

A Novel Semi-Automatic Method for Accurate Registration of FDG_CT and FLT_CT Image Modalities

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Abstract—The widely used 18F-fluorodeoxyglucose (18F-FDG) radiotracer serves as a good imaging tool in Computed Tomography (CT) and is essential for cancer diagnosis as FDG uptake is higher in cancerous lesions and lower in benign ones, while 18F-fluorothymidine (18F-FLT) uptake is shown to be closely correlated with cellular proliferation. The registration of both of these tracers, FDG and FLT, complement one another to increase both sensitivity and specificity for imaging cancer. Accurate registration of both imaging modalities is thus sought in this study to optimize the results of the diagnosis. This paper describes a novel feature-based registration method which employs affine transformation and linear interpolation for FDG_CT and FLT_CT image modalities. Instead of using one set of affine transformation parameters, three slices have been selected to calculate all of the transformation parameters for CT image registration by linear interpolation. This method has the merits of: a) improving the 3D registration results for CT images; b) avoiding arbitrary selection of that one slice for calculating the transformation parameters for registration; and c) being cost-effective in both its implementation and computational requirements. Experimental results show that effective registration of these two imaging modalities could prove very useful for cancer diagnosis, including improved means for quantization and visualization.

Keywords—*image registration; FDG_CT; FLT_CT*

I. INTRODUCTION

Medical imaging technologies, such as CT and PET, continue to have significant impact on medical research and in diagnostic radiology [1]. As CT is known to generate detailed images of soft tissues in the body, combining the complementary strengths of proven tracers like FDG and FLT can only improve the outcome of the diagnosis. Thus integrating images to get more subtle information is often a requisite task in seeking a reliable outcome.

Image registration is the process of aligning different sets of data into one coordinate system in order to compare or integrate them. That process is often to be realized by aligning one image to the coordinate of the other one. The pixel value and position should be both taken into account. Image

registration includes preprocessing, transformation, interpolation, and registration process optimization [2]. Feature-based registration methods find correspondence between image features, such as points and lines. By obtaining the correspondence between a number of points in images, a transformation is then determined to map the input image to the reference image, establishing as a consequence a point-by-point correspondence between a reference image and its input counterpart [3].

An overview of medical image registration methods reveal that progress remains to be made towards a more effective solution [2]. Feature matching methods could make use of similarity measurements as in studies [4, 5]. But in this study, a mutual information registration method using point feature location information was developed to estimate the accuracy in aligning corresponding images in the two imaging modalities. A novel aspect of this method is the emergence of correspondence between two sets of features as a by-product of information maximization [6]. An approach which automatically learns new corresponding landmarks from a database of 3D whole body CT scans, using a limited initial set of expert-labeled ground-truth landmarks was presented in [7]. Based on landmark detection and calibrated camera-projector system, another technique was proposed for registration in minimally invasive spinal surgery [8]. An automated method for vertebra-based registration systems is proposed in [9].

In this study, a semi-automated CT image registration method is proposed to align an FDG_CT image to an FLT_CT image. The method includes five steps: 1) choosing slices for an initial registration; 2) selecting control points; 3) realizing the initial registration; 4) performing interpolation; and 5) finalizing the process with a second phase registration.

II. METHODS

A. Control Points Selection

For the initial registration, a set of control-points (*cp*) should be chosen. The *cpselect* function is utilized to start the control

point selection tool in Matlab. The input image and base image can be seen in the window of the Matlab tool. A blue mark with number 1 will appear when the user clicks on the base image once, then by clicking on the corresponding point in the input image another blue mark with number 1 will appear on it. Blue marks with number 2 form the second control-points set and so on. Four such control-points sets would complete the selection process.

B. Affine Transformation

Affine transformations preserve points, straight lines, and planes in the affine space. Parallel lines remain parallel, and the ratios of distances between points lying on a straight line are preserved. An affine transformation includes translation, rotation, and scaling. Affine transformation as applied in this study are formulated as follows:

$$\begin{pmatrix} x \\ y \end{pmatrix} = \begin{pmatrix} a_1 & a_2 \\ a_3 & a_4 \end{pmatrix} \begin{pmatrix} u \\ v \end{pmatrix} + \begin{pmatrix} a_5 \\ a_6 \end{pmatrix} \quad (1)$$

According to this model, (x, y) is the point in the reference image, and (u, v) is the point in the input image. Six parameters $(a_1, a_2, a_3, a_4, a_5, a_6)$ can be calculated from three pairs of points sets. Therefore, to define an affine transformation, at least three points should be chosen from the input image and the reference image, respectively [10].

C. Interpolation

Interpolation is used in this case to construct new data points within the range of a discrete set of known data points. For example, 3 sets of parameters obtained from the first, middle, and last slice pairs will serve as the known data points. New data points can then be constructed within the range of set 1 to set 2, as well as within the range of set 2 to set 3 by interpolation. Thus, if the total slice number is k , the middle slice number is i , new data points are the parameters from slice 2 to slice $(i-1)$, and slice $(i+1)$ to slice k .

In this study, instead of registering two CT images with a set of registration parameters, k sets of parameters have been used to register each slices pairs. When k is the total number of slices in the given CT image, k sets of parameters will thus be obtained through linear interpolation.

D. Data

This phase I pilot study includes data from five patients with resectable and unresectable pancreatic cancers who underwent ^{18}F -FLT and ^{18}F -FDG imaging, each acquired within a week's duration for a same patient. In these 5 datasets that have been tested, it is noted that each of them had FLT_CT and FDG_CT taken in different days. FDG_CT is used as the reference image which is unmoved, while the FLT_CT is used as the input image which is moving in seeking that perfect alignment. Except for data set 1 which was of size $(512*512*186)$, all other sets were of size $(512*512*244)$ for both FDG_CT and FLT_CT modalities.

E. Experiments

1) Minimizing errors in manual selection of control points

To calculate the parameters of the first step of the registration process, control points have been chosen manually. With the manual selection process, it is difficult to visually select exactly the same point in the two CT images; but choosing four vertexes of a rectangle as the assumed control points is easier as there is contextual information. As can be seen in Fig.1, the four vertexes of the rectangle have been marked with a "+"; thus an initial test would be to assume the input image as a rotated reference image by 90 degrees counter-clockwise; by registering these two images, the "+" marks will overlap perfectly. Thus, if the control points have been chosen correctly, this registration method would yield perfect registration results; which is the intent of this initial registration step.

2) Testing the middle slice of FDG_CT from set 1 to 5

For set 1, slice No. 93 happens to be the middle slice of the FDG_CT. It has been chosen as the reference image because it has more structures that can be chosen as control points. The input image has been obtained by rotating the reference image 90 degree for visual convenience. Then the two images are registered. Fig. 2 shows this test. For set 2 through 5, slice No. 122 has been considered as the reference image for the same reasons mentioned earlier.

3) Testing all slices in set 1 through 5

Select 3 pairs of slices, for example, the first slice, the middle slice, and the last slice in each set, and then register each pair in their respective FDG_CT and FLT_CT modalities. This step constitutes the first part of the registration process. Using the 3 pairs of affine transformation parameters obtained thus far, all other parameters are determined through linear interpolation.

F. Experimental procedure

The objective is to register the NIFTI (nii) formatted 3D reference image FDG_CT.nii, and the 3D input image FLT_CT.nii. The procedure consists of the following 5 steps:

- Step 1: choose the slices from each 3D image for the initial registration step. For example, slice No. 1, No. i , and No. k of each 3D image will be chosen.
- Step 2: choose control points manually in each slice to obtain the base points and the input points for the initial part of the registration process. For affine transformations, at least 3 control-points sets are needed. Here, 4 base points and 4 input points are chosen in slice No.1 of FDG_CT and FLT_CT, respectively.
- Step 3: register those pairs of slices chosen in step1 to determine the desired affine transformation parameters. For example, if we choose 3 slices pairs, we will get 3 sets of registration parameter for set 1, set 2, and set 3.
- Step 4: use the sets of affine transformation parameters determined in step 3 to calculate all the other parameter sets by linear interpolation. Take k slices in total for example, we use parameter set 1 and set 2 to calculate the parameters of slice No. 2 to Slice No. $(i-1)$, $(0 < i < k)$, then we use parameter set 2 and set 3 to calculate the parameters of slice

No. $(i+1)$ to slice No. $(k-1)$, finally, all the affine transformation parameters can be obtained from slice No. 1 to slice No. k .

- Steps 5: the second phase of the registration process registers each slice pairs of the FDG_CT and the FLT_CT by using all the affine transformation parameter sets.

III. EVALUATION METHODS

A. Mutual Information and Normalized Mutual Information

Mutual information between images A and B is defined as:

$$MI(A, B) = H(A) + H(B) - H(A, B) \quad (2)$$

$H(A)$, $H(B)$, $H(A, B)$ are the entropies of image A, image B, and the joint entropy of images A and B [6], where:

$$H(A) = -\sum_a P_A(a) \log_2 P_A(a) \quad (3)$$

$$H(B) = -\sum_b P_B(b) \log_2 P_B(b) \quad (4)$$

$$H(A, B) = -\sum_{a,b} P_{AB}(a, b) \log_2 P_{AB}(a, b) \quad (5)$$

with $a \in A, b \in B$, and $P_A(a)$, $P_B(b)$, $P_{AB}(a, b)$ define the probability distribution of gray values of image A, B and the joint probability distribution of gray values of images A and B. The normalized mutual information can thus be defined as:

$$NMI = \frac{MI}{\sqrt{H(A) \cdot H(B)}} \quad (6)$$

B. Alignment Metric

Consider that images $I_1(x, y)$ and $I_2(x, y)$ are $M \times N$ images, where $H_1(n)$ and $H_2(n)$ are their corresponding histograms. The gray scale of the image is $0 \leq n \leq 255$. If $n = i$, $H_1(n)$ and $H_2(n)$ are the total number of pixels whose gray value is i in image $I_1(x, y)$ and $I_2(x, y)$. The ratio of gray value i in image $I_1(x, y)$ and $I_2(x, y)$ are as follows:

$$p_1(i) = H_1(i) / (M \times N) \quad (7)$$

$$p_2(i) = H_2(i) / (M \times N) \quad (8)$$

For each gray scale n in image $I_1(x, y)$, $H_1(n)$ is the total number of pixels whose gray value is n . Finding out the coordinates of those pixels in $I_1(x, y)$, and by using the same coordinates to search for the pixels in image $I_2(x, y)$ and summing the gray values in those positions, the mean vector $\bar{E}_{1,2}(n)$ and the relative variance $\sigma_{1,2}^2(n)$ can be obtained as:

$$\bar{E}_{1,2}(n) = \frac{1}{H_1(n)} \sum_{I_1(x,y)=n} I_2(x, y) \quad (9)$$

$$\sigma_{1,2}^2(n) = \frac{1}{H_1(n)} \sum_{I_1(x,y)=n} (I_2(x, y) - \bar{E}_{1,2}(n))^2 \quad (10)$$

This process is repeated for $I_2(x, y)$ to yield:

$$\bar{E}_{2,1}(n) = \frac{1}{H_2(n)} \sum_{I_2(x,y)=n} I_1(x, y) \quad (11)$$

$$\sigma_{2,1}^2(n) = \frac{1}{H_2(n)} \sum_{I_2(x,y)=n} (I_1(x, y) - \bar{E}_{2,1}(n))^2 \quad (12)$$

The expectation variances based on $I_1(x, y)$ and $I_2(x, y)$ are

$$\bar{\sigma}_{1,2}^2 = \sum_n p_1(n) \sigma_{1,2}^2(n) \quad (13)$$

$$\bar{\sigma}_{2,1}^2 = \sum_n p_2(n) \sigma_{2,1}^2(n) \quad (14)$$

The cross variance (CI) between the two images is defined as:

$$CI[I_1, I_2] = \frac{\bar{\sigma}_{1,2}^2}{\sigma_1^2} + \frac{\bar{\sigma}_{2,1}^2}{\sigma_2^2} \quad (15)$$

here, μ_1 and μ_2 are the mean values; σ_1^2 and σ_2^2 are the variance of image $I_1(x, y)$ and $I_2(x, y)$, respectively.

$$\sigma_1^2 = \frac{1}{MN} \sum_{(x,y)} (I_1(x, y) - \mu_1)^2 \quad (16)$$

$$\sigma_2^2 = \frac{1}{MN} \sum_{(x,y)} (I_2(x, y) - \mu_2)^2 \quad (17)$$

Obviously, σ_1^2 and σ_2^2 are constants. When registration is performed well, $\bar{\sigma}_{1,2}^2$ and $\bar{\sigma}_{2,1}^2$ are smaller, therefore the CI is also smaller. We could thus define the alignment metric as:

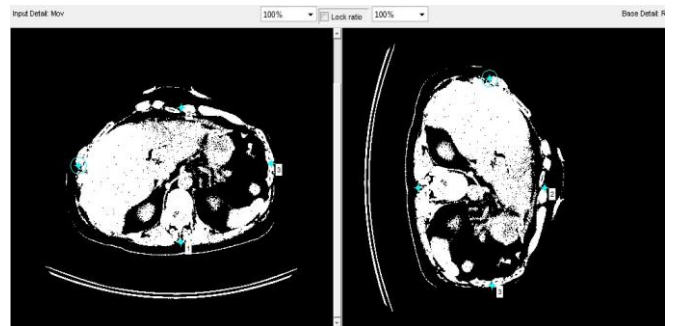
$$AM(I_1, I_2) = \frac{1}{CI[I_1, I_2]} \quad (18)$$

IV. RESULTS

Fig. 1 shows that the results of overlapping the registered rectangle with 4 control marks in gray and the original rectangle with 4 control marks in black. The control markers, as expected, are almost overlapping perfectly with each other. Minimal errors are still observed however for the rectangle as shown in Table 1 to indicate that manual selection of the control points is still difficult to perfect even under visual scrutiny. Table 1 provides the computed MI, NMI, and AM measurements which clearly prove the reliability of the proposed registration method. Fig. 2 shows the results when overlapping the output image to the reference image. According to the results given in Table 1, when the input image is exactly the same as the reference image, the average of maximum MI, NMI and AM are 1.652, 0.499, and 17.721, respectively. The MI, NMI, and AM are higher when FDG_CT and FLT_CT have been registered. Fig. 3 illustrates the results obtained in registering the 3 selected slices (i.e., the first, middle, and last slices) in the initial phase of the registration process. Fig. 4 plots the AM measurements for all 5 sets for visual appreciation and to see how this measurement varies depending on which parts of the body these slices belong to. Fig. 5 provides the results of the overall registration process as illustrated through a typical dataset, similar good results are obtained for the other four datasets. For a visual indication of the merits of these registrations results, focus on the ossature frame, and more specifically on the vertebrae as shown in the FDG_CT and their counterpart in the FLT_CT. Recall that these image modalities were obtained on different days.



Fig. 1. Registered image with 4 “+” marks overlapping the reference image.



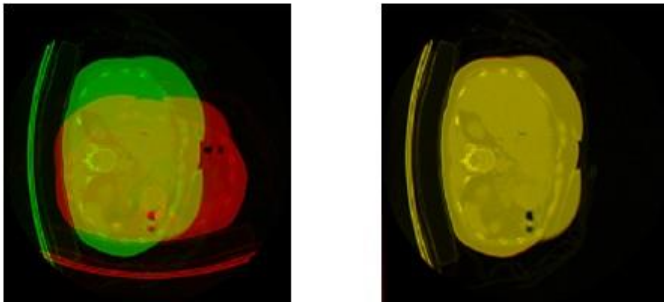


Fig. 2. The first two images are the input image and the reference image with four blue control points marked in each of them. The third image is overlapping the green reference image, slice No. 93 of FDG_CT of set 1, and the red input image which is rotating the green image 90 degree counter-clockwise. The fourth image is overlapping the output image and the reference image.

TABLE 1: REGISTRATION RESULTS: I IS THE INPUT IMAGE, R IS THE REFERENCE IMAGE, AND O IS THE REGISTERED FLT_CT IMAGE
EVALUATION FOR SET 1 TO 5

DATA	SET 1		SET 2		SET 3	
IMAGES	I & R	O & R	I & R	O & R	I & R	O & R
MI	0.72	1.91	0.76	1.64	0.65	1.69
NMI	0.21	0.55	0.21	0.46	0.21	0.54
AM	0.94	23.05	1.09	13.74	0.72	20.06
DATA	SET 4		SET 5		RECTANGLE	
IMAGES	I & R	O & R	I & R	O & R	I & R	O & R
MI	0.65	1.51	0.74	1.51	0.00	0.23
NMI	0.21	0.48	0.23	0.48	0.00	0.91
AM	0.72	11.81	1.11	19.93	0.50	26.93

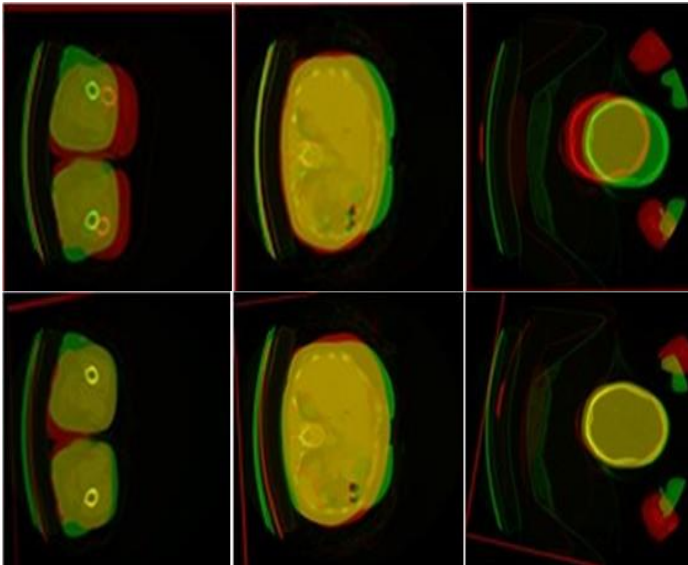
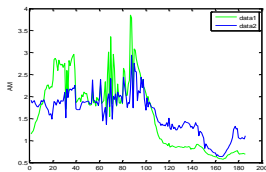
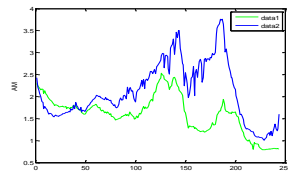


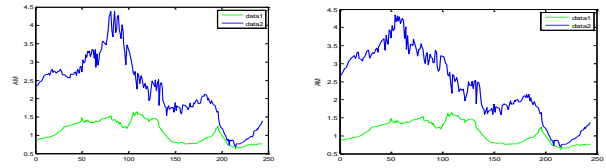
Fig. 3. Set 1: 3 slices used in the initial phase of the registration. The upside three images are the first, middle, and last of the unregistered slices; the downside three images on the right show the registered slices.



(a) Set1

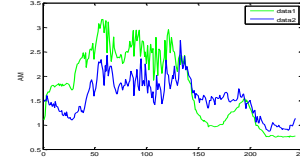


(b) Set2



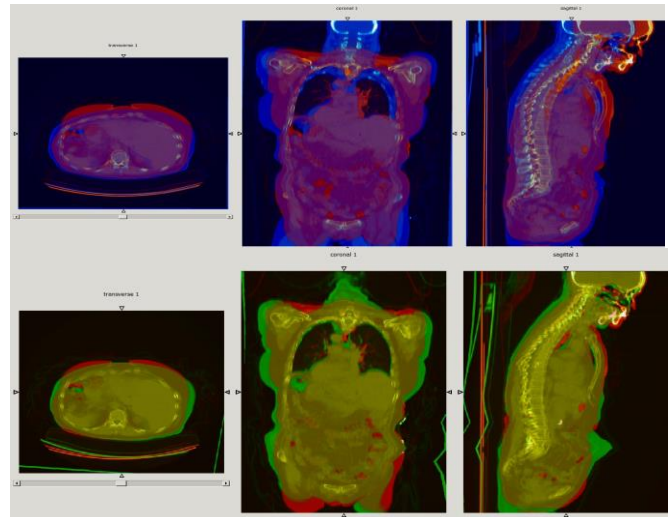
(c) Set 3

(d) Set 4

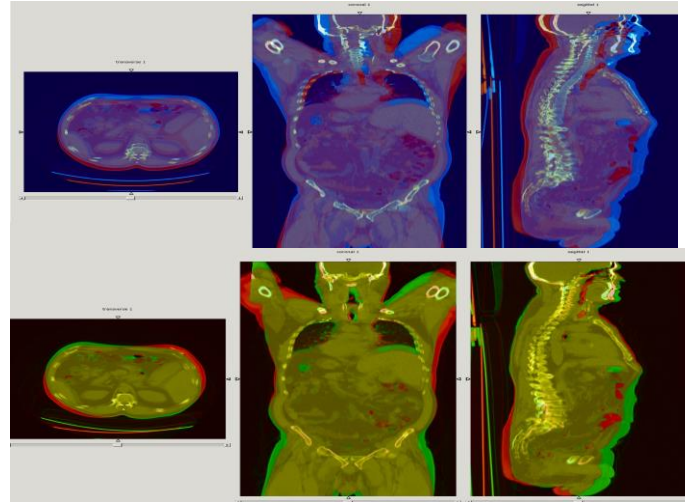


(e) Set 5

Fig. 4. The AM for set 1 to 5. Green data 1 is the AM of FLT_CT and FDG_CT; Blue data 2 is the AM of registered image and FDG_CT. Blue data is higher than green data (registration improved) in these parts: (a) from slice No.1 to slice No.11 and from slice No. 105 to slice No.186; (b) from slice No. 40 to slice No. 244; (c) and (d) all of the slices;(e) from slice No. 139 to slice No. 244 in set 5.



(a) Set 1



(b) Set 2

V. CONCLUSION

In retrospect, the method improved the CT registration of the FDG_CT and FLT_CT imaging modalities by combining the strengths of both tracers for cancer diagnosis. The registration of these 2D slices provides a comprehensive 3D whole body combined FDG-FLT CT image. The improvement can be observed visually by comparing the overlapped registered image to the original image. To avoid arbitrary using one set of affine transformation parameters to register images, three (the first, the middle and the last) slices were all used to calculate the whole set of transformation parameters of the 3D whole body CT image through linear interpolation. Improvements could be observed obviously in the skull and the bottom parts of the whole body CT. This method can accomplish the registration of two 512*512*244 bit CT images in around 1 minute using Matlab on a Windows 7 workstation with 3.40 GHz Intel (R) Core (TM) i7-2600 CPU and 4GB RAM. Experimental results clearly demonstrate the soundness of the proposed method in terms of its small registration errors as indicated in Table 1 as well as in terms of visual appreciation.

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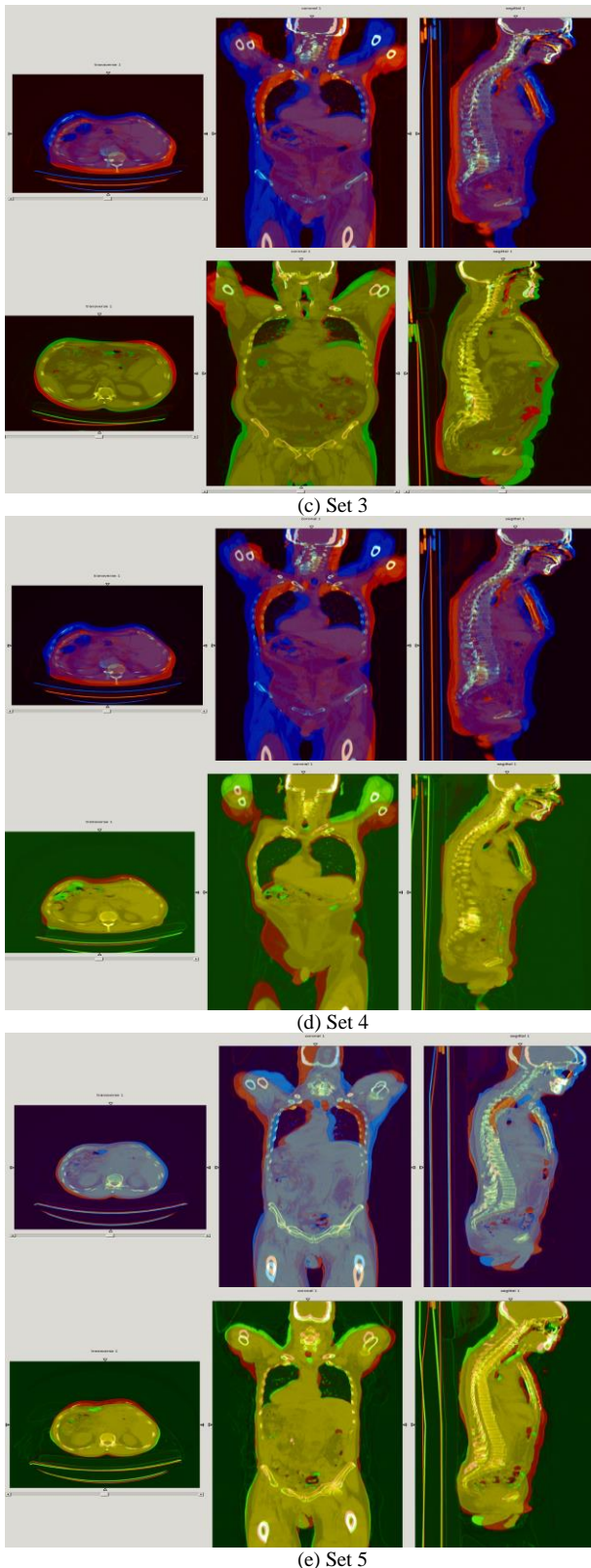


Fig. 5. Set 1 to 5: overlapped unregistered blue FLT_CT and red FDG_CT on the upside; overlapped registered green FLT_CT and red FDG_CT on the downside. These exemplify typical whole body registration for all 5 patients.