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Variational PET/CT Tumor Co-segmentation Integrated with PET Restoration

Laquan Li¹, Wei Lu², Shan Tan¹

¹Key Laboratory of Image Processing and Intelligent Control of Ministry of Education of China, School of Automation, Huazhong University of Science and Technology, Wuhan 430074, China

²Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York 10065, USA

Abstract

PET and CT are widely used imaging modalities in radiation oncology. PET imaging has a high contrast but blurry tumor edges due to its limited spatial resolution, while CT imaging has a high resolution but a low contrast between tumor and soft normal tissues. Tumor segmentation from either a single PET or CT image is difficult. It is known that co-segmentation methods utilizing the complementary information between PET and CT can improve segmentation accuracy. These information can be either consistent or inconsistent in the image-level. How to correctly localize tumor edges with these inconsistent information is a major challenge for co-segmentation methods. In this study, we proposed a novel variational method for tumor co-segmentation in PET/CT, with a fusion strategy specifically designed to handle the information inconsistency between PET and CT in an adaptive way — the method can automatically decide which modality should be more trustful when PET and CT disagree to each other for localizing the tumor boundary. The proposed method was constructed based on the I -convergence approximation of the Mumford-Shah (MS) segmentation model. A PET restoration process was integrated into the co-segmentation process, which further eliminate the uncertainty for tumor segmentation introduced by the blurring of tumor edges in PET. The performance of the proposed method was validated on a test dataset with fifty non-small cell lung cancer patients. Experimental results demonstrated that the proposed method had a high accuracy for PET/CT co-segmentation and PET restoration, and can accurately estimate the blur kernel of the PET scanner as well. For those complex images in which the tumors exhibit Fluorodeoxyglucose (FDG) uptake inhomogeneity or even invade adjacent soft normal tissues, the proposed method can still accurately segment the tumors. It achieved an average dice similarity indexes (DSI) of 0.85 ± 0.06 , volume error (VE) of 0.09 ± 0.08 , and classification error (CE) of 0.31 ± 0.13 .

Keywords

PET/CT co-segmentation; PET restoration; blur kernel estimation; variational method; information fusion strategy

1. Introduction

Accurate tumor segmentation plays a critical role in radiation oncology, where positron emission tomography (PET) and computed tomography (CT) are two widely used imaging

modalities. PET imaging is able to provide functional and metabolic information of the human body, and typically has a high contrast between malignant tumors and normal tissues. Its one limitation with respect to tumor segmentation is that tumor edges in PET are usually blurred (Figs. 1 (c) and (e)) due to the low spatial resolution of the PET scanner, which makes it difficult to accurately segment a tumor from a single PET image. CT imaging is able to provide detailed anatomical information with a high resolution but a relatively low contrast between malignant tumors and normal tissues. Tumor segmentation from a single CT image is also challenging. Fig. 1 (d) displays a CT example where the tumor (non-small cell lung cancer (NSCLC)) invades the chest wall, and there is no clear boundary between the tumor and the normal tissues (Fig. 1 (d), the lower right of the tumor). It was reported that around 5% of the resected patients with lung cancer have tumors invading the chest wall (Stoelben and Ludwig, 2009).

Multi-modality imaging technologies have been routinely used in the clinical practice nowadays. An integrated PET/CT scanner can acquire both functional (PET) and anatomic (CT) images of the whole body in one single procedure (Greco et al., 2007; Ju et al., 2015). Studies have demonstrated that combining PET and CT information can improve tumor segmentation performance, thanks to the complementary information from both modalities (Song et al., 2013; El Naqa et al., 2007; Han et al., 2011; Bagci et al., 2013; Markel et al., 2013b; Markel et al., 2013a; Ju et al., 2015; Xu et al., 2015; Cui et al., 2015; Cui et al., 2016; Foster et al., 2014). El Naqa *et al.* proposed a variational method based on multivalued level set deformable models (El Naqa et al., 2007). This method could not only segment multimodality images, but also simultaneously segment multiple image sets from the same modality. Han *et al.* formulated the PET/CT co-segmentation problem as an optimization problem in Markov Random Field. An energy term was introduced into the objective energy function to penalize the segmentation difference between PET and CT images (Han et al., 2011). Song *et al.* further added an adaptive context term into the energy function to achieve consistent segmentation results between the two modalities (Song et al., 2013). This method allows obtaining different tumor volumes on PET and on CT, respectively. Ju *et al.* incorporated the random walk method and the graph cut method for PET/CT co-segmentation (Ju et al., 2015). Random walk was used as an initial preprocessor to provide object seeds for the graph cut method. A context term was added to the energy function to obtain consistent results between PET and CT. In (Bagci et al., 2013), Bagci *et al.* extended the random walk method for jointly delineating multiple objects from multiple image modalities (PET, CT and MRI) by unifying the graph representation of each image modality in a single product lattice. Markel *et al.* used the Jensen-Rényi divergence to evolve the geometric level set for multimodality segmentation in (Markel et al., 2013b), and designed a 3D texture features-based PET/CT co-segmentation method in (Markel et al., 2013a). The latter approach relied on a combined decision tree with K-nearest neighbors classifiers to classify the voxels using various texture features. In (Xu et al., 2015), Xu *et al.* proposed a co-segmentation method based on a fuzzy connectedness framework and a fuzzy affinity function. This method can segment tumors in different modalities through a modality-specific weight mechanism. Cui *et al.* proposed a ‘topo-poly’ graph model for PET/CT tumor segmentation (Cui et al., 2015). Their model combined the joint PET/CT foreground density similarity and topology information. In (Cui et al., 2016), they designed a label

information propagation model for lung tumor segmentation. This model incorporated spatial–topological information from PET and local intensity changes from CT.

It is obvious that a reasonable use of complementary information from both PET and CT improves segmentation accuracy. However, information from PET and that from CT can be either consistent or inconsistent due to their different imaging mechanisms (Song et al., 2013). The NSCLC case in Fig. 1 is a typical example, in which CT has no clear boundary between the tumor and the chest wall, while PET has one though blur. One of the major challenges in PET/CT co-segmentation is actually how to fuse these complementary but sometimes contradictory information from different imaging modalities to localize the correct tumor boundary.

Two information fusion strategies were typically used in the PET/CT co-segmentation literatures. The first strategy considered PET and CT as two different information sources and two segmentation processes were derived by PET and CT, respectively. Compromised results were obtained by penalizing the contour difference in PET and CT. In this strategy, the final segmentation results can be either an identical contour (Han et al., 2011) or two different contours, one for PET and one for CT (Song et al., 2013; Ju et al., 2015).

The second strategy considered PET and CT as two channels in the same information source, where PET and CT images were assembled as multivalued vectors (El Naqa et al., 2007) or a hyper-graph (product graph) (Bagci et al., 2013; Cui et al., 2015), or used to produce a combining affinity function (Xu et al., 2015). The significance of imaging modality was prioritized through weight parameters set empirically in the assembling process (Bagci et al., 2013). The segmentation process was then conducted on the multivalued vectors using level set (El Naqa et al., 2007; Markel et al., 2013b) or a hyper-graph using discrete optimization (Bagci et al., 2013; Cui et al., 2015). Machine-learning based methods that utilize the combination of various image features extracted from both PET and CT to train a classifier for segmentation can also been categorized into this strategy (Markel et al., 2013a).

In this study, we proposed a novel variational method for tumor co-segmentation using PET/CT. The proposed method can accomplish the PET/CT tumor co-segmentation, PET restoration and blur kernel estimation of the PET scanner simultaneously. The proposed method was constructed based on the Mumford-Shah (MS) segmentation model (Mumford and Shah, 1989), with a novel fusion strategy that was specifically designed to handle the information inconsistency between PET and CT in an adaptive way.

This new strategy can automatically decide which modality should be more trustful when PET and CT disagree to each other for localizing the tumor boundary. Take Fig. 1 as an example. This strategy automatically selected to use more information from CT than from PET for the areas where a tumor had clearer edges in CT (Fig. 1 (d), the up portion of the tumor), considering the higher resolution of the CT scanner. However, in the areas where the tumor was attached to the adjacent structures or normal tissues, there was no clear separation between the tumors and the surrounding normal tissues in the CT image (Fig. 1 (d), the lower right of the tumor). For these areas, the proposed method adaptively defined tumor

edges mainly based on the PET image. Note that the designed fusion strategy was automatically implemented through the proposed variational framework.

Most existing co-segmentation methods directly used the un-deblurred PET image, ignoring the uncertainty introduced by tumor edges blur in PET. To eliminate this uncertainty, we further integrated a PET restoration process into the co-segmentation model to improve the segmentation accuracy. Our previous study has shown that integrating the restoration process into segmentation helped improve the accuracy for tumor segmentation in PET (Li et al., 2017). In the proposed variational method in this study, the CT image further helped restore the PET image due to its higher resolution, which in return improved the tumor segmentation accuracy in the PET/CT co-segmentation scenario.

A common problem for single CT tumor segmentation is the leaking issue — the results often wrongly included edges belonging to adjacent normal tissues (*e.g.*, portions A and B in Fig. 1 (d)) due to its low discrimination ability for soft tissues, leading to an over-segmentation. Taking into account that PET image has a higher contrast and relatively more clean background, we used the foreground information of PET to locate the rough tumor regions and remove the interferences from adjacent normal tissues in CT through a post-processing process.

The performance of the proposed method was validated on a test dataset with fifty NSCLC patients. Experimental results demonstrated that the proposed method could take full advantage of the complementary (either consistent or inconsistent) information of PET and CT. It achieved a high performance for PET/CT tumor co-segmentation and outperformed methods solely using PET or CT. In the same time, the proposed method can restore the PET image and estimate the blur kernel of the PET scanner.

2. Methods

2.1. Related Work

2.1.1. MS Segmentation—In (Mumford and Shah, 1989), Mumford and Shah proposed to implement image segmentation by finding an optimal piecewise smooth function f that approximates the observed image g . Their method was performed by minimizing the following energy functional:

$$F(f, K) = \frac{1}{2} \int_{\Omega} (f - g)^2 dA + \beta \int_{\Omega/K} |\nabla f|^2 dA + \alpha \int_K d\sigma, \quad (1)$$

where $\Omega \subset \mathbb{R}^3$, α and β are both positive parameters, $K \subset \Omega$ represents the edge set of the objects, Ω/K denotes the non-edge areas of the image, $f: \Omega \rightarrow \mathbb{R}$ is continuous or even differentiable in Ω/K but discontinuous across K , dA denotes $dx dy dz$ (dx , dy and dz represent the infinitesimal element of x , y and z , respectively).

The minimization of Eq.(1) is difficult because of the non-convex property of this energy functional and the unknown discontinuity edge set K in the integral domains (Scherzer, 2011). Ambrosio and Tortorelli approximated this energy functional by a sequence of regular functionals $F_\epsilon(f, v)$ using the Γ -convergence (Ambrosio and Tortorelli, 1990):

$$F_{\varepsilon}(f, v) = \frac{1}{2} \int_{\Omega} (f - g)^2 dA + \beta \int_{\Omega} v^2 |\nabla f|^2 dA + \alpha \int_{\Omega} \left(\varepsilon |\nabla v|^2 + \frac{1}{4\varepsilon} (v - 1)^2 \right) dA. \quad (2)$$

The minimizing of the irregular functional $F(f, K)$ in Eq.(1) can thus be replaced by the minimizing of the regular functional $F_{\varepsilon}(f, v)$ with a small positive constant ε , that is $\lim_{\varepsilon \rightarrow 0} F_{\varepsilon}(f, v) = F(f, K)$. v is a smooth auxiliary function, which represents the edge map, i.e., $v(x, y, z) \approx 0$ if (x, y, z) is close to the object edges, and $v(x, y, z) \approx 1$ if (x, y, z) is far away from the object edges:

$$v(x, y, z) \approx \begin{cases} 0, & \text{if } (x, y, z) \in K \\ 1, & \text{Otherwise} \end{cases}. \quad (3)$$

2.1.2. Image Restoration—PET images are usually blurred due to the low spatial resolution of a PET scanner. The imaging process can be described as a 3-D convolution operation (Boussion et al., 2009; El Naqa et al., 2006)

$$g = f^*h + n, \quad (4)$$

where $f: \Omega \rightarrow R$ is a sharp or ideal 3-D image defined on Ω , h is the point spread function (PSF) of the scanner (or named the blur kernel in this study), n is the additive noise, g is the observed PET image, and $*$ is the 3-D convolution operator.

The PSF of a PET scanner is circularly symmetric and varies with the radial position in the full field of view (FOV). Although the PSF at a specific location in FOV can be estimated through experimental measurements of a point source, accurate PSF estimations at every location in the FOV might not be always available in practice. Recovering both the sharp image and the PSF is an ill-posed problem. Regularizations are generally used to solve this ill-posed problem. You and Kaveh (You and Kaveh, 1996) proposed to simultaneously regularize the sharp image f and the PSF h . They established the following restoration model:

$$F(f, h) = \frac{1}{2} \|f^*h - g\|_{L_2(\Omega)}^2 + \alpha_1 \int_{\Omega} |\nabla f|^2 dA + \alpha_2 \int_{\Omega} |\nabla h|^2 dA, \quad (5)$$

where α_1 and α_2 are both positive parameters.

2.2. PET/CT Tumor Co-segmentation Integrated with a PET Restoration Process

2.2.1. Resampling—The proposed method required a one-to-one voxel correspondence between PET and CT images, and a cubic B-spline interpolator was used to up-sample the PET image to have the same voxel dimensionality as the CT image. Both the PET and the CT images were normalized linearly to a common scale [0-1] before applying the proposed method.

2.2.2. The Novel Model of PET/CT Co-segmentation with PET Restoration—

Our PET/CT co-segmentation model was constructed based on the F -convergence approximation of the MS segmentation model (Eq.(2)), with a specific consideration to make full use of the complementary (either consistent or inconsistent) information between PET and CT in an adaptive way for detecting tumor edges. In addition, the PET image restoration using Eq.(5) was consolidated into our co-segmentation model to eliminate the uncertainty introduced by the blurring process in PET. In the PET restoration, the blur kernel h was modeled as an *anisotropic* Gaussians parameterized by different widths in transversal and axial directions to adapt to the different spatial resolution in different directions of a PET scanner. The energy functional of the proposed model was defined as:

$$\begin{aligned}
 F_{\varepsilon}(f_1, f_2, v, \sigma_1, \sigma_2) = & \frac{1}{2} \int \int \int_{\Omega} \left((h_{\sigma_1, \sigma_2} * f_1 - g_1)^2 + (f_2 - g_2)^2 \right) dx dy dz \\
 & + \beta \int \int \int_{\Omega} v^2 \left(|\nabla f_1|^2 + |\nabla f_2|^2 \right) dx dy dz \\
 & + \alpha \int \int \int_{\Omega} \left(\varepsilon |\nabla v|^2 + \frac{(v-1)^2}{4\varepsilon} \right) dx dy dz \\
 & + \gamma \int \int \int_{\Omega} |\nabla h_{\sigma_1, \sigma_2}|^2 dx dy dz,
 \end{aligned} \tag{6}$$

where β , α , γ and ε are positive parameters; f_1 denotes the restored image of the original PET image (g_1) and f_2 denotes the piecewise smooth approximation of the original CT image (g_2); v represents the edge map of the PET and CT images and determines the segmentation result of the tumor; h_{σ_1, σ_2} is an anisotropic Gaussian kernel parameterized by its widths σ_1 (transversal direction) and σ_2 (axial direction):

$$h_{\sigma_1, \sigma_2} = \frac{1}{(2\pi)^{3/2} \sigma_1^2 \sigma_2} e^{-\left(\frac{x^2 + y^2}{2\sigma_1^2} + \frac{z^2}{2\sigma_2^2} \right)}. \tag{7}$$

Moreover, we imposed the following constraints on h_{σ_1, σ_2} , f_1 and f_2 to enhance the robustness and convergence of the algorithm:

$$\begin{aligned}
 \int \int \int_{\Omega} h_{\sigma_1, \sigma_2}(x, y, z) dx dy dz &= 1, \\
 h_{\sigma_1, \sigma_2}(x, y, z) &\geq 0, \\
 f_1(x, y, z) &\geq 0, \\
 f_2(x, y, z) &\geq 0.
 \end{aligned} \tag{8}$$

In Eq.(6), the first term was the data fidelity term, and the second term was the regularization term constraining the smoothness of the non-edge areas of the restored image f_1 and the piecewise smooth image f_2 . Note that the second term also played a crucial role in the evolving of the edge map v . For areas with high gradient magnitudes in the PET or CT images, such as those over the tumor edges, the corresponding values of the edge map v in these areas would gradually tended to 0 during the minimizing process of the energy functional. The proposed model automatically utilized the complementary (either consistent

or inconsistent) information between PET and CT, and decided which modality should be more trustful for localizing the tumor boundary in an adaptive way. In local areas where both PET and CT images had detectable edges, the edge map v (tumor edges) in the second term was mainly determined by CT since the higher resolution of the CT scanner generally made the tumor edges clearer in CT than in PET (hence a larger gradient magnitude $|\nabla f_2|$ (from CT) than the gradient magnitude $|\nabla f_1|$ (from PET)). Please see the upper left of the tumor in Fig. 1(c) and (d) for example). The defined tumor edges (mainly based on CT) in these area further guided the restoration of the PET image. In other areas where a tumor was attached to the adjacent structures or normal tissues, there was no clear boundary between the tumors and the surrounding normal tissues in CT, while detectable tumor edges may exist in PET though these edges might be blurred (Please see the lower right of the tumor in Fig. 1(c) and (d) for example)). For these areas, the proposed model adaptively defined tumor edges mainly based on the PET image. The integrated PET restoration further improved the positioning precision of the tumor edges. The third term in the energy functional Eq.(6) was used to constrain the smoothness of the edge set, and it made the values corresponding to the non-edge areas of the PET and CT images in v gradually tend to 1 during the minimizing process of the energy functional. The fourth term was to regularize the blur kernel. This term was necessary to reduce the fundamental ambiguity in the division of the apparent blur between the restored image and the blur kernel (Bar et al., 2006).

2.2.3. Algorithm Implementation—The energy objective function (Eq.(6)) is not jointly convex with respect to f_1 , f_2 , v and h_{σ_1, σ_2} , but it is convex with respect to any one of the four variables. That is, if any three of the four variables are fixed, the objective function is convex with respect to the fourth variable. According to the above features, we used an alternative minimization (AM) algorithm (You and Kaveh, 1996; Chan and Wong, 1998; Chan and Shen, 2005) to optimize the energy functional. The AM algorithm is a classical method for solving composite minimization problems. In each iteration, the objective functional was minimized only with respect to one variable and other variables remained unchanged. The convergence of the AM algorithm was proved in (Chan and Shen, 2005).

Using the AM algorithm, the energy functional (6) was minimized with respect to v , f_1 , f_2 , σ_1 and σ_2 in turn. The minimization with respect to v , f_1 and f_2 were carried out using the following Euler-Lagrange equations, with Neumann boundary conditions:

$$\frac{\delta F_\epsilon}{\delta v} = 2\beta \left(|\nabla f_1|^2 + |\nabla f_2|^2 \right) v + \alpha \cdot \frac{v-1}{2\epsilon} - 2\alpha\epsilon \nabla^2 v = 0, \quad (9)$$

$$\frac{\delta F_\epsilon}{\delta f_1} = (h_{\sigma_1, \sigma_2} * f_1 - g_1) * h_{\sigma_1, \sigma_2}(-x, -y, -z) - 2\beta \text{Div}(v^2 \nabla f_1) = 0, \quad (10)$$

$$\frac{\delta F_\epsilon}{\delta f_2} = (f_2 - g_2) - 2\beta \text{Div}(v^2 \nabla f_2) = 0. \quad (11)$$

The minimization with respect to the blur kernel widths σ_1 and σ_2 were carried out by the differentiation of the energy functional (6), as follows:

$$\frac{\partial F_\epsilon}{\partial \sigma_1} = \int \int \int_{\Omega} \left[(h_{\sigma_1, \sigma_2} * f_1 - g_1) \left(\frac{\partial h_{\sigma_1, \sigma_2}}{\partial \sigma_1} * f_1 \right) + \gamma \frac{\partial}{\partial \sigma_1} | \nabla h_{\sigma_1, \sigma_2} |^2 \right] dx dy dz = 0, \quad (12)$$

$$\frac{\partial F_\epsilon}{\partial \sigma_2} = \int \int \int_{\Omega} \left[(h_{\sigma_1, \sigma_2} * f_1 - g_1) \left(\frac{\partial h_{\sigma_1, \sigma_2}}{\partial \sigma_2} * f_1 \right) + \gamma \frac{\partial}{\partial \sigma_2} | \nabla h_{\sigma_1, \sigma_2} |^2 \right] dx dy dz = 0. \quad (13)$$

where

$$\frac{\partial h_{\sigma_1, \sigma_2}}{\partial \sigma_1} = \frac{1}{(2\pi)^{3/2} \sigma_1^2 \sigma_2} e^{-\left(\frac{x^2 + y^2}{2\sigma_1^2} + \frac{z^2}{2\sigma_2^2} \right)} \left(\frac{x^2 + y^2}{\sigma_1^3} - \frac{2}{\sigma_1} \right), \quad (14)$$

$$\frac{\partial h_{\sigma_1, \sigma_2}}{\partial \sigma_2} = \frac{1}{(2\pi)^{3/2} \sigma_1^2 \sigma_2} e^{-\left(\frac{x^2 + y^2}{2\sigma_1^2} + \frac{z^2}{2\sigma_2^2} \right)} \left(\frac{z^2}{\sigma_2^3} - \frac{1}{\sigma_2} \right), \quad (15)$$

and

$$\begin{aligned} \frac{\partial}{\partial \sigma_1} | \nabla h_{\sigma_1, \sigma_2} |^2 &= \frac{x^2 + y^2}{4\pi^3 \sigma_1^4 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2} \right)} \left(\frac{x^2 + y^2}{\sigma_1^7} - \frac{4}{\sigma_1^5} \right) \\ &+ \frac{z^2}{4\pi^3 \sigma_1^4 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2} \right)} \left(\frac{x^2 + y^2}{\sigma_1^3 \sigma_2^4} - \frac{2}{\sigma_1 \sigma_2^4} \right), \end{aligned} \quad (16)$$

$$\begin{aligned} \frac{\partial}{\partial \sigma_2} | \nabla h_{\sigma_1, \sigma_2} |^2 &= \frac{x^2 + y^2}{4\pi^3 \sigma_1^4 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2} \right)} \left(\frac{z^2}{\sigma_1^4 \sigma_2^3} - \frac{1}{\sigma_1^4 \sigma_2} \right) \\ &+ \frac{z^2}{4\pi^3 \sigma_1^4 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2} \right)} \left(\frac{z^2}{\sigma_2^7} - \frac{3}{\sigma_2^5} \right). \end{aligned} \quad (17)$$

The blur kernel h_{σ_1, σ_2} were updated using the solutions σ_1 and σ_2 of Eqs.(12) and (13). The detailed derivation of the three Euler-Lagrange equations (Eqs.(9), (10) and (11)) and Eqs. (14) and (16) are presented in Appendix.

2.2.4. Post-processing—It is common that there are some edges of normal tissues around the tumor in CT, such as the upper-right portion (A) and the lower-left portion (B) of Fig. 1 (d). We named it as “the false edges” in the rest of this study. Because the final

segmentation result of the proposed method depended on the edge map v , and v was obtained based on the edge detection, the false edges would interfere with the tumor segmentation process and result in an over-segmentation. Fortunately, the PET image has a higher contrast and relatively more clean background. We used the foreground information of PET to locate the rough tumor regions and remove the interferences from the false edges of the CT image through a post-processing process.

Firstly, a common image segmentation method was used to segment the PET image. The segmented volume was taken as a pre-defined rough tumor region. It must contains the whole tumor region and should not contain too much background region. In the edge map v of the proposed co-segmentation method, those regions outside the pre-defined rough tumor region were considered non-edge areas and all function values in those regions were set to 1.

We used a modified version (Shah, 1996; Jung et al., 2011) of the Γ -convergence approximation of the MS model (Eq.(2)) to segment the PET image for the post-processing. In this modified version, the Tikhonov regularization $\int_{\Omega} v^2 |\nabla f|^2 dA$ of the MS model was replaced by the total variation (TV) regularization $\int_{\Omega} v^2 |\nabla f| dA$. The authors named this method “MSTV”. The energy functional of the MSTV method is

$$F_{\epsilon}(f, v) = \frac{1}{2} \int_{\Omega} (f - g)^2 dA + \beta \int_{\Omega} v^2 |\nabla f| dA + \alpha \int_{\Omega} \left(\epsilon |\nabla v|^2 + \frac{1}{4\epsilon} (v - 1)^2 \right) dA. \quad (18)$$

As the tumor edges in a PET image are usually blurred and the TV regularization has the advantage of protecting edges, the MSTV method is more suitable for the post-processing. Because the uptake inhomogeneity of the tumors in PET and the disadvantage of staircase effect of the TV regularization, the MSTV method might obtain multiple edge contours. The biggest contour could contain the whole tumor region, so it was used to define the rough tumor region.

2.2.5. Discrete Solution—First of all, the restored image f_1 and the piecewise smooth approximation image f_2 were initialized as the original PET and CT image, respectively; the edge map v was initialized using a constant function and the function value was set to 1; the blur kernel widths σ_1 and σ_2 were initialized to a small number to make the blur kernel h_{σ_1, σ_2} approximate the delta function kernel.

Below are the detailed steps of the $(i+1)^{th}$ iteration of our AM algorithm.

The first step was to solve the Euler-Lagrange equation (9) with respect to the edge map v using the gradient descent method. According to the relationship between the Euler-Lagrange equation and the gradient descent flow, we updated the edge map v using the following iterations:

$$v_{t+1}^{i+1} \leftarrow v_t^{i+1} - \varepsilon_v \left[2\beta \left(\left| \nabla f_1^i \right|^2 + \left| \nabla f_2^i \right|^2 \right) v_t^{i+1} + \alpha \cdot \frac{v_t^{i+1} - 1}{2\varepsilon} - 2\varepsilon\alpha \nabla^2 v_t^{i+1} \right], \quad (19)$$

where the step length $\varepsilon_v > 0$, and t represents the iteration number of the gradient descent flow.

The second step was to solve the Euler-Lagrange equation (10) with respect to the restored image f_1 of the PET image using the gradient descent method. The gradient descent result was obtained by the following iteration:

$$f_{1,t+1}^{i+1} \leftarrow f_{1,t}^{i+1} - \varepsilon_f \left[\left(h_{\sigma_1, \sigma_2}^i * f_{1,t}^{i+1} - g_1 \right) * h_{\sigma_1, \sigma_2}^i(-x, -y, -z) - 2\beta \text{Div} \left((v^{i+1})^2 \nabla f_{1,t}^{i+1} \right) \right]. \quad (20)$$

The step length $\varepsilon_f > 0$, and t denotes the iteration number of the gradient descent flow. Then we imposed the following constraint on f_1^{i+1} :

$$f_1^{i+1}(x, y, z) = \begin{cases} f_1^{i+1}(x, y, z), & \text{if } f_1^{i+1}(x, y, z) > 0 \\ 0, & \text{otherwise.} \end{cases} \quad (21)$$

The third step was to solve the Euler-Lagrange equation (11) with respect to the piecewise smooth approximation image f_2 of the CT image using the gradient descent method. f_2^{i+1} was updated by

$$f_{2,t+1}^{i+1} \leftarrow f_{2,t}^{i+1} - \varepsilon_f \left[\left(f_{2,t}^{i+1} - g_2 \right) - 2\beta \text{Div} \left((v^{i+1})^2 \nabla f_{2,t}^{i+1} \right) \right]. \quad (22)$$

Similarly, t denotes the iteration number of the gradient descent flow, and the following constraint was imposed on f_2^{i+1} :

$$f_2^{i+1}(x, y, z) = \begin{cases} f_2^{i+1}(x, y, z), & \text{if } f_2^{i+1}(x, y, z) > 0 \\ 0, & \text{otherwise.} \end{cases} \quad (23)$$

The next steps were to solve the Eqs.(12) and (13) using the bisection method. The obtained σ_1^{i+1} and σ_2^{i+1} were then used to update the blur kernel $h_{\sigma_1, \sigma_2}^{i+1}$ according to Eq.(7). And the blur kernel was constrained by

$$h_{\sigma_1, \sigma_2}^{i+1}(x, y, z) = \begin{cases} h_{\sigma_1, \sigma_2}^{i+1}(x, y, z), & \text{if } h_{\sigma_1, \sigma_2}^{i+1}(x, y, z) > 0 \\ 0, & \text{otherwise,} \end{cases} \quad (24)$$

and

$$h_{\sigma_1, \sigma_2}^{i+1}(x, y, z) = \frac{h_{\sigma_1, \sigma_2}^{i+1}(x, y, z)}{\int_{\Omega} h_{\sigma_1, \sigma_2}^{i+1}(x, y, z) dx dy dz}. \quad (25)$$

The iteration of the AM algorithm was repeated until the difference between the current energy F_e^{i+1} and the previous energy F_e^i of the objective functional (6) was below a certain user-defined threshold.

As described in the previous section about the post-processing, the obtained edge map v^{i+1} need to be projected to the pre-defined rough tumor area to remove the false edges introduced by the CT image.

The above AM algorithm is summarized in Algorithm 1.

Algorithm 1. The AM algorithm to minimize the objective function (6).

Initialization: $f_1 = g_1, f_2 = g_2, v = 1, \sigma_1 = \sigma_2 = \varepsilon_1$;

Iteration: while $|F_e^i - F_e^{i-1}| > \varepsilon_2$ repeat

- (1) Update the edge map v using the gradient descent algorithm, as in Eq.(19), and project v to the pre-defined rough tumor area;
- (2) Update the restored image f_1 using the gradient descent algorithm, as in Eq.(20), and constrain f_1 with Eq.(21);
- (3) Update the piecewise smooth image f_2 using the gradient descent algorithm, as in Eq.(22), and constrain f_2 with Eq.(23);
- (4) Update σ_1 by solving Eq.(12) with the new f_1 using the bisection method;
- (5) Update σ_2 by solving Eq.(13) with the new f_1 using the bisection method;
- (6) Update the blur kernel h_{σ_1, σ_2} using Eq.(7) with new σ_1 and σ_2 and constrain it with Eqs.(24) and (25);
- (7) Calculate the energy F_e of the objective functional (6).

end

Note: i denotes the iteration number of the AM algorithm; ε_2 was set as a small positive constant to control the convergence of the AM algorithm.

3. Experiments and Results

3.1. Experimental Materials

3.1.1. Datasets for Validation—The performance of the proposed method was validated on a dataset with fifty NSCLC patients. All the PET/CT images were obtained on a PET/CT scanner (Reveal HD, CTI, Knoxville, TN, USA) equipped with high-resolution bismuth germanate detectors and a dual-slice CT scanner. The transaxial resolution (3D) of the PET scanner increased from 4.6 mm (full-width at half-maximum, FWHM) at 1 cm from the center to 7.8 mm at a radius of 20 cm. The axial resolution (3D) increases from 3.5 mm at the center to 7.8 mm at a radius of 20 cm (Mawlawi et al., 2004; Humm et al., 2003).

Following an institution standard protocol, all patients fasted for at least 4 hours and then received the intravenous injection of 370–555 MBq of ^{18}F -fluorodeoxyglucose (FDG). One hour after the injection, the whole-body PET/CT imaging scan was started and lasted about 30–35 mins, starting at the thighs and proceeding to the skull base. The PET images were reconstructed using the iterative Ordered Subset Expectation Maximization (OSEM) algorithm with 8 subsets and 2 iterations, and then were processed using a 5 mm FWHM three-dimensional (3D) Gaussian filter. The reconstructed matrix size for each PET slice was 128×128 , with a voxel size $4.69 \times 4.69 \times 3.27 \text{ mm}^3$. For the CT images, the reconstructed matrix size was 512×512 , with a voxel size $0.98 \times 0.98 \times 3.27 \text{ mm}^3$. The ground truth for each of the PET/CT datasets was manually delineated by an experienced radiation oncologist.

For each pair of PET/CT image, a rectangular ROI was manually defined, which enclosed the whole tumor. The proposed method and all comparison algorithms were implemented in the ROI.

3.1.2. Algorithms for Comparison—In order to verify the rationality and validity of the proposed method from various aspects, we compared the proposed method with the following three groups of segmentation algorithms.

1. Several widely used PET segmentation methods were tested to determine the overall performance of the proposed method. These methods included: thresholding algorithms — 42% and 50% of the maximum standardized uptake value (SUV_{max} , 42% Threshold and 50% Threshold) and Otsu automatic thresholding (Otsu, 1975); clustering algorithm — Fuzzy C-means Clustering (FCM); graph theory algorithm — Graph Cuts (GC) (Boykov and Funka-Lea, 2006); and the deformable models — Active Contours (AC) (Chan and Vese, 2001) and Geodesic Active Contours (GAC) (Caselles et al., 1997).
2. To verify the co-segmentation performance of the PET/CT images, we compared the proposed method with the original MS segmentation method (Mumford and Shah, 1989) solely conducted on PET (MS-PET) or on CT (MS-CT) image.
3. To examine whether both PET image restoration and PET/CT co-segmentation contributed to the segmentation, we tested a simultaneous restoration and segmentation algorithm (Li et al., 2017) over the PET image only (Res and Seg of PET) and a co-segmentation algorithm without image restoration over the PET/CT images (Co-Seg without Res). The energy functional of the latter is

$$\begin{aligned}
 F_{\varepsilon}(f_1, f_2, v) = & \frac{1}{2} \int \int \int_{\Omega} ((f_1 - g_1)^2 + (f_2 - g_2)^2) dx dy dz \\
 & + \beta \int \int \int_{\Omega} v^2 (|\nabla f_1|^2 + |\nabla f_2|^2) dx dy dz \\
 & + \alpha \int \int \int_{\Omega} \left(\varepsilon |\nabla v|^2 + \frac{(v-1)^2}{4\varepsilon} \right) dx dy dz.
 \end{aligned} \tag{26}$$

Similar to the proposed method, the above energy functional was minimized using the AM algorithm. Firstly, we derived the Euler-Lagrange equations with respect to the piecewise

smooth images f_1 and f_2 , and the edge map v respectively. Then these three Euler-Lagrange equations were alternately solved using the gradient descent algorithm.

3.1.3. Parameter Setting—The parameters of the proposed method and all comparison algorithms were manually optimized. For the proposed method, we first chose a pair of PET/CT image to adjust the parameters. The parameter α controlled the surface area of the segmented volume, so it was adjusted based on the tumor volume. If the tumor volume was large, a smaller value was assigned to α . We adjusted the parameter β depending largely on the restored image f_1 , and adjusted γ depending on the difference between the corresponding FWHM values of the estimated blur kernel widths σ_1 and σ_2 and the real FWHM values. After every adjustment of the parameters we calculated the segmentation accuracy. When the segmentation accuracy no longer increased, we assumed that the proposed method achieved the best performance. Once the optimum adjustment of the parameters was achieved for the selected PET/CT image, the obtained β and γ values were used for the remaining images because the real blur kernels of different images keep unchanged in a same dataset. We just had to adjust α according to the tumor volume of different patient data. The parameters we used in our experiments are listed as follows: α changed between 5×10^{-6} and 2×10^{-5} , $\beta=3$, $\gamma=10$, $\epsilon=10^{-4}$, $\epsilon_1=0.8$, and $\epsilon_2=10^{-6}$.

3.1.4. Criteria for Segmentation Performance Evaluation—To evaluate the segmentation performance, we compared each segmentation result with the ground truth by computing the dice similarity index (DSI), classification error (CE), and volume error (VE).

DSI measures the similarity (spatial overlap) between the segmentation result and the ground truth. Assuming the segmented volume and the ground truth are denoted by V_A and V_R respectively, the DSI was computed as (Dewalle-Vignion et al., 2011; Zou et al., 2004):

$$DSI(V_A, V_R) = \frac{2 |V_A \cap V_R|}{|V_A| + |V_R|}, \quad (27)$$

where $|X|$ represents the size of the set X . A bigger value of DSI indicates a better segmentation result. DSI reaches the maximum value 1 when the segmented tumor and the ground truth overlap completely, and reaches the minimum value 0 when they have no spatial overlap.

CE measures the spatial location bias of the segmented tumor compared to the ground truth. It was defined as (Hatt et al., 2009):

$$CE(V_A, V_R) = \frac{|V_{FP}| + |V_{FN}|}{|V_R|}, \quad (28)$$

where $|V_{FP}|$ represents the number of false positive errors (background voxels that were wrongly assigned to tumor), $|V_{FN}|$ represents the number of false negative errors (tumor voxels that were wrongly assigned to background).

VE measures the difference between the segmented volume and the ground truth volume. It was expressed as (Dewalle-Vignion et al., 2011):

$$VE(V_A, V_R) = \frac{abs(|V_A| - |V_R|)}{|V_R|}. \quad (29)$$

Contrary to *DSI*, a bigger value of *CE* and *VE* means a worse segmentation result. The values of *CE* and *VE* might be bigger than 1. In order to enhance the observability of the histogram, all the values bigger than 1 were truncated as 1 in our experiments.

3.2. Experimental Results

A. Validation of the Post-processing—In Fig. 2, we compared the co-segmentation results of the proposed method with and without the post-processing for one patient. In this patient, the tumor is very closed to the chest wall (Fig. 2 (b)). As shown in Figs. 2 (g) and (h), without the post-processing for the edge map v , the chest wall was mistaken as the tumor edges. In Figs. 2 (c) and (d), the pre-defined rough tumor region (green contour) obtained by the MSTV method for the post-processing was superimposed on the PET and CT images, respectively. We can see that the pre-defined rough tumor region contains the whole tumor region and does not contain any chest wall. As expected, with the post-processing process, the co-segmentation result (blue contour in Figs. 2 (e) and (f)) was not affected by the chest wall and it coincided well with the manual contour (pink contour). It is common that tumors may abut or invade the adjacent structures. The post-processing is helpful for the PET/CT tumor co-segmentation to exclude the possible false edges near tumors.

B. Validation of Co-segmentation, PET Restoration and Blur Kernel

Estimation—The convergence results with respect to each variable of the proposed energy functional (6) for an ‘isolated’ lung tumor (the lung tumor was located in the lung parenchyma and away from associated structures in the thorax) are displayed in Fig. 3. The horizontal profile (Fig. 3 (i)) along the red line in the PET image (Fig. 3 (a)) demonstrated that the tumor edge in PET was blurred, which made it difficult to segment the tumor based only on the PET image. However, by combining the information of the PET and CT images, the proposed method obtained an exact edge detection result (Fig. 3 (f)). Figs. 3 (g) and (h) show the edge contour (blue contour) of the segmentation result superimposed on PET and CT images, respectively. In Fig. 3 (h), we can see that the edge contour of the segmentation result was well identical with the tumor edge in CT image and agreed well with the manual contour (pink contour), and the false edges in the background of the CT image were completely removed by the post-processing (Fig. 3 (e), green contour). This means that the edge information of the CT image was helpful to define the tumor edge, and the post-processing based on the PET image was effective. In addition, the clearer tumor edge in CT image contributed to the restoration of the PET image. Both the restored image (Fig. 3 (c)) and the horizontal profile (Fig. 3 (j)) indicated that the proposed method achieved a good restoration result for the PET image. The estimated blur kernel widths σ_1 (the transversal direction) and σ_2 (the axial direction) converged to 2.79 mm and 1.58 mm, leading to FWHMs of 6.56 mm and 3.71 mm, respectively, which were very close to the real FWHMs.

In Fig. 4, the results of a ‘complex’ lung tumor are displayed. This tumor was attached to the chest wall. As a result we could hardly separate the tumor from the chest wall only using the CT image (Fig. 4 (b)). Combining the edge information in the lower-right corner of the PET image and the tumor edges in other regions in the CT image, the proposed method still got a satisfactory segmentation result (Figs. 4 (g) and (h), DSI=0.91, CE=0.17, VE=0.03).

Similarly with the case shown in Fig. 3, the proposed method obtained a good restored image (Figs. 4 (c) and (j)) for PET and an accurate blur kernel estimation.

C. Quantitative Validation of the Co-segmentation—The mean and standard deviation of DSI, CE and VE of the segmentation results of the fifty NSCLC patients are shown in Fig. 5 to compare the performance of the proposed method and the other eleven methods. The detailed numerical values are listed in table 1. Overall, the proposed method performed the best according to the three accuracy evaluation criteria (DSI= 0.85, CE=0.31, VE=0.09). The Co-Seg without Res method (DSI= 0.82, CE=0.41, VE=0.25) and the Res and Seg of PET method (DSI= 0.83, CE=0.34, VE=0.10), although not as good as the proposed method, were superior to all other comparison algorithms only using the PET or CT image and without a PET restoration process. This suggested that both PET image restoration and PET/CT co-segmentation helped improve the segmentation performance. Moreover, it indicated that the proposed co-segmentation method integrated with PET restoration was reasonable and effective. Because of the effect of the surrounding structures in the CT image, the MS-CT algorithm had serious leaking problem and it performed the worst. The unsatisfactory performance of those methods solely using the PET image was mainly caused by the blurred tumor edges and the uptake inhomogeneity in PET.

D. Visual Comparison with other Algorithms—In order to visually compare the segmentation performance of different methods, the results of two lung cancer cases are shown in Figs. 6 and 7. For the case in Fig. 6, the tumor invaded the chest wall. It was difficult to separate the tumor from the chest wall in the CT image (Fig. 6 (b)). Fig. 6 (h) shows that the MS-CT method failed to segment the upper-left corner region of the tumor and incorrectly segmented the non-tumor region (lower-left corner) due to the interference of the chest wall. Just as bad, because of the uptake inhomogeneity of the tumor in the PET image (Fig. 6 (a)), all the methods merely based on the PET image could not delineate the whole tumor. The thresholding methods (Otsu, 42% and 50% Threshold, Figs. 6 (j)-(l)), clustering method (FCM, Fig. 6 (m)) and graph theory algorithm (GC, Fig. 6 (p)) could only delineate the tumor regions with high SUVs. All the deformable model-based PET segmentation methods (Res and Seg of PET (Fig. 6 (i)), MS-PET (Fig. 6 (g)), AC (Fig. 6 (n)) and GAC (Fig. 6 (o))) were not able to segment the upper-left corner region of the tumor where the tumor boundary was weaker because of the low SUVs. Combining the information of the PET and CT images, the two co-segmentation methods performed better than all other methods. Without the PET restoration process, however, the Co-Seg without Res method (Figs. 6 (e)-(f)) was still unable to correctly segment the upper-left corner region of the tumor. The proposed method (Figs. 6 (c)-(d)) obtained a satisfactory segmentation result with DSI of 0.88, CE of 0.25 and VE of 0.05.

In Fig. 7, the results are shown in the coronal view for another case. The tumor was attached to the thoracic vertebrae and the chest wall (Fig. 7 (b)), and the tumor had more serious uptake inhomogeneity in PET (Fig. 7 (a)). Similarly as the case in Fig. 6, the MS-TV method failed to segment the tumor from the CT image (Fig. 7 (h)). The common PET segmentation methods could not segment the necrosis regions with low SUVs (Figs. 7 (j)-(p)). The proposed method was significantly superior to these common segmentation methods and achieved an accurate segmentation result (Figs. 7 (c)-(d)).

4. Discussion

Accurate tumor segmentation is crucial for effective radiation therapy, which can ensure maximum dose delivered to the cancer cells in the tumor and potentially reduce exposure and harm to surrounding healthy tissues (Pan and Mawlawi, 2008). However, for any single modality medical image, tumor segmentation is a challenge problem. Considering the complementary information between different modality images, many co-segmentation methods (multimodality image segmentation method) have been proposed for tumor segmentation. Information from different modality images can be either consistent or inconsistent. Those inconsistent information may not only fail to improve the tumor segmentation performance, but interfere the tumor segmentation and introduce other problems. Therefore, how to fuse the complementary information and handle the inconsistent information is the main problem for multimodality image co-segmentation.

Most of the existing tumor co-segmentation methods considered the information fusion of different modality images by penalizing the segmentation difference between the two modalities. Other existing tumor co-segmentation methods fused the information from different modality images by regarding them as the multi-channels in the same information source. However, both strategies considered the information fusion from the viewpoint of energy minimization of the objective function, without taking into account the practical physical meaning of each imaging modality. When the information from different modality images is inconsistent, those methods could only obtain compromised results between the two modalities.

In the proposed PET/CT co-segmentation method, a novel fusion strategy was designed to handle the information inconsistency between PET and CT. This new strategy could automatically decide which modality should be more trustful when PET and CT have inconsistent tumor edges. For instance, in the areas where the tumor invaded the adjacent structures (Figs. 1 (d), 4 (b), 6 (b) and 7 (b)), such as the chest wall, there is no clear tumor edges in CT. Due to the high contrast nature of PET, we can still see the tumor edges in PET (Figs. 1 (c), 4 (a), 6 (a) and 7 (a)), although it is blurred. In this case, the proposed method adaptively defined the tumor edges based on the PET image. Figs. 6 (h) and 7 (h) show that the MS-CT method solely using CT failed to segment those areas invading the normal structures. With the new designed fusion strategy, the Co-Seg without Res method (PET/CT co-segmentation without PET restoration, Figs. 6 (e)-(f) and 7 (e)-(f)) was significantly superior the MS-CT method. Despite this, the Co-Seg without Res method did not achieve the desired segmentation result because of the blurred tumor edges of PET.

As with the single PET segmentation, the blurred tumor edges could easily introduce uncertainty for tumor segmentation. In order to eliminate the uncertainty and improve the co-segmentation performance, we integrated a PET restoration process (You and Kaveh, 1996) into the co-segmentation model. To our knowledge, no one PET/CT tumor co-segmentation method directly considering the PET restoration has been published at present. Comparing the segmentation results of the proposed method (Figs. 6 (c)-(d) and 7 (c)-(d)) with the Co-Seg without Res method (Figs. 6 (e)-(f) and 7 (e)-(f)), we can conclude that the PET restoration process increased the co-segmentation performance effectively. On the other hand, when both PET and CT had tumor edges and the edge information was consistent (Figs. 3 (a)-(b)), the proposed method automatically selected to use more information from CT than from PET to locate the tumor edges. This is because the tumor edges in CT were clearer than those in PET due to the higher resolution of the CT scanner. And then the obtained tumor edges would guide the restoration of the PET image. Figs. 3 (g) and (h) show that the edge contour of the segmentation result coincided well with the tumor edges in CT. Figs. 3 (c) and (j) indicate that the proposed method achieved a good restoration result for PET.

In the CT images, there are usually some edges of the adjacent normal structures and tissues (portions A and B in Fig. 1 (d), and Fig. 2 (b)), which may be mistaken as the tumor edges and result in an over-segmentation (Figs. 2 (g)-(h)). In this study, we designed a post-processing method based on the MSTV segmentation algorithm to solve this problem. Using the high contrast and relatively more clean background of the PET image and the advantage of protecting edge information of the TV regularization, the post-processing effectively removed the false edges (Figs. 2 (e)-(f)). However, the post-processing increased the complexity of the co-segmentation algorithm. In our future work, we will consider how to add the priori information of the PET image into the energy functional (6) directly to avoid the influence of the false edges, without the need for any post-processing.

The proposed method required a one-to-one voxel correspondence between the PET image and the CT image. Typically the PET image and the CT image from an integrated PET/CT scanner were aligned by hardware. In this study, we assumed that both images had been perfectly aligned. However, many factors effects the alignment accuracy. An accurate registration can help to enhance the segmentation performance. But image registration itself remains challenging. A co-segmentation method that does not depend on the image alignment and registration may be more practical and achieve more accurate segmentation results.

As with most other variational image processing algorithms, the energy functional (Eq.(6)) of the proposed method is not jointly convex. Therefore, the optimization algorithms were easily trapped into a local minima. Another urgent and challenging problem is to improve the optimization algorithm and obtain a global optimal solution.

5. Conclusions

In this study, we proposed a novel variational method for PET/CT tumor co-segmentation, with a specifically designed information fusion strategy. And a PET restoration process was

integrated into the co-segmentation process to handle the blurred tumor edges of the PET image. The new information fusion strategy could automatically decide which modality should be more trustful for localizing the tumor boundary, which made the proposed method could not only make full advantage of the consistent information between PET and CT but also cope with the inconsistent information between them. In the areas where PET and CT had consistent edge information, the proposed method automatically selected to use more information from CT to define the tumor edge. In other areas where CT had no clear tumor edges, while PET had one though blurred, the proposed method adaptively defined tumor edges mainly based on the PET image. Then, the PET restoration process could eliminate the uncertainty for tumor edge location introduced by the blurring of tumor edges in PET. Experimental results clearly demonstrated that the proposed method had a good performance for both PET/CT tumor co-segmentation and PET restoration.

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Appendix

Appendix A

The detailed mathematical derivations of the Eqs.(9), (10) and (11) are given in this appendix. In the following derivation, h_{σ} denotes h_{σ_1, σ_2} , and the integration element dA denotes $dx dy dz$.

(1) Variation with respect to v

The variation of F_{ϵ} (Eq.(6)) with respect to v can be expressed as

$$\begin{aligned} & \left. \frac{\partial}{\partial \lambda} F_{\epsilon}(v + \lambda \psi) \right|_{\lambda=0} \\ &= \left. \frac{\partial}{\partial \lambda} \left\{ \beta \int_{\Omega} (v + \lambda \psi)^2 (|\nabla f_1|^2 + |\nabla f_2|^2) dA + \alpha \int_{\Omega} \left(\epsilon |\nabla(v + \lambda \psi)|^2 + \frac{(v + \lambda \psi - 1)^2}{4\epsilon} \right) dA \right\} \right|_{\lambda=0} \quad (A.1) \\ & 0 \\ & . \end{aligned}$$

Let

$$\begin{aligned} \left. \frac{\partial F_{\epsilon}^I}{\partial \lambda} \right|_{\lambda=0} &= \left. \frac{\partial}{\partial \lambda} \left\{ \beta \int_{\Omega} (v + \lambda \psi)^2 (|\nabla f_1|^2 + |\nabla f_2|^2) dA \right\} \right|_{\lambda=0}, \\ \left. \frac{\partial F_{\epsilon}^{II}}{\partial \lambda} \right|_{\lambda=0} &= \left. \frac{\partial}{\partial \lambda} \left\{ \alpha \int_{\Omega} \epsilon |\nabla(v + \lambda \psi)|^2 dA \right\} \right|_{\lambda=0}, \\ \left. \frac{\partial F_{\epsilon}^{III}}{\partial \lambda} \right|_{\lambda=0} &= \left. \frac{\partial}{\partial \lambda} \left\{ \alpha \int_{\Omega} \frac{(v + \lambda \psi - 1)^2}{4\epsilon} dA \right\} \right|_{\lambda=0}, \end{aligned}$$

then

$$\begin{aligned} \left. \frac{\partial F_{\varepsilon}^I}{\partial \lambda} \right|_{\lambda=0} &= \left\{ \beta \int_{\Omega} 2(v + \lambda\psi) \psi (|\nabla f_1|^2 + |\nabla f_2|^2) dA \right\} \Big|_{\lambda=0} \\ &= 2\beta \int_{\Omega} v (|\nabla f_1|^2 + |\nabla f_2|^2) \psi dA, \end{aligned} \quad (\text{A.2})$$

$$\begin{aligned} \left. \frac{\partial F_{\varepsilon}^{II}}{\partial \lambda} \right|_{\lambda=0} &= \left\{ \alpha \int_{\Omega} (2\varepsilon(v_x + \lambda\psi_x)\psi_x + 2\varepsilon(v_y + \lambda\psi_y)\psi_y + 2\varepsilon(v_z + \lambda\psi_z)\psi_z) dA \right\} \Big|_{\lambda=0} \\ &= 2\alpha\varepsilon \int_{\Omega} (v_x\psi_x + v_y\psi_y + v_z\psi_z) dA \\ &= 2\alpha\varepsilon \left\{ \int_{\Omega} \frac{\partial}{\partial x} (v_x\psi) dA + \int_{\Omega} \frac{\partial}{\partial y} (v_y\psi) dA + \int_{\Omega} \frac{\partial}{\partial z} (v_z\psi) dA \right. \\ &\quad \left. - \int_{\Omega} (v_{xx} + v_{yy} + v_{zz}) \psi dA \right\} \end{aligned} \quad (\text{A.3})$$

By using the divergence theorem, we get

$$\int_{\Omega} \frac{\partial}{\partial x} (v_x\psi) dA + \int_{\Omega} \frac{\partial}{\partial y} (v_y\psi) dA + \int_{\Omega} \frac{\partial}{\partial z} (v_z\psi) dA = \int_{\partial\Omega} \psi \nabla v dn, \quad (\text{A.4})$$

where n is the normal vector to the contour. With the Neumann boundary condition:

$$\frac{\partial v}{\partial n} = 0, \quad (x, y, z) \in \partial\Omega,$$

We obtain

$$\int_{\partial\Omega} \psi \nabla v dn = 0. \quad (\text{A.5})$$

By substituting Eqs.(A.4) and (A.5) into Eq.(A.3), we have

$$\left. \frac{\partial F_{\varepsilon}^{II}}{\partial \lambda} \right|_{\lambda=0} = -2\alpha\varepsilon \int_{\Omega} (v_{xx} + v_{yy} + v_{zz}) \psi dA = -2\alpha\varepsilon \int_{\Omega} \nabla^2 v \cdot \psi dA. \quad (\text{A.6})$$

$$\left. \frac{\partial F_{\varepsilon}^{III}}{\partial \lambda} \right|_{\lambda=0} = \left\{ \alpha \int_{\Omega} \frac{2}{4\varepsilon} (v + \lambda\psi - 1) \psi dA \right\} \Big|_{\lambda=0} = \alpha \int_{\Omega} \frac{(v-1)}{2\varepsilon} \psi dA. \quad (\text{A.7})$$

Substituting Eqs.(A.2), (A.6) and (A.7) into Eq.(A.1), we obtain

$$\begin{aligned}
\left. \frac{\partial}{\partial \lambda} F_\varepsilon(v + \lambda \psi) \right|_{\lambda=0} &= \left. \frac{\partial F_\varepsilon^I}{\partial \lambda} \right|_{\lambda=0} + \left. \frac{\partial F_\varepsilon^{II}}{\partial \lambda} \right|_{\lambda=0} + \left. \frac{\partial F_\varepsilon^{III}}{\partial \lambda} \right|_{\lambda=0} \\
&= \int_{\Omega} \left(2\beta v (|\nabla f_1|^2 + |\nabla f_2|^2) - 2\alpha \varepsilon \nabla^2 v \right. \\
&\quad \left. + \alpha \frac{(v-1)}{2\varepsilon} \right) \psi dA = 0.
\end{aligned} \tag{A.8}$$

For (A.8), using the fundamental lemma of calculus of variations, we obtain Eq.(9):

$$\frac{\delta F_\varepsilon}{\delta v} = 2\beta (|\nabla f_1|^2 + |\nabla f_2|^2) v + \alpha \cdot \frac{v-1}{2\varepsilon} - 2\alpha \varepsilon \nabla^2 v = 0.$$

(2) Variation with respect to f_1

The variation of F_ε (Eq.(6)) with respect to f_1 can be expressed as

$$\begin{aligned}
&\left. \frac{\partial}{\partial \lambda} F_\varepsilon(f_1 + \lambda \phi_1) \right|_{\lambda=0} \\
&= \left. \frac{\partial}{\partial \lambda} \left\{ \frac{1}{2} \int_{\Omega} (h_\sigma * (f_1 + \lambda \phi_1) - g_1)^2 dA + \beta \int_{\Omega} v^2 ((f_{1,x} + \lambda \phi_{1,x})^2 + (f_{1,y} + \lambda \phi_{1,y})^2 + (f_{1,z} + \lambda \phi_{1,z})^2) dA \right\} \right|_{\lambda=0} \tag{A.9} \\
&= 0.
\end{aligned}$$

Let

$$\begin{aligned}
\left. \frac{\partial F_\varepsilon^I}{\partial \lambda} \right|_{\lambda=0} &= \left. \frac{\partial}{\partial \lambda} \left\{ \frac{1}{2} \int_{\Omega} (h_\sigma * (f_1 + \lambda \phi_1) - g_1)^2 dA \right\} \right|_{\lambda=0}, \\
\left. \frac{\partial F_\varepsilon^{II}}{\partial \lambda} \right|_{\lambda=0} &= \left. \frac{\partial}{\partial \lambda} \left\{ \beta \int_{\Omega} v^2 ((f_{1,x} + \lambda \phi_{1,x})^2 + (f_{1,y} + \lambda \phi_{1,y})^2 + (f_{1,z} + \lambda \phi_{1,z})^2) dA \right\} \right|_{\lambda=0},
\end{aligned}$$

then

$$\begin{aligned}
\left. \frac{\partial F_\varepsilon^I}{\partial \lambda} \right|_{\lambda=0} &= \left. \left\{ \frac{1}{2} \int_{\Omega} 2(h_\sigma * (f_1 + \lambda \phi_1) - g_1)(h_\sigma * \phi_1) dA \right\} \right|_{\lambda=0} \\
&= \int_{\Omega} (h_\sigma * f_1 - g_1)(h_\sigma * \phi_1) dA.
\end{aligned} \tag{A.10}$$

Let $\ell(x, y, z) = h_\sigma * f_1 - g_1$, then

$$\begin{aligned}
\left. \frac{\partial F_{\epsilon}^I}{\partial \lambda} \right|_{\lambda=0} &= \int_{\Omega} l(x, y, z) (h_{\sigma} * \phi_1) dA \\
&= \iint \int_{\Omega} l(x, y, z) \left(\iint \int_{\Omega} h_{\sigma}(x - x', y - y', z - z') \phi_1(x', y', z') \right. \\
&\quad \left. dx' dy' dz' \right) dx dy dz \\
&= \iint \int_{\Omega} \left(\iint \int_{\Omega} l(x, y, z) h_{\sigma}(x - x', y - y', z - z') dx dy dz \right) \phi_1(x', \\
&\quad y', z') dx' dy' dz' \\
&= \iint \int_{\Omega} (l(x, y, z) * h_{\sigma}(-x, -y, -z)) \phi_1(x, y, z) dx dy dz.
\end{aligned} \tag{A.11}$$

$$\begin{aligned}
\left. \frac{\partial F_{\epsilon}^{II}}{\partial \lambda} \right|_{\lambda=0} &= \left\{ \beta \int_{\Omega} v^2 (2(f_{1,x} + \lambda \phi_{1,x}) \phi_{1,x} + 2(f_{1,y} + \lambda \phi_{1,y}) \phi_{1,y} + 2(f_{1,z} + \lambda \phi_{1,z}) \phi_{1,z}) dA \right\} \Big|_{\lambda=0} \\
&= 2\beta \int_{\Omega} v^2 (f_{1,x} \phi_{1,x} + f_{1,y} \phi_{1,y} + f_{1,z} \phi_{1,z}) dA \\
&= 2\beta \left\{ \int_{\Omega} \frac{\partial}{\partial x} (v^2 \phi_1 f_{1,x}) dA + \int_{\Omega} \frac{\partial}{\partial y} (v^2 \phi_1 f_{1,y}) dA \right. \\
&\quad \left. + \int_{\Omega} \frac{\partial}{\partial z} (v^2 \phi_1 f_{1,z}) dA \right. \\
&\quad \left. - \int_{\Omega} \left(\frac{\partial}{\partial x} (v^2 f_{1,x}) + \frac{\partial}{\partial y} (v^2 f_{1,y}) + \frac{\partial}{\partial z} (v^2 f_{1,z}) \right) \phi_1 dA \right\}
\end{aligned} \tag{A.12}$$

By using the divergence theorem, we get

$$\begin{aligned}
&\int_{\Omega} \frac{\partial}{\partial x} (v^2 \phi_1 f_{1,x}) dA + \int_{\Omega} \frac{\partial}{\partial y} (v^2 \phi_1 f_{1,y}) dA + \int_{\Omega} \frac{\partial}{\partial z} (v^2 \phi_1 f_{1,z}) dA \\
&= \int_{\partial \Omega} v^2 \phi_1 \nabla f_1 dn,
\end{aligned} \tag{A.13}$$

where n is the normal vector to the contour. With the Neumann boundary condition:

$$\frac{\partial f_1}{\partial n} = 0, \quad (x, y, z) \in \partial \Omega,$$

we obtain

$$\int_{\partial \Omega} v^2 \phi_1 \nabla f_1 dn = 0. \tag{A.14}$$

Substituting Eqs.(A.13) and (A.14) into Eq.(A.12), we get

$$\begin{aligned}
\left. \frac{\partial F_{\epsilon}^{II}}{\partial \lambda} \right|_{\lambda=0} &= -2\beta \int_{\Omega} \left(\frac{\partial}{\partial x} (v^2 f_{1,x}) + \frac{\partial}{\partial y} (v^2 f_{1,y}) + \frac{\partial}{\partial z} (v^2 f_{1,z}) \right) \phi_1 dA \\
&= -2\beta \int_{\Omega} (\text{Div}(v^2 \nabla f_1)) \phi_1 dA.
\end{aligned} \tag{A.15}$$

Then, substituting Eqs.(A.11) and (A.15) into Eq.(A.9), we obtain

$$\begin{aligned} \frac{\partial}{\partial \lambda} F_{\epsilon}(f_1 + \lambda \phi_1) \Big|_{\lambda=0} &= \frac{\partial F_{\epsilon}^I}{\partial \lambda} \Big|_{\lambda=0} + \frac{\partial F_{\epsilon}^{II}}{\partial \lambda} \Big|_{\lambda=0} \\ &= \int_{\Omega} ((h_{\sigma} * f_1 - g_1) * h_{\sigma}(-x, -y, -z) \\ &\quad - 2\beta \text{Div}(v^2 \nabla f_1)) \phi_1 dA = 0. \end{aligned} \quad (\text{A.16})$$

For Eq.(A.16), using the fundamental lemma of calculus of variations, we get Eq.(10):

$$\frac{\delta F_{\epsilon}}{\delta f_1} = (h_{\sigma} * f_1 - g_1) * h_{\sigma}(-x, -y, -z) - 2\beta \text{Div}(v^2 \nabla f_1) = 0.$$

(3) Variation with respect to f_2

$$\begin{aligned} &\frac{\partial}{\partial \lambda} F_{\epsilon}(f_2 + \lambda \phi_2) \Big|_{\lambda=0} \\ &= \frac{\partial}{\partial \lambda} \left\{ \frac{1}{2} \int_{\Omega} (f_2 + \lambda \phi_2 - g_2)^2 dA \right. \\ &\quad \left. + \beta \int_{\Omega} v^2 ((f_{2,x} + \lambda \phi_{2,x})^2 + (f_{2,y} + \lambda \phi_{2,y})^2 + (f_{2,z} + \lambda \phi_{2,z})^2) dA \right\} \Big|_{\lambda=0} \\ &= 0. \end{aligned} \quad (\text{A.17})$$

Using the same method as in the previous section, we get

$$\frac{\partial F_{\epsilon}^I}{\partial \lambda} \Big|_{\lambda=0} = \left\{ \frac{1}{2} \int_{\Omega} 2(f_2 + \lambda \phi_2 - g_2) \phi_2 dA \right\} \Big|_{\lambda=0} = \int_{\Omega} (f_2 - g_2) \phi_2 dA \quad (\text{A.18})$$

$$\begin{aligned} \frac{\partial F_{\epsilon}^{II}}{\partial \lambda} \Big|_{\lambda=0} &= \left\{ \beta \int_{\Omega} v^2 (2(f_{2,x} + \lambda \phi_{2,x}) \phi_{2,x} + 2(f_{2,y} + \lambda \phi_{2,y}) \phi_{2,y} + 2(f_{2,z} + \lambda \phi_{2,z}) \phi_{2,z}) dA \right\} \Big|_{\lambda=0} \\ &= -2\beta \int_{\Omega} (\text{Div}(v^2 \nabla f_2)) \phi_2 dA \end{aligned} \quad (\text{A.19})$$

Substituting Eqs.(A.18) and (A.19) into Eq.(A.17), and using the fundamental lemma of calculus of variations, we obtain Eq.(11):

$$\frac{\delta F_{\epsilon}}{\delta f_2} = (f_2 - g_2) - 2\beta \text{Div}(v^2 \nabla f_2) = 0.$$

Appendix B

In this appendix, we present the detailed derivation of Eqs.(14) and (16).

The anisotropic Gaussian kernel is defined as:

$$h_{\sigma_1, \sigma_2} = \frac{1}{(2\pi)^{3/2} \sigma_1^2 \sigma_2} e^{-\left(\frac{x^2 + y^2}{2\sigma_1^2} + \frac{z^2}{2\sigma_2^2}\right)}.$$

Following this definition, Eq.(14) can be obtained using the following steps:

$$\begin{aligned} \frac{\partial h_{\sigma_1, \sigma_2}}{\partial \sigma_1} &= \frac{1}{(2\pi)^{3/2} \sigma_2} e^{-\frac{z^2}{2\sigma_2^2}} \frac{\partial}{\partial \sigma_1} \left(\frac{1}{\sigma_1^2} e^{-\frac{x^2 + y^2}{2\sigma_1^2}} \right) \\ &= \frac{1}{(2\pi)^{3/2} \sigma_2} e^{-\frac{z^2}{2\sigma_2^2}} \left(\frac{-2}{\sigma_1^3} e^{-\frac{x^2 + y^2}{2\sigma_1^2}} + \frac{1}{\sigma_1^2} e^{-\frac{x^2 + y^2}{2\sigma_1^2}} \frac{x^2 + y^2}{\sigma_1^3} \right) \\ &= \frac{1}{(2\pi)^{3/2} \sigma_1^2 \sigma_2} e^{-\left(\frac{x^2 + y^2}{2\sigma_1^2} + \frac{z^2}{2\sigma_2^2}\right)} \left(\frac{x^2 + y^2}{\sigma_1^3} - \frac{2}{\sigma_1} \right). \end{aligned}$$

Similarly, we can derive Eq.(15).

Eq.(16) can be obtained as:

$$\begin{aligned} \frac{\partial}{\partial \sigma_1} | \nabla h_{\sigma_1, \sigma_2} |^2 &= \frac{\partial}{\partial \sigma_1} \left(\left(\frac{\partial}{\partial x} h_{\sigma_1, \sigma_2} \right)^2 + \left(\frac{\partial}{\partial y} h_{\sigma_1, \sigma_2} \right)^2 + \left(\frac{\partial}{\partial z} h_{\sigma_1, \sigma_2} \right)^2 \right) \\ &= \frac{\partial}{\partial \sigma_1} \left(\frac{1}{(2\pi)^3 \sigma_1^4 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2}\right)} \left(\frac{x^2 + y^2}{\sigma_1^4} + \frac{z^2}{\sigma_2^4} \right) \right) \\ &= \frac{\partial}{\partial \sigma_1} \left(\frac{x^2 + y^2}{(2\pi)^3 \sigma_1^8 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2}\right)} \right) + \frac{\partial}{\partial \sigma_1} \left(\frac{z^2}{(2\pi)^3 \sigma_1^6 \sigma_2^6} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2}\right)} \right) \\ &= \frac{x^2 + y^2}{4\pi^3 \sigma_1^4 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2}\right)} \left(\frac{x^2 + y^2}{\sigma_1^7} - \frac{4}{\sigma_1^5} \right) + \frac{z^2}{4\pi^3 \sigma_1^4 \sigma_2^2} e^{-\left(\frac{x^2 + y^2}{\sigma_1^2} + \frac{z^2}{\sigma_2^2}\right)} \left(\frac{x^2 + y^2}{\sigma_1^3 \sigma_2^4} - \frac{2}{\sigma_1 \sigma_2^4} \right). \end{aligned}$$

In the same way, we can derive Eq.(17).

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Figure 1.

PET/CT images. (a) One slice of a PET image and the manual contour (pink contour), (b) the corresponding CT image and the manual contour, (c) the magnified view of the region of interest of the PET image, (d) the magnified view of the region of interest of the CT image, (e) a horizontal profile along the green line in the magnified PET image, (f) a horizontal profile along the green line in the magnified CT image.

Figure 2.

An example showing the rationality and effectiveness of the post-processing. The pink contour is the manual contour. (a) PET image, (b) CT image, (c)-(d) pre-defined rough tumor region (green contour) obtained by the MSTV method for post-processing, (e)-(f) co-segmentation result (blue contour) (DSI=0.88) of the proposed method with post-processing, (g)-(h) co-segmentation result (blue contour) (DSI=0.57) of the proposed method without post-processing.

Figure 3.

Results of each variable of the proposed energy functional for a lung cancer patient with an 'isolated' tumor. The pink contour is the manual contour. (a) PET image, (b) CT image, (c) restored PET image (f_1), (d) piecewise smooth approximation (f_2) of the CT image, (e) rough tumor region (green contour) obtained by the MSTV method for post-processing, (f) edge map v , (g)-(h) result (blue contour) of the proposed method (DSI=0.91) superimposed on the PET (g) and CT (h) images, (i) horizontal profile along the red line in the original

PET image; (j) horizontal profile along the red line in the restored PET image; (k) convergence curve of σ_1 ; (l) convergence curve of σ_2 .

Figure 4.

Results of each variable of the proposed energy functional for a complex lung cancer case. The pink contour is the manual contour. (a) PET image, (b) CT image, (c) restored PET image (f_1), (d) piecewise smooth approximation (f_2) of the CT image, (e) rough tumor region (green contour) obtained by the MSTV method for post-processing, (f) edge map v , (g)-(h) result (blue contour) of the proposed method (DSI=0.91) superimposed on the PET (g) and CT (h) images, (i) horizontal profile along the red line in the original PET image; (j) horizontal profile along the red line in the restored PET image; (k) σ_1 vs Iteration Number; (l) σ_2 vs Iteration Number.

horizontal profile along the red line in the restored PET image; (k) convergence curve of σ_1 ; (l) convergence curve of σ_2 .

Figure 5.
(a) DSI, (b) CE, (c) VE, averaged over fifty patients with NSCLC.

Figure 6.

Visual comparison (axial view) of the segmentation results (blue contours) of different methods and the manual contour (pink contour) for one patient. (a) PET image, (b) CT image, (c)-(d) our proposed co-segmentation result (DSI=0.88) superimposed on the PET (c) and the CT (d) image, (e)-(f) segmentation result of the Co-Seg without Res method (DSI=0.86) superimposed on the PET (e) and the CT (f) image, (g) segmentation result (DSI=0.80) conducted by the MS method solely using the PET image, (h) segmentation result (DSI=0.51) conducted by the MS method solely using the CT image, (i) Res and Seg of PET (DSI=0.85), (j) Otsu (DSI=0.77), (k) 42% Threshold (DSI=0.58), (l) 50% Threshold (DSI=0.44), (m) FCM (DSI=0.76), (n) AC (DSI=0.81), (o) GAC (DSI=0.68), (p) GC (DSI=0.67).

Figure 7.

Visual comparison (coronal view) of the segmentation results (blue contours) of different methods and the manual contour (pink contour) for another patient. (a) PET image, (b) CT image, (c)-(d) our proposed co-segmentation result (DSI=0.89) superimposed on the PET (c) and the CT (d) image, (e)-(f) segmentation result of the Co-Seg without Res method (DSI=0.88) superimposed on the PET (e) and the CT (f) image, (g) segmentation result (DSI=0.80) conducted by the MS method solely using the PET image, (h) segmentation result (DSI=0.45) conducted by the MS method solely using the CT image, (i) Res and Seg of PET (DSI=0.87), (j) Otsu (DSI=0.80), (k) 42% Threshold (DSI=0.48), (l) 50% Threshold (DSI=0.36), (m) FCM (DSI=0.79), (n) AC (DSI=0.84), (o) GAC (DSI=0.75), (p) GC (DSI=0.66).

Table 1.

The mean and standard deviation of DSI, CE and VE of the segmentation results of the proposed method and all comparison algorithms.

Methods	DSI (mean $\pm$ SD)	CE (mean $\pm$ SD)	VE (mean $\pm$ SD)
Ours	0.85 $\pm$ 0.06	0.31 $\pm$ 0.13	0.09 $\pm$ 0.08
Co-Seg without Res	0.82 $\pm$ 0.08	0.41 $\pm$ 0.22	0.25 $\pm$ 0.23
Res and Seg of PET	0.83 $\pm$ 0.06	0.34 $\pm$ 0.13	0.10 $\pm$ 0.07
MS-PET	0.79 $\pm$ 0.12	0.39 $\pm$ 0.19	0.21 $\pm$ 0.20
MS-CT	0.39 $\pm$ 0.15	0.99 $\pm$ 0.01	0.72 $\pm$ 0.35
Otsu	0.79 $\pm$ 0.14	0.42 $\pm$ 0.29	0.31 $\pm$ 0.32
42% Threshold	0.69 $\pm$ 0.18	0.48 $\pm$ 0.18	0.41 $\pm$ 0.22
50% Threshold	0.58 $\pm$ 0.20	0.58 $\pm$ 0.18	0.54 $\pm$ 0.22
FCM	0.80 $\pm$ 0.08	0.40 $\pm$ 0.22	0.27 $\pm$ 0.24
AC	0.77 $\pm$ 0.20	0.43 $\pm$ 0.29	0.30 $\pm$ 0.35
GAC	0.72 $\pm$ 0.15	0.58 $\pm$ 0.23	0.30 $\pm$ 0.25
GC	0.77 $\pm$ 0.12	0.42 $\pm$ 0.19	0.28 $\pm$ 0.21