theta) = \prod_i P(y_i|x_i, \theta_{x_i}) \quad (20) \]

representing a Gaussian distribution.

Considering each possible labelling combination \( X \), as a random field, it can be modelled in this setting as:

\[ x \in L: P(X = x) > 0 \quad (21) \]

The basic principle from the probabilistic estimation of every labelling sequence consists in a homogeneity analysis of the 1st and 2nd order neighbours, whose probabilistic consistency is modelled as:

\[ P(x_s|x_r, r \neq s) = P(x_s|x_r, r \in N_s) \quad (22) \]

where \( N_s \) is a neighbour patch centred in each pixel \( x_r \), whose pair relationships are hence 1st and 2nd clique potentials \( c \in C \). Defining the MRF based on a clique theory and Gibbs distribution of \( P(x) \):

\[ P(x) = \frac{1}{Z} \exp(-\sum_{c \in C} V_c(x)), Z = \exp(-U(x)) = \exp(-\sum_{c \in C} V_c(x)) \quad (23) \]

Representing the sum of all potentials \( c \) and corresponding label configuration \( x \).

Transposing this notation into the image segmentation problem, the Guassian distribution is assumed for each class distribution:

\[ P(y_s|x_s) = \frac{1}{\sqrt{2\pi\sigma_{x_s}}} \exp\left(\frac{y_s-\mu_{x_s}}{2\sigma_{x_s}^2}\right) \quad (24) \]

The Gibbs distribution of \( P(x) \):

\[ P(x) = \frac{1}{Z} \exp(-\sum_{c \in C} V_c(x)) \quad (25) \]
\[
U(x) = \sum_s \log\left(\sqrt{2\pi\sigma_s} \right) \exp\left(\frac{y_s - \mu_s}{2\sigma_s^2} \right) + \sum_{s,r} \beta \delta(x_s, x_r) \tag{26}
\]

The 1st order neighbours are proportional to the simple likelihood of \( x \): \( \log(P(y_s|x_s)) \) and the 2nd order neighbours favour similarities towards the central pixel as:

\[
V_{c_2}(i,j) = \beta \delta(x_s, x_r) = \begin{cases} 
-\beta, & \text{if } x_i = x_r \\
\beta, & \text{if } x_i \neq x_r 
\end{cases}
\tag{27}
\]

In this setting \( \beta \) becomes a model parameter which that increases proportionally to patch region homogeneity.

The MAP -MRF problem becomes:

\[
\hat{x}_{MAP}^* = \arg\max_x (x|y) = \arg\min_x U(x) \tag{28}
\]

Finally, the minimization problem is formulated as an EM parameter estimation, allowing the estimation of parameters based on initial label distribution, followed by new label assignment based on parameter distribution fitting to a mixture of Gaussians model:

**Expectation step:**
\[
x_r = P(x_r|y_s) = \frac{p(y_s|x_r)p(x_r)}{\sum_{x \in L} p(y_s|x_r)p(x_r)} \tag{29}
\]

**Maximization step:**
\[
P(x_r) = \frac{p(x_r|y_s)}{|S|}, \mu_{x_r} = \frac{\Sigma_{S} p(x_r|y_s)y_s}{\Sigma_{S} p(x_r|y_s)} \tag{30}
\]

Hence, the MAP problem in this setting, consists in the minimization of \( U(x) \), and the free parameter \( \beta \) adjusts sensitivity for intensity difference. This method incorporates spatial correlation information to model spatial relations that exist in the neighbourhood of pixels.
Chapter 4

Experiments

4.1 Overview

In this work the study and implementation of two research techniques was evaluated. The development of two types of segmentation algorithms will be exposed, including the final segmentation algorithm, as well as the evaluation of their performances.

In this setting, upon the careful analysis of the literature, two methods of nuclear image segmentation were selected. Considering that the PhD nuclear image dataset is not yet available, the experiments carried out were focused into the segmentation of cerebral nuclear image.

The segmentation problem consisted in the segmentation of brain tissues from PET image data. A database of 10 brain PET/CT scans, conceded by the medical group partner in the development of the PhD project, was used.

In PET-CT brain images, a large portion of voxels are from background and non-brain regions, including air, the scanner bed, non-brain tissues and the skull. Since these regions are irrelevant to our brain segmentation task, excluding them from the segmentation process can potentially reduce the complexity of the proposed algorithm. The segmentation of brain regions is in many cases carried by PET/MRI acquisitions, given that the MRI provides superior brain tissue contrast. However, in the absence of such images, physicians have in many cases to extract information from PET/CT images. The final goal is to read SUV measurements from different brain regions. These evaluations are carried out using brain statistical maps publicly available online. Brain statistical maps provide grey and white matter brain maps, which can be co-registered to image segmentation of these tissues. Having this registration, the final registration of the complete brain region map can be carried via the same transformation.

These methods were tested on a set of 10 image stacks from different patients, consisting in 35 image slices, each, obtained with a GE fifth generation equipment.
4.2 Aims/Objectives

This image collection poses an interesting challenge, and the framework proposed in this document may enhance the processes carried out by physicians in the evaluation of brain PET images. The SUV values measurements, are carried out via manual alignment of the brain maps and images. The development of computational algorithms and tools will intuitively enhance these tasks. The challenges in these types of images consists in the poor image quality and resolution. Moreover, due to the lack of ground truth segmentations the performance evaluation was performed towards the brain tissue probability maps. Specifically, the LONI Probabilistic Brain Atlas (LPBA40), used in this work, is obtained by averaging of 40 MRI scans manually delineated, covering 56 structures in the brain [19].

Figure 1- Examples of three image slices from a given patient (1st column: 10th slice; 2nd column: 15th slice; 3rd row: 17th slice).
Chapter 5

Results

Some relevant sample results of the application of the algorithms developed to segment the brain tissues in PET images are presented. The different stages of the algorithm developed can be evaluated in the scheme represented in Figure 2.

![Scheme of the outline of the algorithms developed in this framework.](image)

Figure 2 - Scheme of the outline of the algorithms developed in this framework.

5.1 Pre-Processing

Regarding the pre-processing steps of eliminating the skull from the images and denoising, the results obtained will be presented. The images were pre-processed using, contrast-limited adaptive histogram equalization, and a median filter, to increase the contrast in the image, and reduce noise, while maintaining the definition of the edges and lines.

A Region Growing mask was developed for each image slice eliminating the present background noise and intensity inconsistencies. Finally, a non-local means (NLM) denoising
algorithm was applied to eliminate the Poissonian noise present in nuclear images. Median non-local means filtering (MNLM) was introduced by Chan et al [17]. In this work, the NLM algorithm is tailored to tackle severe noise in low SNR images, such as PET’s, analysing the ineffectiveness of Euclidean norm for noise that follows a significantly biased distribution.

Analysing the denoising algorithm results, presented in Figure 3, the denoising algorithm reveals efficient for the present noise removal in the images. The algorithm removes a visible amount of present noise, and preserves the image contrast present between the grey and white matter, conferring it an added boundary homogeneity, relatively to the original image. The skull removal step is carried by the region growing algorithm of the image background, and was efficient in all images of the dataset for this task.

This step was fundamental for the elimination of problems in the segmentation of both algorithms tested. The level-set contours produced by the Chan-Vese algorithm could possibly be attracted to the boundaries of the skull bone, or the MRF segmentation could consider the skull boundary and skull-brain air space as an individual cluster region.

Regarding the computational cost of this processing step, the NLM algorithm represents the step with highest processing time. The algorithm implemented is modified from its classical implementation, including steps for computational cost reduction, such as voxel pre-selection and a weighted average distance estimations, to reduce the number of calculations necessary for the proper function of the algorithm. The results of NLM algorithm present fairly good results in the denoising of several medical images, having the main drawback of its computational cost.

### 5.2 Brain tissue segmentation

Given the results obtained from the segmentation using the Chan-Vese method, some of the most relevant results are presented in Figure 4. The algorithm uses as initial contour a canny edge derived from the background elimination mask produced in the pre-processing step. Hence

![Figure 3 - The 19th plane of the tomographic image used is presented (left), corresponding denoising algorithm result via MNLM is presented (centre), CLAHE+RG+MNLM algorithm results (right).](image-url)
the initial contour is placed in the outer boundary of the grey matter. A maximum of 200 iterations were sufficient for the algorithm to reach convergence. The level-set formulation of Chan-Vese further carries out an inward search and divides into two contour with different level-set index, providing hence the discrimination between the two regions automatically.

![Figure 4](image)

Figure 4 - Examples of three image slices from a given patient (1st column: 10th slice; 2nd column: 15th slice; 3rd row: 17th slice). White matter segmentation represented in white and grey matter segmentation represented in black.

The tracer specificity for brain processing of glucose, is represented in the images with higher intensities in the brain regions only, ignoring other head and neck regions that are eliminated due to the lack of tracer uptake. This can be verified on the left column of Figure 4. Moreover, one of the most challenging regions to segment and distinguish in these images is the caudate regions inside the white matter, which may in some slices not be very precise, depending on the intensity contrast. This difference is observable comparing the centre and right columns of figure 4.

Given the results obtained from the segmentation using the MAP-MRF method, some of the most relevant results are presented in Figure 5. The MAP-MRF algorithm requires an initial distribution of the pixel labels, which was carried using k-means. For the purposes of this work,
the segmentation of brain tissues was initiated with k=3 regions, of white matter, grey matter and background intensities.

5.3 Quantitative performance analysis

The brain tissue and brain region maps map retrieved from the LPBA-40 map, is represented in Figure 7, 1st column. Next, the two segmentation algorithms were compared with the brain tissue map provided from the LBPA-40 map. This quantitative analysis, is not performed with real ground truth as would have been possible with phantom PET data, or with PET/MRI images. However, the comparisons to a brain tissue map that represents the mean shape of 40 human brains, allows to quantitatively analyse the segmentations obtained relatively to this mean. The performance of these algorithms was assessed with the overlapping area of the segmentation results and the atlas, which was quantitatively measured by the Dice similarity coefficient (DSC).

\[ DSC = \frac{A_{seg} \cap A_{atlas}}{|A_{seg}| + |A_{atlas}|} \]

Better segmentation results are indicated by a higher DSC value, i.e., closer to one.
Brain atlases are built from one or more representations of brain. They describe one or more aspects of brain structure and/or function and their relationships after applying appropriate registration and warping strategies. Having both grey and white matter segmentations, the registration of the segmented volume is co-registered to the LPBA-40 brain tissue map.

This step has the objective of transforming the individual image volume into correspondence with the atlas, and a common coordinate system enables the pooling of activation data and multi-subject comparisons.

A rigid followed by an affine image registration was carried out to co-register the segmented volumes with individual tissue maps. These transforms were saved and further used to co-register to brain region maps to the target volume. The co-registered map is a labeled pixeled volume corresponding to each of the 56 brain regions.

The registration results are presented in Figure 7.

The co-registration of the brain region atlases allowed the calculation of mean SUV values for each individual brain regions. Exemplary SUV distributions among brain regions is presented in Figure 8. SUV measurements obtained from one subject PET volume with the brain region atlas are presented in Table 1.
Figure 7 – Grey matter brain map volume and co-registered brain region maps of the 18th slice (1st column), pair of map and segmentation volume (2nd column), and co-registered brain region atlas (3rd column).
Table 1. Brain region SUV measurements from the map registrations obtained after the segmentation with Cha-Vese (CV) and MAP-MRF (MRF) algorithms.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>SUV CV</th>
<th>SUV MRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>L lateral orbitofrontal</td>
<td>3.33467</td>
<td>3.152035</td>
</tr>
<tr>
<td>R lateral orbitofrontal</td>
<td>3.358488</td>
<td>2.929666</td>
</tr>
<tr>
<td>L gyrus rectus</td>
<td>3.328654</td>
<td>3.093386</td>
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<tr>
<td>R gyrus rectus</td>
<td>3.382498</td>
<td>3.089232</td>
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<tr>
<td>L postcentral gyrus</td>
<td>3.187167</td>
<td>3.575152</td>
</tr>
<tr>
<td>R postcentral gyrus</td>
<td>3.2296</td>
<td>3.096463</td>
</tr>
<tr>
<td>L superior parietal</td>
<td>3.322154</td>
<td>3.353617</td>
</tr>
<tr>
<td>R superior parietal</td>
<td>3.26969</td>
<td>3.020091</td>
</tr>
<tr>
<td>L supramarginal gyrus</td>
<td>3.169566</td>
<td>3.439798</td>
</tr>
<tr>
<td>R supramarginal gyrus</td>
<td>3.105277</td>
<td>3.01354</td>
</tr>
<tr>
<td>L angular gyrus</td>
<td>3.156964</td>
<td>3.22182</td>
</tr>
<tr>
<td>R angular gyrus</td>
<td>3.066221</td>
<td>2.902537</td>
</tr>
<tr>
<td>L precuneus</td>
<td>3.288369</td>
<td>3.190209</td>
</tr>
<tr>
<td>R precuneus</td>
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<tr>
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<td>3.399986</td>
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<td>R fusiform gyrus</td>
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<td>3.406192</td>
</tr>
<tr>
<td>R insular cortex</td>
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<td>3.393516</td>
</tr>
<tr>
<td>Structure</td>
<td>X Coordinate</td>
<td>Y Coordinate</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>L cingulate gyrus</td>
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</tbody>
</table>
Chapter 6

Discussion

The white and grey matter tissue is vital to understanding connectivity, changes in disease and age in the brain, but researchers are still in need of an effective way to represent and compare the tissue across a population of subjects.

Through the analysis of the results obtained with MRP-MRF and with the Chan-Vese method, it was possible to understand the capabilities, specificities and applicability of each in the particular case of the segmentation of brain tissues in PET image data.

Although snakes have the potential to provide smooth and adequate segmentation, without suffering very much from noise or other variations in intensity inconsistencies, they are also very prone to be influenced by high gradient magnitudes in the neighbourhood of the bladder wall and fail the segmentation. Hence, one of the algorithm chosen for the development of this work was the Chan-Vese method, which tries to unite the region intensity information of Region Growing with the regularization of the snakes, and avoiding the edge dependency of the latter, represents a major contribution in medical image analysis, representing good results in the combination of these two features.

On its turn, a clustering algorithm with a labelling routine based on machine learning, and classification methods would be fitted for this segmentation task. Hence the MAP-MRF algorithm was chosen for the development of this work, to analyse how it deals with the image noise present in PET images. MAP-MRF combines the Markov random field (MRF) theory with statistical decision and the maximum a posteriori (MAP) estimation.

Analysing both segmentation results, it is possible to observe that both segmentation algorithms were able to segment the two regions under study. Through visual inspection of the results it is possible to discern that the Chan-Vese algorithm provides a superior accuracy in finding the grey matter boundaries that MAP-MRF algorithm. MAP-MRF algorithm inspects neighbouring pixels and produces rougher segmentation, less sensitive to sudden variations in the boundaries of the tissues. This performance evaluation is confirmed evaluating the overall. quantitative performance, whereas the dice coefficient is higher in most slices for the Chan-Vese segmentations.
Moreover, the segmentation results can be compared with those of Xia et al. [20]. The authors use MAP-MRF segmentation and obtain similar DSC results ranging between 0.6 and 0.8.

Finally the registration step has allowed the mapping of brain regions, and achieved its best results using a rigid registration to rescale and align the gross brain volume, followed by an affine registration which mapped further intensity matches between both volumes. From the results presented in Table 1 for one subject, it is possible to observe that the different segmentations originated differences in the final SUV measurements. The accuracy of these measurements is of high importance in these studies.

The development of these algorithm has allowed the exploration of segmentation techniques, registration, and organ parametric maps, used in the literature for PET image.

It was also possible to comprehend the behaviour of the noise present in nuclear images and moreover, how it effects the segmentation task.
References


