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Composite Radiation Dose Representation Using Fuzzy Set Theory

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Abstract

Composite plans created from different image sets are generated through Deformable Image Registration (DIR) and present a challenge in accurately presenting uncertainties, which vary with anatomy. Our effort focuses on the application of Fuzzy Set theory to provide an accurate dose representation of such a composite treatment plan. The accuracy of the DIR is generally verified through geometrical visual checks, including the confirmation of the corresponding anatomies with edge features, such as bone or organ boundaries. However, the remaining volume of the image (mostly soft tissues) has few significant image features and therefore greater uncertainty. We fuzzified the deformation vector and derived a Fuzzy composite dose. The fuzzification was implemented using Gaussian functions based on the varying uncertainties in the DIR. After establishing the theoretical basis for this new approach, we present two- and three-dimensional examples as proof-of-concept. Using Fuzzy Set theory, composite dose plans displaying locality-based uncertainties were successfully created, providing information previously unavailable to clinicians. Previous to Fuzzy Set dose presentations, clinicians had no measure of confidence in the accuracy of a composite dose plan. Using fuzzified composite dose presentations, clinicians can determine a safe additional dose to previously treated anatomy. This will possibly increase the treatment success rate and reduce the rate of complications.

Keywords

Fuzzy Set; Deformable Image Registration; Radiation Therapy; Composite Plan

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1 Introduction

In radiation therapy, multiple image sets of a patient are often acquired at different times over the course of their diagnoses and treatment(s). Radiation treatments are determined using computer modeling of the radiation interaction (dose) with the patient's body as represented by a CT image set. Accuracies on the order of mm are required for this computer modeling. Time gaps between image sets frequently range from days to even years. If cancer returns (or a new cancer appears) after an initial course of radiation treatment, it is critical for a clinician to evaluate the composite dose consisting of previous treatments and the newly proposed treatment. Clinicians want to avoid overdosing areas that appear in both treatments, while insuring adequate dosage of the target. An accurate representation of the composite dose will provide the means by which a clinician can deliver an effective dose to the tumor while keeping doses to critical healthy organs to a tolerable level.

Since the human body is not rigid, each image set is not geometrically identical to other image sets. A 3-D radiation treatment plan models delivered radiation using a single 3-D image set. Treatment planning systems (TPS) create a 3-D dose matrix consisting of small volume elements called voxels. The planner defines the dose voxel size. Typically, dose voxels are larger than the image pixel size, and range from 1 to 4 cubic mm. Each voxel carries a dose value in units of Gy (Gray, defined as 1 J/kg). Mapping the 3-D dose matrix to the corresponding 3-D image (used for the calculation) set provides a description of the resulting dose to the patient. Figure 1 shows a sample radiation treatment plan (TP) for a cancer patient with tumors in his left neck. The red cross-lines in each window represent the axes (axial, sagittal, and coronal views) of the cross sectional views. The left upper and lower views are sagittal and coronal slices, respectively.

Accurately matching anatomies between two image sets for summing doses from two treatment plans requires Deformable Image Registration (DIR). Many groups in radiation therapy have published DIR methods.[2, 10, 22] We implemented a multi-resolution B-Spline DIR in our image and plan review system.[20, 21] The B-Spline DIR with a Mutual Information (MI) metric is a popular solution for DIR with multi-modal capability.[22] B-Spline DIR approximates the deformation area using grid points, and expands or compresses elastically between the grid points. B-Spline DIR generates deformation vectors in the image domain.

Creating a composite plan relies on deformation vectors generated through deformable image registration.[27] The accuracy of the deformable image registration may depend on the registration method, the image quality, and the image quality difference between the image sets. Geometric verification of the registration is generally performed through visual checks. Typically, visual checks confirm the anatomies that have clear organ boundaries and bony structures. However, we do not have a means to evaluate the registration accuracy in areas of the images which are mostly tissue (and therefore lack image features) located between and within organs. This can lead to significant flaws in generating a composite dose. Therefore, clinicians need a tool to see the local uncertainties reflected in the radiation dose representations in such composite plans.

There were few manuscripts to handle geometrical uncertainties. Buckley et al introduced Fuzzy point to represent uncertainty in geometric point.[4] Ibáñez et al recently introduced a Fuzzy landmark concept to generate a better landmark by combining multiple landmarks provided by multiple algorithms.[12] In this article, we applied Fuzzy set theory to the interpretation of medical image registration by introducing Fuzzy Deformation Vector. Our effort focuses on the application of Fuzzy Set theory to create an accurate composite dose representation from two plans. Since Fuzzy Set theory is a good method to deal with uncertainty, we introduce the Fuzzy Deformation Vector (FDV) to build the Fuzzy Composite Dose (FCD) by fuzzifying the deformable image registration vectors. A membership function, $\mu_F(r)$, was assigned to each vector in a 3-dimensional deformation matrix. Image areas which have clear radiological features such as organ boundaries and high pixel values (such as bone) can be assigned with sharper membership function, since we know DIR will match accurately in these regions.

Currently, clinicians have no measure of accuracy of a composite dose plan reflecting local uncertainties. In other words, there is no way to display a composite dose in a way that shows the clinician the degree of confidence in the accuracy of the dose at all locations within the patient. Using fuzzified composite dose presentations, clinicians can determine a safe additional dose to previously treated anatomy. In this work, we describe the problem in 2-dimensional space for ease of illustration. However, this effort can easily be expanded to 3-dimension space simply by adding the third dimension.

2 Related Works: Deformable Image Registration and Composite Dose

Volume segments in an organ T , in a new image set V can be represented as $v(i,j)$, illustrated in Figure 2. Let $u(i',j')$ be the corresponding volume segment in a previous image set U . Since V and U are in different geometric spaces, g is a transformation function from the domain of V to the domain of U . We can describe this transformation function as deformation vector $\mathbf{m}(i,j)$, a vector from the point (i,j) to the point (i',j') , which directs the correspondence between two image sets. Note that the point (i,j) is in XY space, the point (i',j') is in X'Y', and the vector $\mathbf{m}(i,j)$ is in dXdY space. We can describe this correspondence as an equation,

$$u(i', j') = u(g[i, j; \mathbf{m}(i, j)]). \quad (1)$$

Therefore, the transformation function g at point (i,j) is described with the deformation vector $\mathbf{m}(i,j)$. And, the result of function g is the transformation of the point (i,j) in XY space to the point (i',j') in X'Y' space.

Deformable Image Registration (DIR) is a process to find the transformation function g between the two image sets, V and U . Image registration is generally defined as a task of searching the correspondence between objects in two images. This correspondence is modeled with a spatial transformation function from one image to the other image. An optimizer finds the best estimation of the transformation function g . DIR is one of image registration methods whose transformation function g is not restricted to preserving the

shape and size of the objects. In this case, it is often referred to as a non-rigid image registration. To check the correspondence, image registration utilizes a similarity metric. Thus, DIR is an iterative process of maximizing the similarity metric between an image and a second transformed image to find the best estimation of the transformation function g . Further details of image registration topics can be found in previously published literature. [1, 3, 9, 10, 22, 29] DIR produces deformation vectors $\mathbf{m}(i,j)$ spanning the image region.

When we calculate composite radiation doses from the plans generated in these two image sets, we utilize the deformation vectors $\mathbf{m}(i,j)$. Let the radiation dose at $\mathbf{v}(i,j)$ be $d_v(i,j)$ and the dose at $\mathbf{u}(\hat{i},\hat{j})$ be $d_u(\hat{i},\hat{j})$. Then, when $\mathbf{v}(i,j)$ and $\mathbf{u}(\hat{i},\hat{j})$ are corresponding volume segments between two image sets, the composite dose $d_c(i,j)$ at $\mathbf{v}(i,j)$ is $d_v(i,j)+d_u(\hat{i},\hat{j})$. Thus, the composite dose $d_c(i,j)$ at $\mathbf{v}(i,j)$ will be described with the deformation vector $\mathbf{m}(i,j)$ as

$$d_c(i,j) = d_v(i,j) + d_u(g[i,j;\mathbf{m}(i,j)]). \quad (2)$$

Figure 2 shows how the deformation vector found by DIR is utilized for a composite dose calculation.

Therefore, the accuracy of the composite dose calculation directly depends on the accuracy of the DIR algorithms. If the DIR algorithm is accurate, we can utilize the deformation vectors, $\mathbf{m}(i,j)$, in dose summation with high confidence. Several research efforts creating composite dose calculations using DIR have been reported. [14, 17] However, they all agree that the clinician should carefully review the result of the DIR because there is no guarantee of accuracy in the DIR algorithm. That is because evaluation of the registration accuracy for in-vivo image registration is not yet possible.

Figure 3 shows an example of registration uncertainty. If the image feature is significant, such as the vector from A to A', we can claim there is minimal uncertainty. However, it is not reasonable to claim that the vector from B to B' is strictly correct, since there is no significant image feature in the neighboring pixels. The similarity metric in a DIR process reports the same or similar value when point B is corresponded to the neighboring pixels of point B'. Therefore, neither computational DIR algorithms nor human visual check can claim that the deformation vector from point B to point B' is correct. We have to deal with the uncertainty of the deformation vectors. In this case, we have to consider the neighboring dose values other than $d_u(\hat{i},\hat{j})$. We need some methods to present the uncertainty in the deformation vector and composite dose. With our proposed work, clinicians can estimate the accuracy of displayed dose to tissues while making medical decisions based on such studies.

3 Uncertainty Presentation of Deformation Vector

3.1 Conventional Approach

If the deformable image registration is strictly correct, then there is no uncertainty. This means $\mathbf{m}(i,j)$ is a single and unique vector. For an example, if a 2-dimensional vector $\mathbf{m}(i,j)$ has components (3,3) on the dX and dY axes, the membership degree of $\mathbf{m}(i,j)$ is 1.0 at (3,3)

and zero at other neighboring points. This means it is impossible for $\mathbf{m}(i,j)$ to be other than (3,3). Therefore, if we say $\mathbf{m}(i,j)$ is a vector $(m_X(i,j), m_Y(i,j))$, then the membership function of $\mathbf{m}(i,j)$ is $\mu_{\mathbf{m}(i,j)}$ and it is described with Dirac delta function:

$$\begin{aligned} \mu_{\mathbf{m}(i,j)}(l,k) &= \delta(l - m_X(i,j), k - m_Y(i,j)) \\ \delta(t,u) &= \begin{cases} 1 & \text{when } (t,u) \text{ is } (0,0) \\ 0 & \text{otherwise} \end{cases} \end{aligned} \quad (3)$$

Figure 4 illustrates this membership function in three-dimensional space, since $\mathbf{m}(i,j)$ is two-dimensional vector.

However, there is no DIR algorithm that can find a perfect correspondence between two dissimilar image sets. We describe two solutions for this problem that can deal with uncertainty in the deformation vector. The first is a statistical approach, and the second is the Fuzzy Set approach.

3.2 Statistical Solution to the Uncertainty of Deformation Vector

When we utilize a statistical approach to apply an uncertainty model, we can assign a Probability Density Function (PDF), $\rho_{\mathbf{m}(i,j)}(l,k)$, to the deformation vector set in place of the Dirac delta function. There is a function. There is a certain probability for the deformation vector to point to various locations other than a point other than a point generated by the DIR. Thus, the deformation vector is no longer a single vector. Figure 5 shows an example PDF for the possible deformation vectors for an image segment, $\nu(i,j)$. For the statistical approach, the probability sum should be 1.0. If the PDF is continuous, the integral of the PDF should be 1.0. If the PDF is discrete, the height of the PDF is normalized so the total sum of the PDF is 1.0. Specific method to calculate PDF is explained in the 3.4 section.

3.3 Fuzzy Set Approach to the Uncertainty of Deformation Vector

Another way to handle the image registration uncertainty is applying Fuzzy Set theory. Fuzzy set is capable to present imprecision of facts.[25, 26, 28] In Fuzzy approach, we use a term ‘membership’ which presents a measure of fact in [0,1] range. Fuzzy Set does not require the membership sum to be 1.0, as the statistical approach requires the probability sum to be 1.0. Buckley and Eslami [4] introduced the concept of Fuzzy point. The possibility for the location of a point to be other than a given point was represented by Fuzzy membership. Since a point and a vector (starting from the origin) has the same mathematical formation, we can write a Fuzzy vector as a Fuzzy point. Thus, we assign a membership function, $\mu_{\mathbf{m}(i,j)}(l,k)$, to $\mathbf{m}(i,j)$. With the assigned membership function, $\mathbf{m}(i,j)$ is no longer a single vector but a Fuzzy Set, designated $\bar{\mathbf{m}}(i,j)$.[4] We describe the Fuzzy Deformation Vector (FDV) with the following notation:

$$\bar{\mathbf{m}}(i,j) = \sum_{l \in dX} \sum_{k \in dY} \mu_{\bar{\mathbf{m}}(i,j)}(l,k) \Big| (l,k) \quad (4)$$

where we use μ_i/A_i to describe a series, which has μ_i membership at a value or position A_i . [16,26]

Figure 6 shows an example of a membership function of FDV $\tilde{m}(i,j)$.

3.4 Uncertainty Model

The uncertainty modeling for fuzzification of deformation vectors requires the careful analysis for a particular DIR algorithm. Some efforts to generate uncertainty model from mathematical analysis were reported.[23] Such methods require known training data. However, comprehensive analyses of DIR algorithms are not yet reported. Therefore, we are introducing a heuristic method utilizing Gaussian functions. Since our DIR algorithm uses the B-Spline method, we use a Gaussian uncertainty model based on the B-Spline DIR method's general characteristic. We chose a Gaussian because it is the most well-known and understood error function.

Although the accuracy of a DIR algorithm can differ with the implementation technique and the quality of image data, Zhong et al. found that the deformation vectors calculated by the Finite Element Model (FEM) and the B-Spline DIR methods showed around a 2mm average difference near the obvious organ edge.[30] Schreibmann et al. also published their narrow-band DIR method had approximately 2mm discrepancy at organ boundaries compared to manual registration.[24] However, in the region where there are no significant gradient features, deformation vectors from various DIR methods showed differences as large as 10mm.[30] Therefore, we can estimate the range of uncertainty based on the amount of gradient features in the image region.

To measure the amount of gradient features in an image region, we utilize a histogram of the image gradient. We calculate a histogram of the image gradient at a range of 10mm from a point of interest. If there are many counts in both high gradient bins and the low gradient bins, the uncertainty of the deformation vector can be small because those regions are distinct image features. On the other hand, if there are only counts in the high gradient bins, the image region has a lot of image noise. If there are many counts in low gradient bins only, the region has few image features. For these two cases, the uncertainty of the deformation vector can be large.

As a heuristic approach, we utilize Gaussian functions to allocate the uncertainty. Based on the references discussed above, we assign 2mm as representing two standard deviations (2σ) in the Gaussian uncertainty model when the uncertainty is smallest. We set a 10mm standard deviation (2σ) when the uncertainty is largest. Otherwise, the standard deviation (2σ) is set between 2mm and 10mm as the measure of the gradient histogram. We implemented Fuzzy inference rule from the measurement of gradient histogram to decide the standard deviation (2σ) of the Gaussian uncertainty model.

Rule1: IF **Gradient-Histogram** is **Many-High-Gradient-Pixels** AND **Many-Low-Gradient-Pixels**, THEN **Uncertainty(2σ)** is **Low**.

Rule2: IF **Gradient-Histogram** is **Many-High-Gradient-Pixels** AND NOT **Many-Low-Gradient-Pixels**, THEN **Uncertainty(2σ)** is **High**.

Rule3: IF **Gradient-Histogram** is NOT **Many-High-Gradient-Pixels** AND **Many-Low-Gradient-Pixels**, THEN **Uncertainty(2 σ)** is **High**.

We normalize the Gaussian-shape membership function so the membership value at the center of the Gaussian is 1.0. The FDV now satisfies the condition of a Fuzzy point.[4]

For the statistical approach, we utilize the same Gaussian-shape uncertainty model, and normalize the Gaussian functions so the sum of Gaussian function is equal to 1.0. Therefore, we can use the function as a PDF for statistical analysis. The deformation vector becomes a Gaussian random vector.[8] For discrete calculations, a Gaussian function can be sampled at the center of each voxel center.

4 Composite Dose Calculation with Uncertainty

4.1 Statistical Composite Dose (SCD) Calculation

Since there is a probability distribution for the deformation vector, we can apply this PDF to equation (2) to calculate the expected composite dose, $\tilde{d}_c$.

$$\tilde{d}_c(i, j) = d_v(i, j) + \sum_l \sum_k p_{\mathbf{m}(i, j)}(l, k) \cdot d_u(g[i, j; (l, k)]), \quad (5)$$

where l and k are elements of dX and dY , respectively. Since the deformation vector has a probability $p_{\mathbf{m}(i, j)}(l, k)$ to become (l, k) which is a finite vector set around $\mathbf{m}(i, j)$, the dose value from the previous plan $d_u(g[i, j; (l, k)])$ also has the probability $p_{\mathbf{m}(i, j)}(l, k)$ at the dose value where the deformation vector (l, k) directs from the point (i, j) of a new plan to the previous plan. Through this process, we transfer the PDF of the deformation vector in vector space into the PDF of the dose in scalar space.

Therefore, the statistical approach calculates the average dose value using the given PDFs applied to the deformation vector. In the same manner, the standard deviation of composite dose can be calculated from the same PDF. Statistical Composite Dose (SCD) can be represented by an expectation value of the composite dose and the variance (2σ) of the composite dose. By measuring two standard deviations ($2\sigma=\pm\sigma$) of the composite dose, the clinician can see the 68% confidence range of the composite dose when we assume the error of DIR follows a normal distribution.

4.2 Fuzzy Composite Dose (FCD) Calculation

We can use the Fuzzy Deformation Vector (FDV) to calculate a Fuzzy Composite Dose (FCD). Just as the conventional deformation vector is utilized to calculate the composite dose in the equation(2), we can get the Fuzzy Composite Dose (FCD) $\bar{d}_c(i, j)$ by applying the FDV $\bar{\mathbf{m}}(i, j)$ to equation(2)

$$\bar{d}_c(i, j) = d_v(i, j) + \bar{d}_u(g[i, j; \bar{\mathbf{m}}(i, j)]) \quad (6)$$

$$\text{where } \bar{d}_u(g[i, j; \bar{\mathbf{m}}(i, j)]) = \sum_l \sum_k \mu_{\bar{\mathbf{m}}(i, j)}(l, k) \left/ d_u(g[i, j; (l, k)]) \right. \quad (7)$$

In the same manner as the statistical approach, the membership degree of the deformation vector (l, k) is $\mu_{\bar{\mathbf{m}}(i, j)}(l, k)$. Therefore, we can apply the same membership degree, $\mu_{\bar{\mathbf{m}}(i, j)}(l, k)$ to the dose value from the previous plan $d_u(g[i, j; (l, k)])$ where the deformation vector (l, k) maps from the point (i, j) of new plan to the previous plan. Thus, we derive the membership degree of the dose value in scalar space from the membership degree of the deformation vector in vector space.

When we derive the fuzzy dose values from the fuzzy deformation vectors, we need to aggregate membership values at identical dose levels within an uncertainty range.[6, 7] When there are more than two dose voxels with the same dose value, the membership degree at the dose value should increase. We utilize a fuzzy union operator (*t-conorms*) to calculate an aggregated membership value for that dose value. We utilized the second order ($\omega=2$) Yager operator for this work since it can accumulate the membership values.[15] We do not utilize the bounded-sum operator because it can easily raise the membership up to the maximum 1.0.

The final expected composite dose value can be calculated using the center of gravity method.[18] The defuzzified dose obtained by the center of gravity defuzzification can be interpreted as an expected dose value. We also utilize the α -cut method to delineate the range of the dose value when we set the threshold at a membership value.[16] For example, when $\alpha^{0.6}$ -cut is applied, the composite dose value at the point of interest is presented as the dose value range that has the membership value equal to or greater than 0.6. Since the scope of this work is presenting the dose uncertainty induced by a DIR uncertainty, we selected 0.6 and 0.8 as α -cuts to generate an example of our methodology. However, the selection should be determined by the significance of events that can occur at various radiation doses. For an example: spinal cord radiation damage can have devastating effects on a patient, so the α -cut threshold value should be small. Although both of the variance of statistical approach and an α -cut of Fuzzy Set approach can show a range of uncertainty, the α -cut is a better representation of dose uncertainty because the α -cut can show asymmetry from the center of gravity value. In addition, the Fuzzy Set approach leaves the choice in the range of confidence to the clinicians, who can apply expert medical knowledge in setting the level.

We did not use simple fuzzy arithmetic to sum doses. Even though dose values are numbers, the fuzzy set of the new composite dose may not be a fuzzy number. This is because the set may not be a normal fuzzy set. Only when the membership distribution has a single peak (with a value of 1.0) can it be a normal fuzzy set. This fact creates a difficulty in applying a simple summation of fuzzy composite doses. It may introduce more uncertainty when the fuzzy composite dose is not a normal fuzzy set and the α -cut has more than a single interval.

5 Examples

5.1 Simple 2-Dimensional Example

Figure 7 shows an example illustrating the dose uncertainty calculation. In this example, we do not use Gaussian-shape uncertainty model for more general illustration. We are calculating the composite dose $d_c(i, j)$ at (i, j) point. If the deformation vector $\mathbf{m}(i, j)$ from $v(i, j)$ to $u(i', j')$ is pointing to (l, k) , the conventional composite dose is 44Gy since $d_v(i, j)$ is 20Gy and $d_u(i', j')$ is 24Gy.

However, when we apply the uncertainty to the deformation vector $\mathbf{m}(i, j)$, it can point to other elements than (l, k) . For statistical approach, let the PDF of the deformation vector be Figure 7(c). The deformation vector $\mathbf{m}(i, j)$ now has probability values 0.4 at (l, k) , 0.1 at $(l+1, k)$, and 0.2 at $(l, k-1)$. As a result, the probability of the dose value 26Gy at $(i+1, j')$ is 0.1 since $\mu_{\mathbf{m}(i, j)}(l+1, k)$ is 0.1. The SCD and its standard deviation derived from the PDF in the figure is calculated as follows,

$$\begin{aligned}\tilde{d}_c(i, j) &= 20\text{Gy} + 0.1 \times 22\text{Gy} + 0.2 \times 22\text{Gy} + 0.4 \times 24\text{Gy} + 0.1 \times 26\text{Gy} + 0.2 \times 25\text{Gy} \\ &= 43.8\text{Gy}\end{aligned}\quad (8)$$

$$\begin{aligned}\text{dev } d_c(i, j) &= ((20\text{Gy} + 22\text{Gy})^2 \times 0.1 + (20\text{Gy} + 22\text{Gy})^2 \times 0.2 + (20\text{Gy} + 24\text{Gy})^2 \times 0.4 \\ &\quad + (20\text{Gy} + 26\text{Gy})^2 \times 0.1 + (20\text{Gy} + 25\text{Gy})^2 \times 0.2 - \tilde{d}_c(i, j)^2)^{1/2} \\ &= \sqrt{1.76}\text{Gy} \approx 1.33\text{Gy}\end{aligned}\quad (9)$$

Figure 7(d) shows an example membership function used to calculate a Fuzzy Composite Dose (FCD). To derive the FCD, we need the fuzzified dose of the previous plan along with the FDV. Similar to the statistical approach, the membership degree of the dose value 26Gy at $(i+1, j')$ is 0.25 since $\mu_{\mathbf{m}(i, j)}(l+1, k)$ is 0.25. The Fuzzy Set representation of the dose from the previous plan is now:

$$\tilde{d}_u(g[i, j; \bar{\mathbf{m}}(i, j)]) = \{0.5 / 22\text{Gy}, \underline{0.25 / 22\text{Gy}}, 1.0 / 24\text{Gy}, 0.5 / 25\text{Gy}, 0.25 / 26\text{Gy}\} \quad (10)$$

Since there are two 22Gy points in the previous plan (as underlined in Equation(10)), we utilize a fuzzy union operator. The final membership value of 22Gy becomes $0.56 = \min[1, (0.5^2 + 0.25^2)^{1/2}]$ by the second order Yager union. Therefore, the final FCD is

$$\tilde{d}_c(g[i, j; \bar{\mathbf{m}}(i, j)]) = \{0.56 / 42\text{Gy}, 1.0 / 44\text{Gy}, 0.6 / 45\text{Gy}, 0.25 / 46\text{Gy}\} \quad (11)$$

The center of gravity is 43.99Gy. The α -cut at membership 0.6 of the FCD is [44Gy, 45Gy], and the α -cut at membership 0.8 of the FCD is [44Gy, 44Gy].

We selected 0.6 and 0.8 as α -cuts for the purpose of demonstrating our methodology. However, the selection should be determined by the medical circumstances of the study, which will probably be dominated by the nature of the anatomy in question. For an example, a vital nerve (spinal cord, optical nerve, etc.) can easily be damaged by excessive irradiation, so the threshold of the α -cut value should be small.

5.2 Computational 3-Dimensional Example (Actual Patient Case)

Our second example uses actual patient data. The patient had radiation treatment to the right lung. Three months later, the patient returned to the hospital to have another radiation treatment to the right rib cage near the liver. Figure 8 shows the composite radiation dose distribution of the two treatments. We utilized B-Spline DIR to create the composite dose. The images in Figure 8 are overlaid CT images. The gray is the image set of the new treatment plan and the orange is the transformed image set from the previous treatment plan. Figure 8 (a) is showing a Coronal slice and (b) is showing a Transversal slice, respectively. Since DIR cannot find a perfect alignment, a little mismatch is visible. Three points of interests were selected in locations with high, medium, and low image features. Figure 9 (a) shows the position of the three points on another Transversal slice. Point A is at the edge of the rib— a high image feature area, Point B is in muscle near the edge of the liver – an area with medium image features, and Point C is in the liver – an area of low image feature

In this example, we utilized the Gaussian-shape uncertainty model. The histogram of the image gradient for the region at each point was generated, and the variance (2σ) of the Gaussian-shape PDF and membership function was calculated using the Fuzzy inference rules. The graph in Figure 9 shows the membership degree of the FCD of the three points. The membership function of the FCD was generated from discrete samples of dose values with the interval of 0.5mm for each axis. By utilizing an interpolation scheme, we could get a smooth, curved membership function of the FCD.[13, 19] Since the FCD is not a single value, it is a membership function on the dose axis. The point C in the liver shows the largest uncertainty in dose distribution since there is a lack of image features near the point C. Table 1 shows the summary of this experiment.

5.3 Dose Uncertainty Map

To display the dose uncertainty for a clinician to review, we utilized the same patient case as the previous example. We built a 3-dimensional grid by sampling each axis on a 3mm interval. Then, we calculated SCD and FCD for every grid point. Thus, we could achieve the 3-dimensional distribution of SCD and FCD.

Figure 10 shows the overlaid color map of the uncertainty range of deformation vectors calculated by Fuzzy inference rules on the CT image slices. The uncertainty ranges are generated from the histogram of the image gradient for a 10mm region for each grid point. The regions without sufficient image features, such as inside the liver, show the highest uncertainty ($2\sigma=10\text{mm}$) and have a red color map. The regions having the lowest uncertainty, such as at the edge of bones, show the lowest uncertainty ($2\sigma=2\text{mm}$). The low uncertainty region has been given a transparent purple color so the CT image is clearly shown.

Figure 11 shows the magnitude of uncertainty in the composite doses, which we overlaid with color map on the same CT image slices as Figure 10. Figure 11 shows the FCD using isodose lines. The isodose lines were generated from the defuzzified dose using the center of gravity of the FCD. The uncertainty range of the FCD, which is the interval of $\alpha^{0.8}$ -cut was displayed with color painting on the CT slice.

If the radiation doses are uniform in a certain area where there is also a large uncertainty in deformation, the resulting composite dose has little uncertainty. The composite dose has a small dose variation and a narrow range of the α -cut (in spite of the large uncertainty in the deformation vector). On the other hand, if the radiation dose gradient is large in an area where there is little uncertainty in deformation, the resulting composite dose may have a large uncertainty. The maximum dose uncertainty can be seen in the area where a large dose gradient occurs and a lack of image features.

6 Discussion and Conclusion

In current clinical practice, composite doses are presented without a quantified uncertainty in the deformable image registration. Such practices can lead to a false sense of confidence in the operation, particularly as viewed by a clinician not involved in the image registration. We succeeded in presenting the uncertainty in the composite dose for radiation treatment plans using both statistical and fuzzy approaches. Clinicians reviewing the Fuzzy composite dose plan will have an opportunity to analyze treatment dose scenarios with a metric showing the confidence with which the dose is predicted to be delivered. This will enable the clinician to deliver effective doses to a recurrent tumor or new tumor near the previously treated site while minimizing complications.

We devised our heuristic uncertainty allocation method and successfully tested our B-Spline DIR algorithm. The question of applying this fuzzy technique to other DIR algorithms can possibly be inferred from comparing the various DIR algorithms. Zhong et al. reported the differences of deformation vectors between DIR algorithms using the Finite Element Method (FEM) as a reference method. Zhong found the difference between FEM and Demon, and between FEM and B-Spline were similar.[30] Thus, we believe our heuristic uncertainty allocation method can also be applied to the Demon DIR method.

This study does not model the deformation elasticity differences between the various body tissues. Future investigations will be directed at the refinement of the heuristic uncertainty allocation method by considering tissue deformation characteristics, and mathematical modeling of specific DIR algorithm's characteristics. To find the best uncertainty model, we will consider applying other Fuzzy theory schemes, such as interval-valued fuzzy sets, and/or ignorance functions. [5, 11]

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Figure 1.
A radiotherapy plan for a patient with a tumor on the left side of the neck is shown. Color lines represent identical dose lines, or ‘isodoses’. Isodose lines connect voxels with identical dose values. For example, the interpolated 40Gy voxels connect to create the green isodose line.

Figure 2.

An illustration of Deformable Image Registration (DIR) mapping Organ T between image sets U and V by generating the deformation vector set m . These vectors are then utilized to add the dose values of plan V and plan U to make a composite dose d_c .

Figure 3.

Deformation vectors have greater uncertainties in areas with no significant image features (such as point B to B' above). The deformation vector from A to A' can be confirmed with high confidence due to presence of the small bone (a high intensity gradient).

Figure 4.

An example of the membership function of $\mu_{\mathbf{m}(i,j)}(l,k)$ for a deformation vector.

Figure 5.

A probability density function $p_{\mathbf{m}(i,j)}(l,k)$ is applied to a deformation vector, $\mathbf{m}(i,j)$.

Figure 6.

An example of the membership function, $\mu_{\mathbf{m}(i,j)}(I,k)$ for Fuzzy set presentation

Figure 7.

Two-dimensional example illustrating the combination of two plan doses. (a) and (b) show two different dose distributions. (c) and (d) show the uncertainty of the deformation vector from voxel $v(i, j)$ to voxel $u(i', j')$. (c) shows a Probability Distribution Function (PDF) of statistical approach. (d) shows a fuzzy membership function of a Fuzzy Deformation Vector (FDV).

Figure 8.
Simple Composite Dose Distribution created without consideration of local uncertainties (typical current practice). N is the new treatment site and O is the old treatment site. B-Spline deformable registration is used to combine the images and dose matrices.

(a)

(b)

Figure 9.

(a) Three points of interest are selected to demonstrate combined Fuzzy Composite Dose (FCD). Point A is chosen at the edge of bone (a high image feature area), Point B is falls in a medium feature area, and Point C is a low feature area. (b) In the graph, a membership function of FCD with a wider dose range means more dose uncertainty at the point.

Figure 10.

Color map images showing the ranges of uncertainty were overlaid on the CT image of the new plan. Uncertainty ranges were calculated from the histogram of gradient. Fifty percentage of transparency were applied to the color map when it is overlaid on the patient CT

Figure 11. Isodose lines show the center of gravity dose value and color map image show the range of dose values at $\alpha^{0.8}$ -cut of Fuzzy Composite Dose (FCD).

Table 1.

Results Summary of the selected points in the computational example

Point	Uncertainty in deformation vector 2σ [mm]	Point Dose (New) [Gy]	Point Dose (Previous) [Gy]	Conventional Dose Sum [Gy]	Statistical Composite Dose (SCD)		Fuzzy Composite Dose (FCD)		
					Average [Gy]	Standard Deviation 2σ [Gy]	Center of Gravity [Gy]	$\alpha^{0.8}$ -cut [Gy]	$\alpha^{0.6}$ -cut [Gy]
Bone (A)	2.0	62.6	16.4	79.7	79.7	3.6	79.8	[77.4,81.7]	[77.0,82.1]
Muscle (B)	3.7	62.6	16.5	80.0	80.3	6.8	80.8	[75.0,85.7]	[74.6,86.3]
Liver (C)	9.8	54.5	30.1	84.3	84.2	16.4	85.5	[69.3,100.4]	[68.4,101.7]