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A smart and operator independent system to delineate tumours in Positron Emission Tomography scans

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ABSTRACT

Positron Emission Tomography (PET) imaging has an enormous potential to improve radiation therapy treatment planning offering complementary functional information with respect to other anatomical imaging approaches.

The aim of this study is to develop an operator independent, reliable, and clinically feasible system for biological tumour volume delineation from PET images. Under this design hypothesis, we combine several known approaches in an original way to deploy a system with a high level of automation.

The proposed system automatically identifies the optimal region of interest around the tumour and performs a slice-by-slice marching local active contour segmentation. It automatically stops when a "cancer-free" slice is identified. User intervention is limited at drawing an initial rough contour around the cancer region. By design, the algorithm performs the segmentation minimizing any dependence from the initial input, so that the final result is extremely repeatable.

To assess the performances under different conditions, our system is evaluated on a dataset comprising five synthetic experiments and fifty oncological lesions located in different anatomical regions (i.e. lung, head and neck, and brain) using PET studies with 18F-fluoro-2-deoxy-*d*-glucose and 11C-labeled Methionine radio-tracers.

Results on synthetic lesions demonstrate enhanced performances when compared against the most common PET segmentation methods. In clinical cases, the proposed system produces accurate segmentations (average dice similarity coefficient: 85.36 ± 2.94%, 85.98 ± 3.40%, 88.02 ± 2.75% in the lung, head and neck, and brain district, respectively) with high agreement with the gold standard (determination coefficient $R^2 = 0.98$). We believe that the proposed system could be efficiently used in the everyday clinical routine as a medical decision tool, and to provide the clinicians with additional information, derived from PET, which can be of use in radiation therapy, treatment, and planning.

1. Introduction

Positron Emission Tomography (PET) is a non-invasive medical imaging technique which has the advantage over other anatomical imaging techniques, such as Computerized Tomography (CT) and Magnetic Resonance (MR) of providing direct information about patient's functional processes. Metabolic indicators, and in general parameters derived from PET imaging, might be predictive of patient therapy response to the pharmacological treatment of cancer [1] and are useful in obtaining an objective evaluation of the changes in the patient condition [2,3]. As a matter of fact, metabolic parameters are often faster changing and more indicative of therapy effects than morphological changes [2]. PET imaging possesses an enormous potential to improve clinical cancer treatment decision making [4]. For this reason, PET imaging is being increasingly considered for the quantitative assessment of individual response to therapy and for clinical testing of novel cancer therapy protocols. In this context, the first parameter historically introduced, the Standardized Uptake Value (SUV) provides punctual information about the investigated tissue and has gained a central role in PET studies [5]. Unfortunately, SUV alone

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does not provide any information about lesion volume and consequently additional quantitative indices have been introduced, such as the biological tumour volume (BTV) and the tumour lesion glycolysis (TLG) [6,7]. TLG, in particular, is obtained as the product of the SUV with the BTV and provides both volumetric and metabolic information. Therefore, for efficient identification of the TGL, and to obtain accurate and reproducible PET parameters, it is of utmost importance to employ a reliable BTV segmentation strategy.

In addition, quantitative analysis of cancer tissues in PET is a crucial step towards precise radiation therapy treatment planning. To date, MR plays a key role in radiation therapy planning, providing several advantages over CT including high quality detailed images, and excellent soft-tissue contrast. Conversely, CT attenuation maps convey a fundamental source of geometric information which is not available in MR, where image distortion could be produced by static magnetic field non-uniformities [8]. Inclusion of PET in radiotherapy protocols can provide additional information to target the oncological lesion even more efficiently [9]. Accurate BTV definition is essential for escalating the radiation dose without increasing normal tissue injury, and may be used for enhanced dose delivery to the target, in turn improving the Radiation Treatment Planning (RTP) [10]. Nevertheless, the BTV segmentation in PET images is a precarious task both because of their typically low resolution and the relatively high level of noise [11,12]. Further, results strongly depend on the algorithm used [13]. The choice of a standard method for BTV contouring is still a challenging and debated issue, so that manual contouring is still typically adopted in clinical practice. Of course, manual contouring depends on the operator expertise and clinical specialization. It is also extremely time-expensive because dozens of slices must be inspected. To date, several automatic or semi-automatic PET segmentation methods have been proposed [13–15]. A brief overview of the state-of-the-art is reported in Section 1.1. In general, the level of performance imposed by the everyday clinical routine, makes properties such as repeatability (i.e. the result should be operator independent), and a real-time data processing workflow not only desirable, but necessary.

In the proposed study, we focus on the uptake of 18F-fluoro-2-deoxy-*d*-glucose (FDG) and 11C-labeled Methionine (MET) to establish an innovative segmentation system and assess its performances under different conditions in the clinical environment. The use of FDG for oncology imaging accounts for approximately 90% of all PET imaging procedures. When compared with its neighbouring normal tissue, a pathological mass presents an increased adsorption of FDG (which is an analogue of glucose). By this mechanism, a new characterization of the oncological diseases is possible, thereby opening new opportunities for a patient-customized approach to diagnosis and therapy. However, FDG is not an efficient radio-tracer when the body district of interest presents highly active metabolic activity and a different radio-tracer must be used. A typical example is the brain, where high uptake of glucose is a normal condition. It has been reported that the extent of tumour cell invasion in brain metastases can be detected by MET PET even more clearly than by CT or MRI [16,17]. For this reason, we considered MET as an alternative radio-tracer.

The present study tackles the volume reconstruction challenge using SUV. We combined several known approaches in an original way to devise a system with a high level of automation. Reconstruction is started by creating an optimal initial mask on an automatically identified slice. The mask is evolved into an optimal contour which is then propagated to the neighbouring layers using a slice-by-slice marching approach. Finally, volume reconstruction is automatically stopped when a suitable stopping condition is met. This latter feature represents a key point toward the automatic and operator independent BTV segmentation. To assess the performance of the present system and to investigate the reliability and repeatability of the results, we performed comparative tests with other methods. To do so, we used both body phantoms containing objects of known a-priori volume and shape, and fifty tumours located at various anatomical districts (i.e. lung, head and neck, and brain) and different PET radio-tracers.

The article is organized as follows: Section 2 describes the proposed segmentation system and the framework used to assess the system performance. The dataset used for the system evaluation is described in Section 3, test results are shown in Section 4, while discussion and conclusions are provided in Sections 5 and 6, respectively.

1.1. Background

A huge number of PET segmentation methods are present in the literature. Among others, thresholding [18,19] and region growing (RG) [20] methods are the most widely adopted, especially because they are simple to implement. Unfortunately, they show a drop in performance when low contrast, and heterogeneous cancer regions are considered [14,21]. Indeed, segmentations of small or non-spherical tumours are often below the expectations [22]. The new adaptive RG algorithm [23] repeatedly applies a confidence connected RG algorithm with an increasing relaxing factor *f*. A maximum curvature strategy is used to automatically identify the optimal *f*-value. This algorithm, in the case of relatively homogeneous background, results robust to parameter settings and region of interest selection, without scanner, imaging protocol, or tumour dependencies.

Variational approaches based on gradient differences between healthy and cancer tissues are mathematically efficient but sensitive to noise and subject to numerical fluctuation [24,25]. Learning methods, such as artificial neural networks [26], and support vector machines [27] are efficient, but the training of such algorithms usually requires large and diversified databases. Fuzzy C-Means (FCM) [28] is extensively used in PET image delineation for the fuzzy nature of the lesion contours. The FCM reveals accurate for large targets of simple shape, while lesions of complex shape are not easily managed [29]. Affinity propagation [30] considers multi-focal radiotracer uptake patterns, but so far it has been proved a viable solution only in animal studies. Stochastic models, such as Gaussian mixture model, based on statistical differences in intensity distribution between foreground and background can be considered optimal for noisy images, provided that a proper noise model is used [31–33]. The latter approaches have been tested on simulated studies or on a few patient studies where the ground truth is defined manually by a nuclear medicine expert. In active contour (AC) algorithms, an initial contour around the target deforms and moves towards the target edges. This deformation is handled by minimizing what is termed as the energy function. Li et al. [34] used RG as a pre-processing step to optimize the AC's initial contour. Unfortunately, the result tended to overestimate the tumour volume [23]. Similarly, ACs can be found combined with anisotropic diffusion filtering, followed by a multi-resolution contourlet transform [35]. However, the latter approach main limitation is a heavy dependence on user-defined parameters. In order to improve delineation accuracy, histogram FCM clustering and textural information were used to constrain the AC [36]. The method however proved to suffers in presence of nearby high physiologic uptake and was susceptible to initial cropping area. Graph-based approaches yield efficient segmentation by using foreground and background seeds to locate different tissues [37]. However, while seed identification can be automated (e.g. Ref. [29]), normal anatomical structures (i.e. brain, heart, bladder, and kidneys) are prone to be mistakenly identified as initial target seeds, giving misleading guidance to the segmentation process [38,39].

Alternative studies exist which tackle the challenge of automatically discriminating between normal and pathological tissues in PET. Unfortunately, a full comparison of such algorithms is not possible as the relative studies often concern different body district and specific types of abnormality, e.g., lung tumours [40–42], oesophageal tumours [43], and nasopharyngeal tumours [44]. Studies on discrimination of pathological structures in whole-body PET have been conducted as