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A segmentation framework towards automatic generation of boost subvolumes for FDG-PET tumors: a digital phantom study

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Abstract

Potential benefits of administering nonuniform radiation dose to heterogeneous tumors imaged with FDG-PET have been widely demonstrated; whereas the number of discrete dose levels to be utilized and corresponding locations for prescription inside tumors vary significantly with current existing methods. In this paper, an automated and unsupervised segmentation framework constituted mainly by an image restoration mechanism based on variational decomposition and a voxel clustering scheme based on spectral clustering was presented towards partitioning FDG-PET imaged tumors into subvolumes characterized with the total intra-subvolume activity similarity and the total inter-subvolume activity dissimilarity being simultaneously maximized. Experiments to evaluate the proposed system were carried out with using FDG-PET data generated from a digital phantom that employed SimSET (Simulation System for Emission Tomography) to simulate PET acquisition of tumors. The obtained results show the feasibility of the proposed system in dividing FDG-PET imaged tumor volumes into subvolumes with intratumoral heterogeneity being properly characterized, irrespective of variation in tumor morphology as well as diversity in intratumoral heterogeneity pattern.

Keywords

FDG-PET; intratumoral heterogeneity; variational decomposition; spectral clustering

1. Introduction

As a functional image modality capable of providing information pertaining to tumor metabolism, hypoxia, proliferation, along with other physiologic characteristics, positron emission tomography (PET) with ¹⁸F fluorodeoxyglucose (FDG) has been widely used in the field of radiation oncology ranging from detecting and staging malignant tumors to monitoring treatment response to discriminating malignant lesion from benign lesions [1, 2]. Lately, ¹⁸F-FDG PET has also been gaining ground in radiation therapy [3, 4]. With furnishing added values on functional variation within tumors, FDG-PET renders the

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possibility for radiotherapy planning to prescribe and deliver of a nonuniform dose to the clinical target tumor volume. The potential benefits of prescribing nonuniform radiation dose for heterogeneous tumors have been widely demonstrated [4, 5]. Two prototypical strategies have been considered for nonuniform dose prescription: subvolume boosting [6] and dose painting [7]. In the former an imaging-defined boost subvolume is administered with an additional radiation dose, while in the latter dose prescription is generated at the voxel level and the dose plan optimizer is employed to obtain a physically deliverable dose distribution which approximates the optimal dose distribution. More commonly in practices, a tradeoff strategy is used in which the target is divided into a small number of subvolumes with each prescribed a distinct dose [4, 6]. However, the number of subvolumes and tumor voxels contained in different subvolumes vary significantly [8, 9]. The aim of this work was to introduce an image-based framework to automatically derive the number of the boost subvolumes along with their belonging voxels.

The presented framework incorporates a restoration process stemming from variation decomposition and a segmentation process based on spectral clustering. An overview of this image processing framework is shown in Figure 1 and it includes four phases: Phase I: the pre-processing phase, Phase II: the restoration phase, Phase III: the segmentation phase, and Phase IV: the post-processing phase. In the pre-processing phase, the tumor on each PET image is first isolated within an image volume, followed with applying a binary mask delineating the tumor to filter this volume. With applying such a binary mask to the image volume, only image content inside the tumor is retained and all the background content is filtered out. The second phase involves restoring the resultant image volumes. Restorations are carried out with a variational decomposition model [10] that decomposes an image into two independent components, with one comprising the desired restored image and the other the remaining unwanted portion of the image featured with highly oscillatory content. The resultant restored images are then used by the third phase for intratumoral volume partitioning. The third phase starts with constructing a graph representation for the voxels inside a tumor, followed with applying a spectral clustering algorithm to automatically group the intratumoral voxels into distinct clusters according to pairwise similarity measures. Finally, in the post-processing phase, an island removal morphological operation is applied to the segmentation maps generated from phase III to further refine the results.

The rest of this paper is organized as follows. Section 2 first presents the proposed intratumoral segmentation framework with three subsections to describe the main processes: restoration with variational decomposition, segmentation with spectral clustering, and refinement with morphological operations, followed by a subsection to describe the generation of simulated PET data. Segmentation results on the simulated PET data, along with an appraisal of the restoration performance, is presented in Section 3. Section 4 presents a discussion of the current work and finally Section 5 concludes the paper.

2. Methods

2.1. PET image restoration with variational decomposition

Due to the ill-posed nature of the reconstruction process, PET images produced are highly noisy and blurred [11]. The identified tumor volumes therefore first underwent a restoration process to enhance the image features and reduce the noise. In this study, the image restoration was performed with a variational decomposition model [10], which decomposes the image being restored (f) into two independent components (u, v) with u containing the desired restored image, which typically reveals a blocky structure and is often referred to as the cartoon part of the decomposition, and v comprising the highly oscillatory contents of the original image, which is considered noise and is often referred to as the difference

image. With the assumption that u lies in the Besov space $(B_1^{1,1})$ and v in the $H^{-\beta}$ space [12], the decomposition model can be formulated as follows:

$$\tilde{u} = \arg \min_{u \in B_1^{1,1}} \{ \|f - (u+v)\|_{L^2}^2 + \gamma \|v\|_{H^{-\beta}}^2 + 2\alpha \|u\|_{B_1^{1,1}} \}, \quad (1)$$

where $\tilde{u}$ is the near optimal solution for the desired restored image, $\|\cdot\|_{L^2}$ is the norm in the L^2 space, $\|\cdot\|_{H^{-\beta}}$ is the norm in the $H^{-\beta}$ space, and $\|\cdot\|_{B_1^{1,1}}$ is the norm in the $B_1^{1,1}$ space.

Because the spaces of L^2 and $H^{-\beta}$ as well as $B_1^{1,1}$ can all be simply described in terms of wavelet coefficients, the variational minimization problem described in Equation 1 can thus be solved with computationally efficient schemes based on wavelet representations. With respect to the involved parameters, namely α , β , and γ , the present work attempted to minimize the number of free parameters to a single one while not compromising the restoring effectiveness of the model. It has been shown that the ratio γ/α governs the extent to which details in the original image move from u to v , the size of α and γ determines the magnitude of the residual $r := f - u - v$, and β controls the extent of noise to be moved to v [12]. Therefore, in the present study, γ was assigned with a fixed value of 5×10^{-3} so that the residual r can be negligible and β assumed a fixed value of -0.1 so as to allow a large amount of noise while only a small amount of details to be moved to v . With having β and γ both fixed, the current model was left with only one parameter α . α was tunable with a default value of 10^{-3} in this work and examining of its impact on performance of the proposed system was conducted. Among various wavelet-based schemes, the one proposed by Stefan et al. [13] based on the 3D Redundant Discrete Wavelet Transform (RDWT) was adopted to solve the minimization problem arising in the variational decomposition model.

2.2. Unsupervised spectral clustering with local scaling

PET images containing the identified primary tumor after restored with the variational decomposition algorithm can now be employed as the initial input to the second phase for segmentation. In the present study, segmentation was carried out with a spectral clustering algorithm. As any other graph-based segmentation methods, the spectral clustering algorithm used in this study started with constructing a graph representation $G(V, E)$ of the image being segmented. Each vertex V in the graph represents a voxel in the image, and the weight associated with the edge E connecting two vertices reflects the similarity between the two vertices. In the current application, the weight associated with the edge connecting vertex i and vertex j was defined by measuring the activity similarity between their corresponding voxels in the image such as:

$$w_{i,j} = \begin{cases} e^{-\frac{\|I(i) - \bar{I}(j)\|_{L^2}^2}{\sigma_i \sigma_j}} & \text{if } \|X(i) - X(j)\| < R \text{ and } i \neq j \\ 0 & \text{otherwise} \end{cases}, \quad (2)$$

where $I(i)$ denotes the image brightness of the voxel associated with the vertex i ; $X(i)$ is the spatial locations of the voxel corresponding to vertex i ; σ_i , a local scaling factor for vertex i , is defined as the absolute difference between $I(i)$ and the mean brightness of the n nearest neighbors of the voxel corresponding to vertex i . $I(j)$, $X(j)$ and σ_j in Equation 2 are similarly defined for vertex j . For two vertices with their corresponding voxels separated by a large distance ($> R$), their similarity was set to 0 explicitly considering nearby voxels would be much more likely than faraway voxels to fall into a same cluster. Thus for a tumor volume with N voxels the weight matrix W associated with its weighted graph $G(V, E)$ is an $N \times N$ symmetric matrix with $W(i, j) = w_{i,j}$. Let D be a diagonal matrix with entry $D(i, i) = \sum_j W(i, j)$ and the normalized similarity matrix L can therefore be formed such that $L =$

$D^{-1/2}WD^{-1/2}$. After finding the K top eigenvectors of L , the optimal number of the clusters κ was derived with rotating the eigenvector matrix of L for the maximally sparse representation [14]. Upon determining the optimal number of clusters, the k-means algorithm was initialized to classify the rows of the matrix formed with the top rotated eigenvectors of L into κ clusters, thereby partitioning the tumor volume into κ distinct subvolumes.

With using a local scaling scheme for pairwise similarity measure and analyzing the structure of the eigenvectors of the normalized similarity matrix for automatically deriving the optimal number of clusters, the current implementation of the spectral clustering algorithm involved three parameters: R , n and K . R for each segmentation task was adaptively set to one quarter of the maximum dimension of the identified tumor. The selection of n is independent of the intensity scale and for achieving better overall results its value was set to 80 (equivalent to a sphere of radius 2.5 voxel units centered on the voxel of interest). K , the largest possible number of subvolumes allowed for a given segmentation, was specified to 5 as suggested by Bentzen et al. [9]

2.3. Island removal morphological operation

Segmentation with the spectral clustering algorithm may result in, though seldom in the present study, clusters consisting only of a very small number of voxels onto which precise delivery of the desired irradiation dose using the current treatment systems would be exceeding difficult, if not impossible. Therefore, an island removal operation was employed afterwards as a solution to adjust the initial segmentation output of the spectral clustering algorithm to make it readily usable for treatment planning. In the current study, island removal was done automatically by merging clusters comprising under 10 voxels into their surrounding clusters when enclosed by a single cluster or to one of their adjacent clusters that have nearest mean intensity when surrounded by multiple clusters.

2.4. FDG-PET tumor image simulation

As PET data with tumor heterogeneity being well characterized is not yet available, the performance of the proposed framework was evaluated on a set of simulated PET data generated from a digital PET phantom [15]. Simulations of PET imaging in the digital phantom were performed using SimSET (Simulation System for Emission Tomography) with the Zubal phantom employed as a source for deriving attenuation maps. The PET system modeled was a Reveal HD scanner equipped with a continuous cylindrical BGO detector (40cm in radius). The heterogeneous activity maps of the simulated tumors were formed by first spatially randomly adding a number of 3D Gaussian distributions with equal intensity but arbitrary variance into the defined tumor region, followed by thresholding the resulting aggregate distribution to the desired intensity level. Monte Carlo simulations of PET acquisition of tumors were carried out by the aid of SimSET with imbedding the constructed tumor activity maps in the attenuation medium created from the Zubal phantom. Each tumor sinogram was merged with the sinogram acquired from the normal anatomy of the Zubal phantom. The merged sinograms were reconstructed with the ordered subset expectation maximization (OSEM) algorithm for eight iterations with four subsets, and the obtained reconstructed images were then smoothed with a 5mm full width at half maximum (FWHM) 3D Gaussian filter. Validation of the digital phantom for simulating PET acquisition was demonstrated by the congruence between the simulated and the clinical images with respect to intensity profile, intensity appearance, and image texture [15]. A total of 15 (S1–S15) lesions seated in the lungs with irregular shape and heterogeneous activity were simulated. Volumes of the simulated tumors ranged from 29.8mL to 345.1mL ($mean \pm SD = 114.8 \pm 82.1mL$).

3. Results

Restorations with variational decomposition models are characterized with reducing noise while preserving edges. To verify this effect, one of the simulation cases, *S8*, was taken as an example and the intensity profile comparisons along two perpendicular lines at its central slice (as shown in panel (a) of Figure 2) were realized between the original image, the restored image, and the ground truth. Panel (b) and (c) of Figure 2 present the results. First, the plots visually show that the restored profiles compared to the profiles of the original image are closer to the ground truth. To quantify the closeness between different profiles, a line profile was regarded as a set of voxels that specify the Cartesian coordinates of a point with respect to a set of axes (one axis per voxel). With this interpretation, one profile could be thought of as a point in an abstract high dimensional space and the distance between two profiles could thus be characterized with the Euclidean distance between the corresponding high dimensional points. For profiles along Line 1, the calculated distance between the restored and the ground truth is 0.213, while between the original and the ground truth the calculated distance is 0.410, quantitatively showing along Line 1 the restored image closer to the ground truth than the original image. The same occurs for profiles along Line 2 with calculated distance of 0.311 between the restored profile and the ground truth while 0.466 between the original and the ground truth. Secondly, comparison of profiles between the restored image and the ground truth demonstrates that edge locations were well preserved as desired and also shows that after restoration the edge dynamics had slight increase. Thirdly, these plots show that the restoration impact is especially efficient at the relatively flat regions, for instance the middle portion of either line profile in this case, where the restored profiles closely match the ground truth and oscillations caused by noise have been greatly eliminated.

As mentioned previously, the variational decomposition model employed in this study for image restorations contained three parameters: namely two fixed parameters β and γ and a tunable parameter α . To examine how and to what extent the selection of the parameter α may affect the behavior of the proposed system, the segmentation process was conducted on the simulated PET data with parameter α in the restoration phase set to five different values: 10^{-1} , 10^{-2} , 10^{-3} , 10^{-4} , and 0. Figure 3 presents the results with using lesion *S8* as an example. The ground truth and the simulated image are shown in the first two columns, respectively. As presented in the third column from row *C1* to *C4*, the restored image u for cases with non-zero α exhibits image contents to some degree more similar to the ground truth than the original simulated image dose. This can also be appraised by their corresponding difference image v , as presented in the ensuing column, which contains mostly the highly oscillatory portion, *i.e.*, the noise, of the original image. In the special case where α assumed a value of zero, no restoration was performed to the original image and the restored image was simply identical to the original, as shown in the bottom row of Figure 3. Furthermore, the results reveal that with the other two parameters being fixed α governs the extent to which details in the original image move from u to v . A large value for α will produce restored images with few details while a small one will yield restored images that is almost unchanged from the original. This effect was also reflected on the final segmentation results, as shown in the last column of Figure 3. For cases with α ranging from 10^{-2} to 10^{-4} , the proposed framework was able to recognize the uneven distributed uptake inside the lesion. Especially when α took on a value identical to 10^{-3} , a segmentation map with fairly proper characterization of the intratumoral heterogeneity as defined in the ground truth was produced. For the other two cases where α took on values of 10^{-1} and 0, the system was unable to identify the defined high uptake region. The reason for the former is that using a relatively large value for α resulted in loss of details and led to feed an over-smoothed image with voxels exhibiting near-equal intensity values to the spectral clustering algorithm which, as before described, was based essentially on intensity similarity measured between

voxels; while the latter is largely due to the presence of noise resulting in highly contaminated voxel similarity measures and therefore leading to the spectral clustering algorithm being unable to discriminate voxels initially defined with appreciably distinct values in the activity map. Though the optimal values for parameter α may vary depending upon the specific image data involved, empirical investigations presented herein on the effect of parameter α on the performance of the proposed system indicate that preferred selections of α for typical PET data would be in the range of 10^{-2} to 10^{-4} . Unless otherwise specified, all the segmentations in this study were carried out with parameter α assuming a value of 10^{-3} .

Results obtained for the rest of the simulated lesions are presented in Figure 4 and Figure 5. In either figure, the ground truth, the simulated PET image, and the isolated tumor image of each lesion are listed in the first three columns, respectively. The restored tumor image, presented in the ensuing column, underlines the capability of the employed restoration approach to noise suppression and edge preservation. Segmentation results, presented in last column, show intratumoral segmentation using the proposed framework resulted in a partition of the tumor volumes into a set of disjoint clusters featured with the total intracluster similarity and the total intercluster dissimilarity being simultaneously maximized. More significantly, those regions specified with high activity values in the ground truth image were identified either individually as seen in the produced segmentation maps for lesions *S1–S12* or jointly with nearby high activity regions as seen in the results for lesions *S13–S15*.

4. Discussion

The goal of this work was to provide an automated intra-volume partitioning strategy for FDG-PET imaged tumors. To this end, an unsupervised and automated segmentation framework largely leaning on an image restoration mechanism in conjunction with a voxel clustering scheme was proposed in the current paper. The presented framework consisted of a total of four phases, in the first of which tumor volumes were identified from the PET images. The obtained tumor volumes were then subjected to a restoration process in the second phase. The restoration was carried out with the aid of the variational decomposition model that, unlike other restoration approaches resorting to sophisticated modeling of the noise statistics, employed image features, especially sparseness properties of the gradient, to eliminate the highly oscillatory contents inside tumor volumes and was thus able to achieve concurrent noise suppression and edge preservation, a feature particular desired for PET data as in where image details are corrupted by the presence of high-level noise [13]. The effectiveness of this peculiar feature is evidently demonstrated in Figure 2 with the restored image exhibiting higher fidelity to the ground truth than the simulated image; and it was also this feature that made it feasible for the subsequent phases to produce segmentation results with intratumoral activity heterogeneity being characterized properly. The segmentation was performed in the third phase with the assistance of the spectral clustering method grouping intratumoral voxels into distinct clusters such that the total intracluster similarity and the total intercluster dissimilarity were maximized. The upper limit on the number of clusters that could be attained for a given segmentation task was set to 5 as per the suggestions of Bentzen et al. [9]; and the optimal cluster number under the upper limit for each tumor being segmented was automatically inferred, thereby making the segmentation process unsupervised. Finally, in the last phase, an island removal morphological operation was applied, if necessary, to eliminate clusters consisting of very few voxels through merging them to the surrounding or abutting clusters.

Fifteen simulated FDG-PET lesions with irregular shape and heterogeneous activity were used to assess the performance of the proposed segmentation system. It was found out from

testing with these simulated lesions that the presented system is able to identify the uptake nonuniformity inside the lesion volumes and produce segmentation results with activity heterogeneity characterized in fairly well agreement with that defined in the activity map for each lesion. As seen in Figure 4 and Figure 5, a series of nested regions with good spatial correspondence to the high activity area defined in the initial activity map were created in the segmentation results for lesions exhibiting a single high uptake region on PET images. As for lesions appearing multiple high uptake regions on PET images, the system was tending more towards generating segmentation results in which neighboring regions defined with high values in the activity maps were consolidated into one single region. This is largely due to two reasons: first, the ill-posed PET reconstruction along with the restoration procedure taken elevated intensity values for areas between neighboring high uptake regions and thus led to these neighboring high uptake regions aggregating into a larger unit that exhibited high degree of internal intensity similarity prior to sending to the spectral clustering algorithm for segmentation; second, the constraint imposed on the maximum number of clusters attainable in segmenting a lesion might also force the system to consolidate neighboring high uptake regions. In addition, the proposed system worked with all the simulated lesions despite their vast differences in size, shape, and activity distribution, showing its robustness against tumor morphological variation as well as intratumoral activity diversity in partitioning tumor intra-volumes.

Due to the difficulties imposed on intratumoral segmentation by the noisy and blurry nature of PET data, lesion images were first restored in the proposed system with using the variation decomposition technique. The present implementation of this technique involved three parameters: namely two fixed parameter β and γ and a tunable parameter α . A set of experiments, which compared the segmentation results obtained for different assumptions in the selection for parameter α , were performed with the simulated lesions. It was learned from these experiments that with the other two parameters being fixed parameter α largely determines the extent to which details in the original image are retained in the restored image and partitioning tumor volumes with activity heterogeneity being properly characterized is achievable using the proposed system with appropriate choices for parameter α . Although various parameter selection paradigms have been suggested in past by previous studies [16, 17], here this study chose to minimize the number of parameters while without compromising the effectiveness of the employed variational decomposition technique in restoring PET data. The adoption of such a strategy was mainly from the consideration of allowing users to select the most appropriate partitioning result from different solutions for a given segmentation task according to corresponding proprietary acquisition settings. As might be expected, parameter values for α would be determined for a given protocol with specific acquisition details on aspects such as imaging duration, tracer concentration, and scanner resolution, etc., thus obviating the need to select the parameter for each and every scan.

The existing work can be further improved by integrating a number of other techniques into the current framework. For example, instead of using hard constraints as was in the present work, a tumor volume-varying constraint may be imposed on the maximum number of clusters attainable in segmenting a lesion, thus allowing segmentation results with more refined characterization of intratumoral heterogeneity, in particular, for lesions with large volume. In addition, similarity measure used by the spectral clustering algorithm in the segmentation process can be enhanced by investigating new image cues with augmented discriminative characterization of tumor heterogeneity. The present work, assuming tumor volumes were known, did not concern delineating tumor boundaries from PET data. With a great number of well-behaved methods [18–20] being proposed for automatic tumor volume segmentation, another possible improvement would be to incorporate one of these methods into the pre-processing phase to further automate the proposed system.

5. Conclusion

The current paper presented an automated and unsupervised segmentation framework constituted mainly by an image restoration mechanism based on variational decomposition and a voxel clustering scheme based on spectral clustering. Segmentation results obtained from experiments carried out on simulated PET data demonstrates the feasibility of the proposed system in partitioning FDG-PET imaged tumor volumes into subvolumes with intratumoral heterogeneity being properly characterized.

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Figure 1.
Illustration of the intratumoral segmentation framework.

Figure 2.

Comparisons of intensity profiles between the original image, the restored image, and the ground truth of Lesion 58 at the central slice. Panel (a) gives the positions for the lines (labeled as 1 and 2) along which intensity profiles were measured. Panel (b) shows the intensity profile comparison for Line 1 and panel (c) for Line 2. For the plots in panel (b) and panel (c), the thick grey line shows the profile of the original image, the thin grey line shows the profile of the restored image, and the thin dashed line shows the profile of the ground truth.

Figure 3.

Axial views of the ground truth (a), the simulated tumor PET image (b), the restored image (c), the difference image (d), and the segmentation result (e) of lesion S8 with value of the parameter α in the variation decomposition model set at 10^{-1} (C1), 10^{-2} (C2), 10^{-3} (C3), 10^{-4} (C4), 0 (C5).

Figure 4. Axial views of the segmentation results for lesions ($S1 - S7$). (a) ground truth; (b) simulated PET image; (c) isolated tumor image; (d) restored tumor image; (e) segmentation result.

Figure 5.

Axial views of the segmentation results for lesions ($S9 - S15$). (a) ground truth; (b) simulated PET image; (c) isolated tumor image; (d) restored tumor image; (e) segmentation result.